Role of the Interval from Completion of Neoadjuvant Therapy to Surgery in Postoperative Morbidity in Patients with Locally Advanced Rectal Cancer

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SYNOPSIS

In multivariable analysis, the interval between neoadjuvant therapy and surgery was not an independent predictor of postoperative complications in rectal cancer patients. Complications were associated with male sex, tumor location, open operative approach, and neoadjuvant chemoradiotherapy administered alone.

ABSTRACT

Background. Increasing the interval from completion of neoadjuvant therapy to surgery beyond 8 weeks has been reported to increase complications. However, a recent study found that delay beyond 8 weeks is not associated with higher perioperative morbidity.

Methods. Patients who presented with a tumor within 15 cm of the anal verge in 2009–2015 were grouped according to the interval between completion of neoadjuvant therapy and surgery: <8 weeks, 8 to 12 weeks, and >12 to 16 weeks.

Results. Among 607 patients, the surgery was performed at <8 weeks in 317 patients, 8 to 12 weeks in 229 patients, and >12 to 16 weeks in 61 patients. Patients who underwent surgery at 8 to 12 weeks and patients who underwent surgery at <8 weeks had comparable rates of complications (37 and 44%, respectively). Univariable analysis identified male sex, earlier date of diagnosis, tumor location within 5 cm of the anal verge, open operative approach, abdominoperineal resection, and use of neoadjuvant chemoradiotherapy alone to be associated with higher rates of complications. In multivariable analysis, male sex, tumor location within 5 cm of the anal verge, open operative approach, and neoadjuvant chemoradiotherapy administered alone were independently associated with the presence of a complication. The interval between neoadjuvant therapy and surgery was not an independent predictor of postoperative complications.

Conclusions. Delaying surgery beyond 8 weeks from completion of neoadjuvant therapy does not appear to increase surgical morbidity in rectal cancer patients.

INTRODUCTION

Rectal cancer treatment is multimodal. The standard approach in North America includes preoperative chemoradiotherapy (chemoRT) for tumors of clinical stage II or III (cT3/4, cN+) based on MRI or endorectal ultrasound.[1] This approach confers excellent local control, with local-recurrence rates less than 5%.[2] The most common type of relapse is distant failure.[3,4]

Following completion of neoadjuvant therapy, surgery is delayed for several weeks to allow the response to treatment to continue. In recent years, prolongation of the interval between completion of neoadjuvant therapy and surgery has gained popularity based on evidence that prolongation is associated with higher rates of downstaging and pathologic complete response.[5-10] However, surgeons have traditionally expressed concern over pelvic fibrosis associated with radiotherapy when surgery is delayed beyond 8 weeks, because pelvic fibrosis makes surgery more technically challenging and increases morbidity.

The optimal time for operative intervention remains a topic of debate among clinicians. The current guidelines of the National Comprehensive Cancer Network recommend surgical intervention at 5 to 12 weeks.[1] Two recent studies evaluating data from the National Cancer Database found that delaying surgery beyond 8 weeks was associated with a higher rate of positive surgical margins and a lower rate of sphincter preservation.[11,12] The GRECCAR-6 trial found that in patients who underwent surgery at 11 weeks, the quality of the mesorectal resection specimen was poorer and the rate of complications was higher than in patients who underwent surgery at 7 weeks (45% vs. 32%).[13] However, the difference in the rates of complications was attributable to medical rather than surgical comorbidity. A phase II trial of neoadjuvant FOLFOX in combination with chemoRT found that patients who underwent surgery at 12 to 26 weeks did not have higher rates of pelvic fibrosis or surgical morbidity.[14]

At Memorial Sloan Kettering Cancer Center (MSK), neoadjuvant strategies for rectal cancer include chemoRT alone, systemic chemotherapy alone, and the combination of chemotherapy and chemoRT, which is referred to as total neoadjuvant therapy (TNT).[15] Deferral of surgery after an apparent complete clinical response has become commonplace,[16] and an increasing proportion of patients undergo delayed resection following neoadjuvant therapy. Patients with near-complete response are often monitored for 8 to 12 weeks and even longer before having definitive surgery. In order to plan appropriate management and also to optimize clinical outcome, it is important to determine whether the timing of surgery influences surgical risk. This study was aimed at comparing the rates of postoperative morbidity among patients who differed in the length of the interval from completion of neoadjuvant therapy to surgery. Our hypothesis was that postoperative morbidity is not higher in patients who undergo surgery more than 8 weeks after completion of neoadjuvant therapy.

METHODS

Patients

A waiver of authorization was obtained from the institutional review board to review patient records. We searched an MSK database to identify patients seen at the MSK colorectal surgical oncology clinic between June 1, 2009, and March 1, 2015, with biopsy-proven nonmetastatic primary locally advanced rectal adenocarcinoma within 15 cm of the anal verge (based on proctoscopy), who received neoadjuvant therapy. Locally advanced rectal adenocarcinoma was defined in accordance with the guidelines of the National Comprehensive

Cancer Network as a stage cT3/cT4 N0 or cT(any) cN1/2 tumor based on endorectal ultrasound or MRI.[1] Additionally, CT of the chest, abdomen, and pelvis was performed for local disease staging prior to initiation of treatment. Patients were excluded if they had previously undergone a surgical intervention for rectal cancer, had recurrent or metastatic disease at initial assessment or diagnosed during neoadjuvant treatment, or had complicated fistulizing inflammatory bowel disease in the rectum or perineum.

Neoadjuvant Therapy

The neoadjuvant regimen was chemotherapy alone, chemoRT alone, or TNT. Chemotherapy alone generally included fluorouracil in combination with oxaliplatin (FOLFOX) administered over a 4- to 6-month period prior to surgery. ChemoRT involved long-course radiation delivered in 28 fractions with concurrent infusional fluorouracil or oral capecitabine. TNT involved combinations of fluorouracil and oxaliplatin administered before or after chemoRT (as induction or consolidation chemotherapy, respectively). Upon completion of neoadjuvant therapy, the decision on whether to proceed with surgery was based on the degree of clinical response to treatment, based on clinical, endoscopic, and radiological assessments. Timing of surgery throughout the study period was at the discretion of the surgical team.

Clinical Response to Neoadjuvant Therapy

Nonoperative management or deferral of surgery was part of the course of treatment for selected patients who had a clinical complete response to neoadjuvant therapy. The clinical and radiological features used to determine the presence of a clinical complete response have been described previously, as have the initial results of using nonoperative management for such

patients.[16] Patients who did not undergo surgery upon completion of neoadjuvant therapy entered a surveillance protocol. In cases where there was clinical concern for tumor regrowth or patient choice to move off a nonoperative approach, a delayed resection was performed.

Patients who did not have a clinical complete response underwent radical resectional surgery, generally within 16 weeks of completing neoadjuvant therapy. The patients were grouped by length of time between the last day of receiving neoadjuvant treatment and the date of surgery: <8 weeks (28 to 55 days), 8 to 12 weeks (56 to 84 days), and >12 to 16 weeks (85 to 112 days). All surgeries were performed by MSK surgeons according to the principles of anatomic mesorectal excision using either an open or a minimally invasive approach, defined as sharp mesorectal dissection under direct visualization and as laparoscopic or robotically assisted surgery, respectively. A diverting ileostomy was created at the surgeon's discretion.

Pathological Response to Neoadjuvant Therapy

Pathology data were collected from analyses of resection specimens performed shortly after surgery. The specimens were evaluated in accordance with standard protocols for rectal cancer pathology.[17] Pathologic complete response to neoadjuvant treatment was defined as absence of viable tumor cells in the final resection specimen.

Complications

Data on complications that occurred in the first 90 days after surgery were collected from a prospectively maintained institutional database[18] and from patient records, including inpatient, outpatient, discharge summary, and readmission notes and correspondence. Complications were graded according to the Clavien-Dindo classification system.[8] Complications due to adjuvant

chemotherapy or subsequent surgery unrelated to rectal cancer were deemed nonattributable and were excluded. Clavien-Dindo grade 1–5 complications were grouped in the category “any complications”. Anastomotic leaks (leak or dehiscence) were identified on radiographic imaging with contrast (e.g., CT scan with contrast or Gastrografin enema) or direct visualization with endoscopy. Such investigations were not performed routinely but were prompted in cases of clinical suspicion.

Statistical Analyses

Clinical and pathological data were grouped according to standard thresholds. Groups were compared using the chi-square test for trend for categorical data and the Kruskal-Wallis test for continuous data, with a significance level of $P < 0.05$. Associations between individual variables and the presence of any complications after surgery were evaluated with univariable and multivariable binary logistic regression. A significance threshold of $P < 0.05$ was set for inclusion in the multivariable model. The data were analyzed using SPSS software (IBM).

RESULTS

Of the patients who attended the colorectal surgical clinic at MSK between June 1, 2009, and March 1, 2015, 798 received neoadjuvant therapy. Following neoadjuvant therapy, 657 (82%) patients underwent surgery within 12 months, of whom 607 (76% of 798) had surgery within 16 weeks. Deferral of surgery beyond 16 weeks was due to entry into a watch-and-wait protocol or to various medical or surgical reasons (e.g., treatment of medical comorbidities), and those patients were excluded from analysis. The clinical and pathological characteristics of

patients who underwent rectal resection within 16 weeks of completing neoadjuvant therapy are listed in Table 1.

We did not observe any significant relationships between time to surgery and postoperative morbidity when time was analyzed as a continuous variable (data not shown). Patients were therefore grouped by categories considered clinically relevant, in agreement with previous reports.[11-13] Three hundred seventeen patients (52%) had surgery <8 weeks after completing neoadjuvant therapy (mean, 46 ± 7.4 [standard deviation] days), 229 patients (38%) had surgery at 8 to 12 weeks (mean, 65 ± 7.8 days), and 61 patients (10%) had surgery at >12 to 16 weeks (mean, 93 ± 7.9 days).

Patients who underwent surgery ≥8 weeks after completion of neoadjuvant therapy were significantly more likely to be older than 75 years, to have begun treatment in 2014-2015, and to have a tumor within 5 cm of the anal verge (requiring abdominoperineal resection). They were also more likely to have received TNT and to have had a diverting ileostomy after a sphincter-saving procedure. Minimally invasive surgery was less common in patients who underwent surgery at >12 to 16 weeks (Table 1).

Complications occurred in 256 (42%) of patients (Table 2). Surgery at >12 to 16 weeks was associated with a significantly higher overall rate of complications (56%) than surgery at <8 weeks (44%) or surgery at 8–12 weeks (37%) (P = 0.02 [Chi square for trend]). However, the three groups of patients did not differ significantly in the rates of surgical site infection (SSI), grade 3–5 complications, or anastomotic leak. They also did not differ significantly in median length of hospital stay or the proportion of patients whose hospital stay exceeded 7 days (Table 2). Patients who underwent surgery at <8 weeks and patients who underwent surgery at 8–16

weeks had comparable rates of complications (Tables S1 and S2 in the Supplement). Subanalysis of data for 281 patients who received chemoRT alone produced similar results (Tables S3 and S4 in the Supplement).

Further subgroup analysis showed that among patients who had sphincter-preserving low anterior resection, those who underwent surgery at >12 to 16 weeks had a higher rate of complications (53% vs. 41% and 31%; $P = 0.025$). Likewise, among patients with a poor response to treatment (absence of T downstaging), those who underwent surgery at >12 to 16 weeks had a higher rate of complications (66% vs. 44% and 33%; $P = 0.008$). No other relationships between time to surgery and complications were observed for other subgroups.

The data on the incidence of complications in relation to the patients' clinical and pathological characteristics are listed in Table 3. Associations were observed between the occurrence of any complication and male sex, earlier year of diagnosis, tumor within 5 cm of the anal verge, open surgery, abdominoperineal resection, use of ileostomy after low anterior resection, and use of chemoRT alone. Grade 3–5 complications were more common in patients without T or N downstaging. The incidence of SSI was associated with earlier year of diagnosis, open surgery, abdominoperineal resection, use of chemoRT alone, increasing ypN stage, and absence of N downstaging. Anastomotic leak after low anterior resection was associated with open surgery ($P < 0.05$).

The results of binary logistic regression analysis for factors potentially associated ($P < 0.1$) with the occurrence of any complication after surgery are listed in Table 4. On univariable logistic regression, male sex, earlier year of diagnosis (2009–2011), tumor within 5 cm of the anal verge, advanced ypT stage (ypT 4), open surgery, abdominoperineal resection, and

chemoRT administered alone were associated with complications. In multivariable analysis, male sex, tumor within 5 cm of the anal verge, open surgery, and chemoRT alone were independently associated with complications.

DISCUSSION

Time to surgery did not appear to increase the risk of complications on univariate or multivariable analysis. We did observe a weak association with higher complication rates in patients who underwent surgery at >12 to 16 weeks, but those patients were also more likely to be older than 75 years, to undergo abdominoperineal resection, and to undergo open (rather than minimally invasive) surgery—factors likely to confound an ostensible association with complications.

Our findings are consistent with those of the GRECCAR-6 trial[13] in that any potential increase in complications associated with a delay in surgery did not include changes in the rates of SSI, grade 3–5 complications, or anastomotic leak. Similarly, a recent phase II trial reported no increase in surgical morbidity or operator-perceived technical difficulty for surgery performed between 12 and 26 weeks.[14] These results contrast to an extent with the recent reports based on National Cancer Database audit data in which surgery beyond 8 weeks was associated with an increased rate of positive surgical margins.[11,12] We observed no increase in resection margin positivity with deferred surgery. However, similarly to those studies, we did note an increased proportion of abdominoperineal resections in the later surgery groups. Rather than stemming from the possible technical difficulty of achieving sphincter preservation when surgery is delayed, this increase is probably attributable to a longer wait time for maximal response to treatment and to the extensive planning required for this complex surgery.

Grade 3–5 complications are the most clinically relevant, and it is reassuring that their rates remained comparable across the time-to-surgery groupings. Of interest, grade 3–5 complications and SSI were associated with poor response to neoadjuvant therapy (absence of T or N downstaging), suggesting that delaying surgery may not be advisable in patients with a poor treatment response. Complications were also associated with male sex and tumor location within 5 cm of the anal verge (requiring abdominoperineal resection), which are well-known risk factors,[19] and with the type of neoadjuvant regimen. In multivariable analysis, chemoRT was associated with higher rates of complications compared to TNT or chemotherapy alone. Minimally invasive surgery was associated with fewer complications than open surgery.

A small proportion (10%) of the patients in our study underwent surgery between 12 and 16 weeks following completion of neoadjuvant therapy. All of those patients had an incomplete response to treatment, but surgery was delayed because of various medical or surgical factors that affected surgery planning or because of patient preference. This subgroup had a relatively high proportion of older patients who were more likely to have medical comorbidities and a relatively high proportion of patients with lower tumors requiring abdominoperineal resection. We included these patients in our analyses because the above factors are relevant to the incidence of postoperative complications, and exclusion of this subgroup could potentially bias results.

In addition to its retrospective design and analysis, the study's limitations include potentially narrow generalizability. Nonoperative management was offered to patients who had a clinical complete response after neoadjuvant therapy, and 24% of the patients treated for locally advanced rectal adenocarcinoma at MSK during 2009–2015 did not undergo surgery within 16 weeks. This large proportion of patients in nonoperative management protocols may complicate

comparisons with series from other institutions. The analysis is also potentially limited by temporal trends in postoperative outcomes, as the overall rate of complications, the rate of SSI, and the rate of anastomotic leaks declined in the later years of the study. Another potentially confounding factor was that a higher proportion of patients who had surgery at ≥8 weeks received TNT. Because our study was retrospective, we were not able to obtain details of treatment decisions with respect to the selection of a specific neoadjuvant approach or operative technique. Finally, an additional limitation was the fact that some potentially important covariates known to be associated with perioperative outcomes were not available. These include detailed information on body habitus/BMI, patient comorbidities, and smoking status.

The strengths of our study include the large cohort of patients, who received treatment in a modern setting in which nonoperative management was increasingly commonplace. As nonoperative management gains popularity, it is of critical importance to accurately detail the outcomes for patients who do not achieve a complete response to neoadjuvant therapy. Although the data presented here suggest that delaying surgery does not increase surgical morbidity in general, it is not known whether delaying surgery in patients with a poor treatment response may compromise outcomes. In this study, we observed higher rates of grade 3–5 complications in patients without T or N downstaging ($P < 0.05$) and a similar trend in patients with lower tumor regression ($P < 0.1$). Further research is required to clarify the impact of delaying surgery in such patients. There may be a role for a two-step assessment of response to treatment, with the goal of identifying patients with a poor response earlier in order to plan surgery. In our own practice, we currently advocate full clinical and endoscopic staging at approximately 8 weeks. If a complete or near-complete response is observed and the patient prefers to delay surgery, reassessment is performed at around 12 weeks with a view to considering nonoperative

management (watch and wait). For patients with an obvious incomplete treatment response at 12 weeks and significant tumor bulk remaining, no advantage can likely be gained from further delay of surgery. Another novel aspect of the study is the demonstration that, in comparison with chemoRT alone, extended neoadjuvant therapy (TNT) does not appear to compromise surgical outcomes.

In summary, our findings indicate that time to surgery from completion of neoadjuvant therapy for locally advanced rectal adenocarcinoma does not appear to be a significant risk factor for postoperative complications. Tumor location, the type of neoadjuvant treatment, the operative approach, and response to neoadjuvant therapy are likely more important.

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SUPPLEMENT

Table S1. Patient characteristics in relation to the timing of surgery among patients who received either chemoradiotherapy alone or total neoadjuvant therapy.

Table S2. Postoperative complications in relation to the timing of surgery among patients who received either chemoradiotherapy alone or total neoadjuvant therapy.

Table S3**.** Patient characteristics in relation to the timing of surgery among patients who received chemoradiotherapy alone.

Table S4. Postoperative complications in relation to the timing of surgery among patients who received chemoradiotherapy alone.

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