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TIMING OF RECTAL CANCER RESPONSE TO CHEMORADIATION

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Abstract

BACKGROUND: Neoadjuvant chemoradiation is increasingly utilized for rectal cancer, with resection typically six weeks after completion of radiotherapy. We observed that further delay after radiotherapy led to increased downsizing. We performed this retrospective analysis to evaluate the safety of this approach.

METHODS: A retrospective review was performed of 48 patients with distal or mid-rectal cancer who were operated on eight weeks or less after chemoradiation ended (Group 1, n=16), and more than eight weeks later (Group 2, n=32). We looked at the effect of delaying surgery on intraoperative blood loss, operative and hospital duration, postoperative complications, readmissions, and mortality.

RESULTS: The median interval between radiation and operation was seven weeks in Group 1 and eleven weeks in Group 2. There was no significant difference between the two groups in terms of intraoperative blood loss, postoperative complications, or readmissions. Length of operation and length of stay were slightly longer.

CONCLUSIONS: Delaying surgery after neoadjuvant treatment is safe, with morbidity and mortality similar to that with surgery less than eight weeks after chemoradiation.

Introduction

The incidence of rectal cancer in the U.S. in 2005 was approximately 40,000.¹ Multimodality treatment, with surgical resection and adjuvant chemotherapy and radiation, has been deemed the standard of care for Stage II and III rectal cancers.² In recent years, neoadjuvant chemoradiation and subsequent surgical resection with total mesorectal excision (TME), has been shown to increase local control with decreased toxicity, although overall survival has remained unaffected.³⁻⁷ The Swedish rectal cancer trial showed a short term regimen of high dose radiation and surgery in one week resulted in reduced local recurrence.⁸ In addition, T-level downstaging and complete pathological response has been shown to be associated with decreased local recurrence and improved disease free survival.⁹ Due to higher toxicity and lack of sphincter preservation, however, intensive short course radiation has not gained favor in North America.¹⁰

Francois et al demonstrated that, by delaying surgery for six to eight weeks after completion of radiation, versus two to three weeks after, there was a significant increase in sphincter preservation rates without an increase in complications.¹¹ This six-to-eight-week interval has since become part of the standard protocol for the treatment of rectal cancer. However, there has been scant other data as to whether further delaying surgery beyond 6-8 weeks would result in further tumor “downstaging” or “downsizing” without oncologic or safety compromise. To date, there has been little more than anecdotal evidence that patients have had more tumor shrinkage when surgery was deferred for a few more weeks. We have observed such further downsizing in patients in whom surgery was delayed up to 14 weeks, and adopted a delay of 10-14 weeks for patients

with bulky tumors. As we have gained experience and comfort with these delays, other patients with less advanced tumors were occasionally treated with additional delays for scheduling convenience/preference. No patients received additional chemotherapy during this interval between completion of radiation and surgery. To analyze the safety and efficacy of our approach, we reviewed our data, comparing the outcomes of patients who were operated on more than eight weeks after completion of radiotherapy to that of patients who were operated on eight weeks or less following radiotherapy. Our hypothesis was that by postponing surgical resection beyond eight weeks, the beneficial effects of preoperative chemoradiation would be maximized with minimal adverse consequences.

Materials and Methods

A retrospective review was undertaken of all the patients who were treated for mid to distal rectal cancer (defined as a tumor 10 cm or less from the anal verge) by one of three attending physicians at the University of California, Irvine, Medical Center, Harbor-UCLA Medical Center, and Torrance Memorial Medical Center from 1997 to 2004. 97 patients were identified with rectal cancer ten centimeters or less from the anal verge and, of these, thirty-nine patients were excluded because they had not been treated with preoperative chemoradiation. Another patient was excluded secondary to refusal to undergo surgery after neoadjuvant therapy. An additional nine patients were excluded due to incomplete records and/or follow-up. The remaining forty-eight patients underwent 5-fluorouracil based chemotherapy and 4500-5400cGy radiation, followed by surgical resection (sphincter-sparing versus abdominoperineal resection) with total

mesorectal excision. These patients were divided into two groups, Group 1 and Group 2. The patients in Group 1 (n=16) underwent surgery eight weeks or less after the completion of radiation therapy (median, seven weeks; range, 3-8 weeks). The Group 2 patients (n=32) had their surgical resections more than eight weeks after the end of radiation (median, eleven weeks; range, 8-43 weeks). Patient selection for short time delay or long time delay was by attending surgeon and was typically influenced by tumor size/bulk and the perceived need for tumor shrinkage for resectability and/or sphincter salvage. Both groups of patients were clinically staged before neoadjuvant therapy using digital rectal exam, colonoscopy, rigid proctoscopy, computerized tomography (CT) and/or endorectal ultrasound.

After Institutional Review Board approval was obtained for all three hospitals, the following data was collected with regards to each patient: age at diagnosis; time interval between the conclusion of radiation treatment and surgical resection; tumor location; type of operation (i.e., sphincter-sparing versus not); operative blood loss; length of operation and hospital stay; tumor marker level and stage at diagnosis, after neoadjuvant therapy, and postoperatively; postoperative complications and readmissions; tumor recurrence; and mortality.

The postoperative complications were divided into four categories. Major surgical complications included anastomotic leak, intraabdominal abscess, and fistula formation. Postoperative ileus, wound infection, small bowel obstruction, and hernia formation were considered minor surgical complications. Major nonsurgical complications consisted of pulmonary embolus, myocardial infarction, and acute

respiratory distress syndrome. Minor nonsurgical complications were urinary retention, urinary tract infection, and femoral neuropathy.

Statistical analysis was performed using Fisher's exact test and Wilcoxon Two-Sample test.

Results

The patient characteristics for both groups are shown in Table 1. Both groups were similar in average age, 62.3 years (Group 1) versus 58.1 years (Group 2). Gender distribution was also similar, with 63% males in Group 1 and 56% males in Group 2. The Group 1 patients were evenly split between stage 2 and stage 3 at initial presentation. The majority of the Group 2 patients were stage 2 (56%), while eleven patients were Stage 3 (34%), with one Stage 1 patient and one Stage 4 patient. All of the cancers in both groups were in the mid- to low-rectum, with 56% of the tumors in Group 1 and 59% of the tumors in Group 2 five centimeters or less from the anal verge, and 44% in Group 1 and 41% in Group 2 six to ten centimeters from the anal verge. The median distance from the anal verge was 5.8 centimeters in the Group 1 patients, and four centimeters in the Group 2 patients.

Overall, there was no significant difference in downstaging between the two groups (44% versus 41%, $p=0.92$). Thirteen of the Group 2 patients (41%) did have a decline in "T" stage, as opposed to four of the Group 1 patients (25%). However, this was not statistically significant ($p=0.49$). There was a higher likelihood of upstaging with regards to "T" stage in Group 1 (6% versus 3%), but it was not statistically significant ($p=0.5$). There was no significant difference in nodal downstaging (25%

versus 22%, $p=0.41$), decrease in carcinoembryonic antigen (CEA) level (38% versus 47%, $p=0.57$), incidence of sphincter-salvage operations (75% versus 75%, $p=1.0$) or protective ileostomies (25% versus 50%, $p=0.21$), intraoperative estimated blood loss (average, 345 milliliters versus 339 milliliters, $p=0.66$), pathologic complete response (6% versus 9%, $p=0.19$), or incidence of short-term and long-term postoperative complications (75% versus 59%, $p=0.54$). The patients in Group 2 did have longer operative times (average, 210 minutes versus 258 minutes, $p=0.05$).

Nine of the Group 1 patients had a total of nine postoperative complications: three major surgical (intraabdominal abscess, rectovaginal fistula, and nonhealing perineum); four minor surgical (postoperative ileus, small bowel obstruction requiring surgery, retrograde ejaculation, and ventral hernia); and two minor nonsurgical (urinary tract infection and urinary retention). Sixteen of the Group 2 patients experienced a total of 24 postoperative complications: eight major surgical (four patients had intraabdominal abscesses, two patients developed rectovaginal fistulas, one patient had a perineal wound evisceration, and one patient developed a J-pouch perforation); eight minor surgical (four patients had postoperative ileuses, two patients had small bowel obstruction, one patient had gastroparesis, and one patient had a superficial wound infection); three major nonsurgical (one patient had acute respiratory distress syndrome requiring prolonged ventilation and one patient had aspiration pneumonia and also developed acute renal failure); and five minor nonsurgical (three patients had urinary retention, one patient had urinary incontinence, and one patient developed a femoral neuropathy). The difference between the two groups in terms of each type of complication was not statistically significant ($p=0.06$).

The short-term complication rate (within thirty days of operation) for the two groups were 56% and 50%, respectively ($p=0.76$). There were no 30-day or in-hospital mortalities in either group. The patients in Group 1 had a shorter average length of hospital stay (7.7 days, range 5-21 days) than did the Group 2 patients (9.9 days, range 4-32, $p=0.02$). Two of the Group 1 patients (13%) did require readmissions for their complications, whereas five of the Group 2 patients (16%) needed to be readmitted ($p=1.0$).

The average patient follow-up was 27.7 months (range, 4 months to 78 months). The tumor recurrence and overall mortality rates were equivalent in both groups. Five of the Group 1 patients (31%) developed metastatic disease, versus eleven of the Group 2 patients (34%, $p=0.53$). One of the eleven patients in Group 2 experienced local recurrence, as well as distant metastatic disease.

Discussion

Preoperative (neoadjuvant) chemoradiation is now standard for stage 2 and 3 mid and low rectal cancer. Indeed, Guillem *et al* showed that those patients who achieve >95% response to preoperative combined modality treatment have an improved long-term oncologic outcome.⁵ Despite several decades of experience with this approach, and numerous randomized studies, there is remarkably little variation in timing of surgery relative to completion of therapy, with the exception of the short-course radiation popular in Europe. The traditional delay of 6-8 weeks is well-established but not well-founded in terms of efficacy or safety relative to other durations. Many surgeons are concerned that further delays will lead to more difficulty with the operation, including fibrosis. We did

not encounter any such additional difficulties, either anecdotally or as reflected in intraoperative blood loss. Our increased duration of operation in Group 2 reflects more the proximity of the tumors to the anal sphincter than the radiation-operation interval. Specifically, our results showed that there was no statistical difference between Groups 1 and 2 in terms of intraoperative blood loss, complication and readmission rates, or perioperative mortality. A longer length of stay was seen for the Group 2 patients, which may be due to higher number of patients receiving temporary ileostomies to protect a low anastomosis.

Our study failed to show any significant improvement in downstaging when surgery was delayed beyond 8 weeks to achieve any possible oncologic benefits. The patients in Group 2 did have a nonsignificant higher percentage of low rectal tumors and also had greater T stage downstaging compared to Group 1, with equivalent sphincter salvage rates. The patients with the lower tumors tended to have their operations postponed longer after radiation therapy. Nodal status, overall stage, as well as tumor recurrence rates and overall mortality appeared to be comparable between the two groups, although the small size of our study and the retrospective nature do not allow any valid conclusions to be made in terms of efficacy.

There is an inherent concern of technical difficulties related to radiation and possible regrowth of cancer leading to metastasis with further delay of surgery. To our knowledge, there have been only a few studies that have looked in detail at the influence of radiation-surgery interval on tumor downstaging and postoperative complications. Francois *et al* compared 102 patients operated within two weeks after radiation to 99 patients (short interval, or SI) operated on 6-8 weeks later (long interval, or LI), and

found that the LI group had a significantly better response rate (71.7% versus 53.1%), with a consequent higher rate of sphincter-preserving operations (76% versus 68%). They also noted comparable postoperative morbidity and mortality rates. Subsequently, the standard radiation-surgery interval for the treatment of rectal cancer has been 6-8 weeks.¹¹ A study from Memorial Sloan Kettering showed a trend toward increased pathologic complete response and increased downstaging when surgery was delayed over 44 days compared to less than 44 days, with similar overall morbidity between the two groups.¹² Furthermore, Withers *et al* established that after a radiation dose of 44-50 Grey, there is little chance of surviving tumor cells reproducing to a metastasis-yielding volume in any reasonable radiation-surgery interval.¹³

Brierley *et al* treated a fairly large number of patients (n=229) with advanced rectal cancer, utilizing radiotherapy alone due to unresectability, patient refusal of operation, or due to the patient's medical condition. Tumor stage and response before and after radiation were assessed clinically. Complete response of the tumor to treatment was seen in 50% of mobile tumors, with almost two-thirds achieving maximal response by 4 months after start of radiotherapy, but with an additional 30% showing complete response as late as 8 months after initiation of therapy.¹⁴ Since radiation treatments typically take 5-6 weeks to complete, this would be equivalent to 10 weeks versus 26 weeks after completion of radiotherapy. This study supports the observation that maximal tumor response occurs significantly later than 6-8 weeks following treatment with radiotherapy. One argument against further delay is the concern that the tumor might progress or metastasize after chemoradiation but prior to definitive operation. Although a small number of patients did have "upstaging" of their tumors, this was likely

due to the inaccuracy of the clinical staging rather than true progression. This belief is supported by the fact that “upstaging” was more common in Group 1 than Group 2 patients. Additionally, no patient had progression to metastatic disease.

Even though our study was small and retrospective, there did not appear to be higher morbidity or mortality associated with delaying surgery for more than eight weeks after chemoradiation.

Conclusion

Although we were unable to show a statistically significant increase in tumor downstaging with delaying surgery beyond 6-8 weeks after chemoradiation, our data does show that it is safe to do so (up to fourteen weeks). There is currently a prospective randomized multicenter trial in progress that will help answer this question.¹⁵

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	Radiation-Surgery Interval	
	≤ 8 weeks	> 8 weeks
Age (years)	62.3 (40-76)	58.1 (22-83)
Gender		
Male	10 (62%)	18 (56%)
Female	6 (38%)	14 (44%)
Stage at presentation		
1	0 (0%)	1 (3%)
2	8 (50%)	18 (56%)
3	8 (50%)	11 (34%)
4	0 (0%)	1 (3%)
Distance from Anal Verge (cm)		
0-5	9 (56%)	19 (59%)
6-10	7 (44%)	13 (41%)

Table I. Patient Characteristics