Changes in the Multidisciplinary Management of Rectal Cancer from 2009 to 2015 and Associated Improvements in Short-Term Outcomes

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Abstract

Aim Significant recent changes in management of locally advanced rectal cancer include preoperative staging, use of extended neoadjuvant therapies, and minimally invasive surgery (MIS). This study was aimed at characterizing those changes and associated short-term outcomes.

Method We retrospectively analyzed treatment and outcome data from patients with T3/4 or N+ locally advanced rectal cancer ≤15 cm from the anal verge who were evaluated at a comprehensive cancer center in 2009–2015.

Results In total, 798 patients were identified and grouped into five cohorts based on treatment year: 2009-2010, 2011, 2012, 2013, and 2014-2015. Temporal changes included increased reliance on MRI staging, from 57% in 2009-2010 to 98% in 2014-2015 ($p < 0.001$); increased use of total neoadjuvant therapy, from 17% to 76% ($p < 0.001$); and increased use of MIS, from 33% to 70% ($p < 0.001$). Concurrently, median hospital stay decreased (from 7 to 5 days; $p < 0.001$), as did the rates of grade III-V complications (from 13% to 7%; $p < 0.05$), surgical site infections (from 24% to 8%; $p < 0.001$), anastomotic leak (from 11% to 3%; $p < 0.05$), and positive circumferential resection margin (from 9% to 4%; $p < 0.05$). TNM downstaging increased from 62% to 74% ($p = 0.002$).

Conclusion Shifts toward MRI-based staging, total neoadjuvant therapy, and MIS occurred between 2009 and 2015. Over the same period, treatment responses improved, and lengths of stay and the incidence of complications decreased.

What does this paper add to the literature?

Shifts toward MRI-based staging, extended neoadjuvant therapy, and minimally invasive surgery for locally advanced rectal cancer have likely contributed to the observed improvements in the rates of downstaging, complications, and positive circumferential resection margins and in median hospital stay.

Introduction

Clinical management of locally advanced rectal cancer (LARC) rapidly evolved over the past 30 years, including improved staging; implementation of modern multimodality therapy consisting of chemotherapy, radiation, and surgery; and minimally invasive surgery (MIS). The emergence of adjuvant chemoradiotherapy in the 1980s followed by adoption of neoadjuvant chemoradiotherapy (chemoRT), along with refinement in surgical technique, have markedly reduced local recurrence [1]. Improved staging with MRI has assisted in patient selection for neoadjuvant therapy and facilitated preoperative planning to achieve complete margin-negative resection [2, 3]. MIS and associated enhanced recovery programs have accelerated postoperative recovery and further reduced treatment-related morbidity [4, 5].

Currently, distant metastases remain the greatest risk for rectal cancer patients. Total neoadjuvant therapy (TNT) is aimed at early treatment of possible distant micrometastatic disease by delivering the full course of prescribed systemic chemotherapy in addition to standard chemoRT before surgery [6].

In recent years, several of these major developments have been implemented into routine clinical practice shaping the management of LARC at many centers. It is not known whether these multiple modifications to LARC management, implemented over a relatively short period, act in synergy to improve short-term outcomes. Furthermore, the impact of extended neoadjuvant regimens on short-term surgical outcomes is yet to be fully reported. With modern surgical treatments, including robotic assisted surgery, there also remains an ongoing need to prospectively evaluate surgical advances as a measure of progress and to justify such modifications in management. The aim of this study was to identify and detail modern trends in the surgical management of LARC at Memorial Sloan Kettering Cancer Center (MSK) between 2009 and 2015 (a period during which several potentially significant

changes in treatment practices had been implemented) and to evaluate associated short-term surgical and oncologic outcomes over this time.

Method

Patients

MSK is a comprehensive cancer center with a high volume of rectal cancer patients. A waiver was obtained from the Institutional Review Board, and the MSK Colorectal Surgery Database was queried for patients presenting to the colorectal surgery clinic with LARC between June 1, 2009, and March 1, 2015 and considered for neoadjuvant therapy. This database provided basic demographics and treatment details, and a formal review of electronic medical records was conducted to collect additional data. We included patients with primary, nonmetastatic LARC confirmed as adenocarcinoma by pretreatment biopsy. LARC was defined in accordance with National Comprehensive Cancer Network (NCCN) guidelines based on staging with endorectal ultrasound (ERUS) or MRI as clinical (c)T3/T4 N0 or cN1/2 [7]. Staging computed tomography (CT) of the chest, abdomen, and pelvis with oral and intravenous contrast was performed prior to treatment.

Patients were excluded if they had undergone previous surgery for metachronous rectal cancer, recurrent, or metastatic disease diagnosed at initial assessment or during neoadjuvant therapy or had complicated fistulizing anorectal inflammatory bowel disease. Patients with rectal cancer above 15 cm from the anal verge or clinically above the peritoneal reflection were also excluded.

Neoadjuvant and Adjuvant Therapy

Neoadjuvant therapy was administered in accordance with the NCCN guidelines [7], which recommend it for disease of clinical stage T3, T4, or T-any N+. The majority of patients were treated according to the following planned neoadjuvant treatment paradigms: 1) chemoRT alone (or long-

course chemoRT), surgery, and adjuvant chemotherapy; 2) TNT followed by surgery; 3) systemic chemotherapy alone followed by surgery. In the TNT cohort, chemotherapy was delivered before chemoRT (referred to as induction chemotherapy) or after chemoRT (referred to as consolidation chemotherapy). Since delivery of both chemoRT and systemic chemotherapy occurs before surgery in the TNT paradigm, no postoperative therapy is required.

Systemic chemotherapy generally consisted of capecitabine-oxaliplatin or folinic acid-fluorouracil-oxaliplatin (FOLFOX) administered over 4 months. Long-course chemoRT was delivered over 28 standard fractions of radiotherapy with concurrent infusional fluorouracil or oral capecitabine.

Assessment of Clinical Response

Clinical office examination included digital examination and flexible or rigid proctoscopy. Patients undergoing TNT underwent clinical office exam at midtreatment and then at completion of treatment to gauge tumor response. Patients underwent restaging with CT and rectal MRI following completion of neoadjuvant therapy and before surgery.

When a clinical complete response (cCR) was observed on examination, the possibility of pathologic complete response (pCR) was discussed with patients. cCR was defined as absence of viable tumor on digital examination, proctoscopy, and rectal MRI at 8 weeks after completion of radiotherapy [8]. Proctoscopic and digital assessment for sustained cCR was typically based on previously described criteria [8-10] (flat white scar or telangiectasia with absence of mucosal ulceration or nodularity). In borderline cases, discussion at the multidisciplinary meeting reached consensus agreement. Patients with cCR who deferred surgery and elected nonoperative management underwent close surveillance for local regrowth, including digital and proctoscopic exam along with MRI every 3-6 months, as

previously described [8]. The decision on whether to operate was generally made by 12-16 weeks following neoadjuvant therapy.

All patients who received neoadjuvant therapy had a minimum follow-up of 12 months after completion of treatment. For analysis, the pCR rate and sustained cCR rate at 12 months were grouped together to determine the overall CR rate.

Surgery

Radical surgery was performed by MSK colorectal surgeons in accordance with the principles of anatomic total mesorectal excision using either the open (direct visualization) or the MIS (laparoscopic or robotic) approach. Temporary diverting ileostomies were created and closed at the surgeon's discretion. Operations performed more than 12 months after completion of neoadjuvant therapy were excluded from analyses.

Pathology

Resection specimens were processed and evaluated in accordance with standard protocols.[11] The circumferential resection margin (CRM) and distal resection margin were considered involved if the tumor was $\leq$1 mm from the resection margin. pCR was defined as absence of viable tumor cells in the resection specimen after neoadjuvant therapy. Treatment responses in tumor specimens were graded as percent regression and for analysis were grouped as follows: 0, no tumor regression; 1, <25% regression; 2, 25% to 50% regression; 3, >50% regression; 4, 100% regression (pCR) [12].

Recurrence and Statistical Analysis

Distant-recurrence-free survival was calculated from completion of neoadjuvant therapy, and patients were censored at the date of last follow-up or the date of detection of local recurrence. Patients with residual disease after neoadjuvant therapy who declined further treatment were excluded from

survival analyses. The date of any recurrence was defined as the date of initial radiographic assessment indicating a likely recurrence with or without biopsy. Pelvic recurrences were categorized as local, and recurrences at other sites were categorized as distant. Mucosal regrowth after sustained cCR was considered a local recurrence, and patients with mucosal regrowth were therefore evaluated for distant recurrence. Recurrence-free survival events were defined as recurrence or death of any cause, while patients who were alive and free of recurrence were censored.

Standard thresholds were used to group clinical and pathological data. Data are presented as medians with interquartile ranges unless otherwise stated. Groups were compared using the chi-square test for trend (categorical data) or the Kruskal-Wallis test (continuous data). Statistical analyses were performed using SPSS software (IBM).

Results

Of the 798 LARC patients included in the study, 67 patients were evaluated between June 1 and December 31, 2009; 135 patients in calendar year 2010; 98 in 2011; 110 in 2012; 145 in 2013; 179 in 2014; and 64 between January 1 and March 1, 2015. For analysis, the 202 patients evaluated between June 1, 2009, and December 31, 2010, were grouped together. The 243 patients evaluated between January 1, 2014, and March 1, 2015, were grouped together as well. Clinicopathologic characteristics were evaluated for all patients, and trends were evaluated over time in the five cohorts based on year of treatment. Baseline clinical characteristics and treatments are listed in **Table 1**.

Rectal MRI was obtained in 84% of patients, while ERUS was the sole rectal staging modality in 16%. Most tumors were clinically staged cT3 (84%) and cN+ (78%). The use of MRI increased from 57% of patients in 2009-2010 to 98% in 2014-2015 ($p < 0.001$) (**Figure 1**). The proportion of pretreatment cN+ staged tumors increased from 72% in 2009-2010 to 83% in 2014-2015 ($p = 0.001$).

Prescribed neoadjuvant therapies were as follows: TNT in 51% of patients, chemoRT with planned adjuvant chemotherapy in 40%, and chemotherapy alone in 9%. Postoperative chemotherapy was administered in 73% of the chemoRT with planned adjuvant chemotherapy cohort and 37% of the total (**Table 1**). The use of chemoRT with planned adjuvant chemotherapy fell from 77% in 2009-2010 to 16% in 2014-2015, while TNT increased from 17% to 76% during that period ($p < 0.001$ for both comparisons; **Figure 1**).

Eighty-two percent of all patients underwent radical rectal resection within 12 months of completing neoadjuvant therapy. The proportion of patients managed nonoperatively (watch and wait) who completed at least 12 months of follow-up without requiring radical surgery increased from 10% in 2009-2010 to 22% in 2014-2015 ($p < 0.001$; **Table 1**).

Surgery details and perioperative outcomes for patients who underwent resection within 12 months of completing neoadjuvant therapy (n = 657) are listed in **Table 2**. The time to surgery increased over the study period, and the proportion of patients who underwent surgery more than 8 weeks after neoadjuvant therapy rose from 41% in 2009-2010 to 65% in 2014-2015 ($p < 0.001$). Among patients who were treated with chemoRT and planned adjuvant chemotherapy, the proportion of those who underwent surgery more than 8 weeks following chemoRT increased from 42% in 2009-2010 to 69% in 2014-2015 ($p < 0.05$).

The proportion of cases treated with MIS increased from 33% in 2009-2010 to 70% in 2014-2015 ($p < 0.001$) (**Figure 1**). In 2014-2015, 98% of MIS operations were robot assisted. Ileostomy rates were unchanged, but ileostomy closure within 15 weeks of low anterior resection rose from 8% in 2009-2010 to 75% in 2014-2015 ($p < 0.001$). Length of stay fell over time ($p < 0.001$), with the proportion

of patients staying 5 days or less increasing from 21% to 53% ($p < 0.001$). Clavien-Dindo grade III-V complications decreased from 13% in 2009-2010 to 7% in 2014-2015 ($p = 0.020$), SSIs decreased from 24% to 8% ($p < 0.001$), and anastomotic leak after low anterior resection decreased from 11% to 3% ($p = 0.011$) (**Table 2**).

Short-term oncologic outcomes and pathologic characteristics are listed in **Table 3**. The rate of CR (pCR or sustained cCR at 12 months) rose from 26% in 2009-2010 to 34% in 2014-2015 ($p = 0.029$) (**Table 3**). This was primarily due to an increase in cCRs from 10% to 21% *($p < 0.001$).* The median number of lymph nodes in resected specimens increased from 14 in 2009-2010 to 19 in 2014-2015 ($p < 0.001$). The rate of clear CRM increased from 91% in 2009-2010 to 96% in 2014-2015 ($p = 0.046$).

Discussion

We found several major changes in clinical and surgical management of LARC at MSK between 2009 and 2015. There was a marked increase in utilization of TNT and a clear shift toward MRI as the pretreatment staging modality. Concurrent with the adoption of TNT we observed a rise in rates of TNM downstaging and complete response (defined by either pCR or sustained cCR at 12 months) and a lowering of the rate of involved CRM at surgery during the study period. There was a shift toward MIS and robotic surgery performed later, more than 8 weeks after completion of neoadjuvant therapy. In addition, the proportion of patients choosing nonoperative management steadily increased over the study period. As these changes in clinical management were implemented, we also found improvements in perioperative outcomes: fewer grade III-V complications, SSIs, and anastomotic leaks as well as shorter postoperative lengths of stay. The temporal changes in clinical practice and associated short-term outcome do not prove causality. Nonetheless, we believe these data add to the

existing rationale for extended neoadjuvant regimens in LARC and the use of minimally invasive and robotic surgery.

The use of TNT, which combines induction or consolidation chemotherapy in addition to chemoRT before surgery, is a therapeutic option in NCCN guidelines [7] and represents a major change in LARC management at MSK. Previous reports from MSK have demonstrated higher rates of pCR and sustained cCR with adoption of TNT as well as a high level of treatment tolerance [13, 14].

Outside the United States, TNT is still considered experimental. The recent Spanish GCR-3 phase II randomized trial found that the main benefit of induction chemotherapy prior to chemoRT was improved delivery of systemic chemotherapy and lower chemotherapy-related toxicity compared with postoperative adjuvant therapy; the rates of complete response were comparable to those for chemoRT alone. The Stockholm III trial reported higher rates of pCR with short-course radiotherapy and delayed surgery versus immediate surgery [15], and the addition of consolidative FOLFOX following short-course radiotherapy has been reported to result in a pCR rate of 17% [16]. The results of the RAPIDO trial on short-course radiotherapy followed by neoadjuvant chemotherapy are keenly anticipated [17]. In addition, TNT-based strategies are central to the NRG-GI002 phase II clinical trial, which has recently commenced recruitment [18].

The results of our study indicate that the TNT approach does not compromise surgical or perioperative outcomes and likely contributed to ongoing improvements in rectal cancer care. The optimal timing of preoperative chemotherapy, either before (induction) or after (consolidation) chemoRT has not been determined, and this question is subject to an ongoing prospective evaluation [8]. In previous reports [19, 20], long-term survival was not associated with pretreatment stage but was associated with response to therapy and posttreatment stage. Therefore, it may be anticipated that

optimization of the neoadjuvant approach using strategies such as TNT to maximize treatment response may translate into improved long-term outcomes.

The time to surgery after completion of neoadjuvant therapy has increased, and by 2014-2015, 62% of patients underwent surgery more than 8 weeks after neoadjuvant therapy. In the chemoRT with planned adjuvant chemotherapy group, 72% of patients underwent surgery more than 8 weeks after completion of neoadjuvant therapy in 2014-2015. It is increasingly clear that responses to neoadjuvant therapy continue for at least 12 weeks from chemoRT, providing a rationale for delaying surgery beyond 8 weeks [21-23]. Interestingly, a recent French trial evaluating short-term outcomes after surgery at 7 versus 11 weeks post-completion of neoadjuvant treatment reported increased postoperative morbidity in the 11-week cohort (32% versus 45%), with no difference in pCR rates [24]. The difference in morbidity was primarily the result of increased medical complications (e.g., urinary and respiratory complications) in the 11-week group, with no increase in the anastomotic leak rate or reintervention/reoperation rate. Similarly to other recent reports [25, 26], we did not observe such findings in our study when surgery was performed beyond 12 weeks, and we did not note a compromise in short-term surgical outcome.

The shift from ERUS to MRI seems to have resulted in a higher proportion of stage III (lymph node positive) disease diagnoses. Although both MRI and ERUS tend to be associated with overcalling of regional lymph nodes, MRI does allow discrimination by size and morphology, improving accuracy [27, 28], MRI evaluates the entire pelvis, including proximal mesorectal, lateral pelvic sidewall, and inferior mesenteric nodes and also accurately delineates T3/4 disease, involvement of adjacent structures, and CRM status. MRI is also capable of quantifying response to neoadjuvant therapy, and there is an emerging role for diffusion-weighted MRI [29], increasingly pertinent to management after apparent cCR. The observed decrease in CRM positivity in resected specimens in our series is

likely multifactorial, but improved post-treatment MRI imaging undoubtedly assists surgical planning.

Over the past two decades, widespread adoption of MIS has taken place in colorectal cancer management. The ROLARR trial [30] recently reported excellent results for robotic surgery performed by surgeons with varying experience of robotic surgery, with low rates of conversion to open surgery and low CRM positivity, similar to those for laparoscopic surgery.

Data from multicenter randomized trials demonstrate clear benefits of MIS for colon cancer, with improved short-term outcomes without oncologic compromise [31]. Although MIS for rectal cancer surgery is now widespread, debate remains over the oncologic safety of the approach, driven by results from randomized controlled trials that call into question the oncologic adequacy of the laparoscopic total mesorectal excision specimen [32-35]. However, two large multicenter randomized controlled trials [4, 36] reported oncologic equivalency. Clearly, careful patient selection is important in determining which approach is optimal [37]. Unlike laparoscopic surgery, a robotic approach has been adopted by all surgeons at MSK, which speaks to the benefit perceived by surgeons [38]. We believe that improved visualization, better exposure, easier tissue dissection with wristed instrumentation, and enhanced stapling technology address many of the shortcomings of laparoscopic rectal surgery.

There is increasing evidence that patients with cCR after neoadjuvant therapy can be managed expectantly, avoiding immediate surgery with potential for rectal preservation [9, 10, 39, 40]. The nonoperative approach requires strict follow-up to identify recurrence without oncologic compromise [9, 10, 39, 40]. With TNT, we have observed increasing numbers of patients with early cCR going beyond 6 months without radical resection [8]. Local regrowth is anticipated in 20–30% of patients

who undergo nonoperative management, necessitating salvage treatment usually within 12 months [39-43].

Because our study was retrospective, these results are limited by potential unrecognized biases defining treatment allocation and outcomes throughout the period studied. Determining possible causative links between changes in management and clinical outcomes is not possible due to the retrospective nature of the study, and as a result we sought only to detail these changes. The observed improvements in short-term outcomes may also reflect changes in case selection or treatment guidelines. In addition, results from a high-volume comprehensive cancer center may not be directly translatable to other populations or health care systems.

One criticism of the TNT approach is that it does not allow for adaptive treatment strategies based on individual clinical staging and could lead to potential overtreatment, particularly for stage II disease. Nonetheless, we believe it is important to document and analyze the considerable recent changes in rectal cancer management, which may influence short-term outcomes. It is reassuring that despite the multitude of changes to clinical practice, we do appear to see a consistent improvement in short-term outcomes during the treatment period.

In conclusion, over the past decade, we have seen an evolution in the surgical management of LARC at MSK, against a background of increasing use of pre-operative MRI staging and adoption of the TNT approach, in which chemotherapy and chemoRT are delivered preoperatively. Over the same period, we observed increased rates of tumor downsizing, now seen in the majority of patients. Rectal resection is now most commonly performed 8 to 12 weeks after neoadjuvant therapy. Adoption of MIS with robotic rectal resection, enhanced recovery protocols, and SSI reduction strategies, may have contributed to the observed reductions in perioperative morbidity rates and the average length of

hospital stay. Increasingly, patients are expressing a strong preference for a nonoperative, watch-and-wait approach, which in our experience is facilitated by TNT. Continued observational studies, including registries, are required to monitor results and optimize care of LARC patients.

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Figure 1. Trends in Management of LARC at MSK between June 2009 and March 2015. (A) The use of MRI and ERUS as the primary pretreatment staging modality at MSK between 2009 and 2015 (n = 676). (B) Neoadjuvant treatment for LARC between 2009-2015 at MSK (n = 798). (C) Operative approach for surgical management of LARC between 2009 and 2015 at MSK (n = 657). (D) Rates of postoperative complications after surgery for LARC between 2009 and 2015 at MSK (n = 657).

Table 1. Clinical and Treatment Characteristics

Characteristic	No. (%) of Patients						*P*[†]
	Total* (n = 798)	2009-2010 (n = 202)	2011 (n = 98)	2012 (n = 110)	2013 (n = 145)	2014-2015 (n = 243)	
Age (years)							0.290
<55	359 (45)	79 (39)	49 (50)	55 (50)	66 (46)	110 (45)	
55-75	358 (45)	99 (49)	41 (42)	45 (41)	60 (41)	113 (47)	
>75	81 (10)	24 (12)	8 (8)	10 (9)	19 (13)	20 (8)	
Sex							0.330
Female	327 (41)	80 (40)	34 (35)	43 (39)	58 (40)	112 (46)	
Male	471 (59)	122 (60)	64 (65)	67 (61)	87 (60)	131 (54)	
Tumor height (cm) above anal verge							0.986
<5	264 (33)	57 (28)	34 (35)	36 (33)	51 (35)	86 (35)	
5-10	384 (48)	115 (57)	46 (47)	56 (51)	60 (41)	107 (44)	
>10	150 (19)	30 (15)	18 (18)	18 (16)	34 (23)	50 (21)	
Pretreatment staging modality[‡]							
ERUS	348 (51)	120 (76)	47 (64)	68 (73)	67 (51)	46 (21)	<0.001
MRI	568 (84)	90 (57)	65 (88)	72 (77)	124 (94)	217 (98)	<0.001
ERUS and MRI	238 (35)	53 (34)	38 (51)	47 (51)	59 (45)	41 (19)	<0.001
cT stage							0.203
cT1/2	54 (7)	16 (8)	5 (5)	6 (6)	14 (10)	13 (5)	
cT3	670 (84)	171 (85)	81 (83)	97 (88)	122 (84)	199 (82)	
cT4	74 (9)	15 (7)	12 (12)	7 (6)	9 (6)	31 (13)	
cN stage							0.001
cN0	174 (22)	57 (28)	27 (28)	24 (23)	24 (17)	42 (17)	
cN+	624 (78)	145 (72)	71 (73)	86 (78)	121 (83)	201 (83)	
Neoadjuvant therapy							<0.001
ChemoRT with adjuvant chemo	320 (40)	155 (77)	62 (63)	43 (39)	22 (15)	38 (16)	
Chemo alone[§]	68 (9)	12 (6)	4 (4)	10 (9)	21 (15)	21 (9)	
TNT	410 (51)	35 (17)	32 (33)	57 (52)	102 (70)	184 (76)	

Radical resection within 12 months after neoadjuvant therapy							<0.001
No[#]	141 (18)	21 (10)	10 (10)	21 (19)	36 (25)	53 (22)	
Yes	657 (82)	181 (90)	88 (90)	89 (81)	109 (75)	190 (78)	
Postoperative chemotherapy (after resection within 12 months)	*n=657*	*n=181*	*n=88*	*n=89*	*n=109*	*n=190*	<0.001
No	360 (55)	40 (22)	34 (39)	53 (60)	79 (72)	154 (81)	
Yes	297 (45)	141 (78)	54 (61)	36 (40)	30 (28)	36 (19)	
Postoperative CT (in patients receiving chemoRT with adjuvant chemo)	*n=320*	*n=155*	*n=62*	*n=43*	*n=22*	*n=38*	0.002
No	86 (27)	30 (19)	15 (24)	14 (33)	8 (36)	19 (50)	
Yes	234 (73)	125 (81)	47 (76)	29 (67)	14 (34)	19 (50)	

Abbreviations: ERUS, endorectal ultrasound; MRI, magnetic resonance imaging; TNT, total neoadjuvant therapy.

*Patients who underwent initial assessment at Memorial Sloan Kettering between June 1, 2009, and March 1, 2015.

[†]Chi-square test for trend.

[‡]At Memorial Sloan Kettering. For 120 patients, preoperative staging was performed at other facilities.

[§]The strategy of chemotherapy alone was employed as part of a split regimen of pre- and postoperative chemotherapy or as neoadjuvant treatment in patients who had previously received pelvic irradiation for another malignancy (e.g., cervix or prostate). It was also employed in patients who proceeded directly to surgery after an excellent response to induction chemotherapy and patients who declined radiotherapy (e.g., younger patients who wanted to preserve their fertility).

[#]Patients who did not undergo resection due to nonoperative management after cCR or due to other medical reasons.

Table 2. Treatment Characteristics for Patients Undergoing Resection within 12 Months after Completion of Neoadjuvant Therapy

Characteristic	No. (%) of Patients						$P^{\dagger}$
	Total* (n = 657)	2009-2010 (n = 181)	2011 (n = 88)	2012 (n = 89)	2013 (n = 109)	2014-2015 (n = 190)	
Time to surgery after NT (weeks)							<0.001
<8	317 (48)	106 (59)	54 (61)	38 (43)	52 (48)	67 (35)	
8-12	228 (35)	54 (30)	23 (26)	35 (40)	42 (39)	74 (39)	
12-26	91 (14)	17 (9)	11 (13)	14 (16)	13 (12)	36 (19)	
26-52	21 (3)	4 (2)	0 (0)	2 (2)	2 (2)	13 (7)	
Restorative procedure							0.696
Yes	502 (76)	141 (78)	66 (75)	70 (78)	83 (76)	142 (75)	
No[‡]	155 (24)	40 (22)	22 (25)	19 (22)	28 (24)	48 (25)	
Surgical approach							<0.001
Open	278 (42)	121 (67)	48 (54)	19 (22)	33 (30)	57 (30)	
MIS	379 (58)	60 (33)	40 (46)	70 (78)	76 (70)	133 (70)	
MIS type							<0.001
Laparoscopic	70 (18)	31 (52)	19 (47)	14 (20)	3 (4)	3 (2)	
Robotic	309 (82)	29 (48)	21 (53)	56 (80)	73 (96)	130 (98)	
Median hospital stay, days (IQR)	6.0 (4.5-7.5)	7.0 (6-8)	7.0 (5-9)	6.0 (4-8)	6.0 (4.5-7.5)	5.0 (3.5-6.5)	<0.001
Length of hospital stay							<0.001
≤5 days	248 (38)	37 (21)	22 (25)	32 (36)	55 (50)	102 (53)	
>5 days	409 (62)	144 (79)	66 (75)	57 (64)	54 (50)	88 (47)	
Diverting ileostomy[§]	*n = 502*	*n = 141*	*n = 66*	*n = 70*	*n = 83*	*n = 142*	0.985
No	79 (16)	23 (16)	9 (14)	12 (17)	13 (16)	22 (16)	
Yes	423 (84)	118 (84)	57 (86)	58 (83)	70 (84)	120 (84)	
Ileostomy closure within 15 weeks	*n = 423*	*n = 118*	*n = 57*	*n = 58*	*n = 70*	*n = 120*	<0.001
No	259 (61)	109 (92)	48 (84)	38 (66)	32 (46)	32 (27)	
Yes	164 (39)	9 (8)	9 (16)	20 (34)	38 (54)	88 (73)	

Postoperative complications within 30 days							
Grade III-V complications							0.020
No	590 (90)	157 (87)	77 (89)	74 (86)	103 (94)	176 (93)	
Yes	67 (10)	24 (13)	11 (11)	12 (14)	6 (6)	14 (7)	
Surgical site infection							<0.001
No	553 (84)	137 (76)	66 (75)	75 (84)	98 (90)	175 (92)	
Yes	106 (16)	44 (24)	22 (25)	14 (16)	11 (10)	15 (8)	
Anastomotic leak (grade III) [§]	*n = 502*	*n = 141*	*n = 66*	*n = 70*	*n = 83*	*n = 142*	0.008
No	463 (92)	126 (89)	61 (92)	59 (84)	79 (95)	138 (97)	
Yes	39 (8)	15 (11)	5 (8)	11 (16)	4 (5)	4 (3)	

Abbreviations: NT, neoadjuvant therapy; MIS, minimally invasive surgery; IQR, interquartile range.

*Patients who underwent initial assessment at Memorial Sloan Kettering between June 1, 2009, and March 1, 2015.

[†]Chi-square test for trend.

[‡]Abdominoperineal resection or rectal resections with a permanent colostomy (e.g., low Hartmann's procedure).

[§]After a low anterior resection.

Table 3. Short-Term Oncological Outcomes and Pathologic Characteristics for Entire Cohort

Outcome or characteristic	No. (%) of Patients						*P*[†]
	Total*	2009-2010	2011	2012	2013	2014-2015	
Outcomes	*n = 798*	*n = 202*	*n = 98*	*n = 110*	*n = 145*	*n = 243*	
Complete response 12 months after NT							0.029
No	551 (69)	149 (74)	75 (76)	71 (65)	95 (66)	161 (66)	
Yes[‡]	247 (31)	53 (26)	23 (24)	39 (35)	50 (34)	82 (34)	
cCR 12 months after NT	135 (17)	21 (10)	10 (10)	20 (18)	32 (22)	52 (21)	<0.001
Downstaging after NT							
T downstaging							0.724
No	256 (32)	68 (34)	37 (38)	28 (25)	39 (27)	84 (35)	
Yes	542 (68)	134 (66)	61 (62)	82 (75)	106 (73)	159 (65)	
N downstaging							0.019
No	327 (41)	93 (46)	44 (45)	49 (44)	51 (35)	90 (37)	
Yes	471 (59)	109 (54)	54 (55)	61 (56)	94 (65)	153 (63)	
TNM downstaging							0.002
No	242 (30)	77 (38)	31 (32)	36 (33)	35 (24)	63 (26)	
Yes	556 (70)	125 (62)	67 (68)	74 (67)	110 (76)	180 (74)	
Pathology results	*n = 657*	*n = 181*	*n = 88*	*n = 89*	*n = 109*	*n = 190*	
pCR in specimen							0.715
No	545 (83)	149 (82)	75 (85)	70 (79)	91 (83)	160 (84)	
Yes	112 (17)	32 (18)	13 (15)	19 (21)	18 (17)	30 (16)	
>95% response in specimen[§]	*n = 642*	*n = 176*	*n = 82*	*n = 88*	*n = 107*	*n = 189*	0.598
No	429 (67)	123 (70)	51 (62)	58 (66)	73 (68)	124 (66)	
Yes	213 (33)	53 (30)	31 (38)	30 (34)	34 (32)	65 (34)	
Tumor regression (Rodel scale)							0.001

0/1 (0 to <25%)	63 (10)	4 (2)	6 (87)	7 (7)	11 (10)	35 (19)	
2 (25 to 50%)	119 (19)	40 (23)	11 (13)	18 (21)	19 (18)	31 (16)	
3 (>50%)	349 (54)	100 (57)	52 (63)	45 (51)	59 (55)	93 (49)	
4 (100%)	111 (17)	32 (18)	13 (16)	18 (21)	18 (17)	30 (16)	
No. of LN resected, median (IQR)	16 (12.5-20.5)	14 (11-117)	15 (12-18)	15 (12.5-18.5)	20 (14.5-25.5)	19 (13.5-24.5)	<0.001
Negative CRM[#]							
All surgeries (n = 657)	617 (94.1)	165 (91)	82 (93)	85 (96)	104 (95)	182 (96)	0.046
Open surgery (n = 278)	245 (91.0)	109 (90)	45 (94)	16 (84)	30 (91)	53 (93)	0.683
MIS (n = 379)	364 (96.3)	56 (93)	37 (93)	69 (99)	74 (97)	129 (97)	0.148
Negative DRM[#]							
All surgeries (n = 657)	645 (98.2)	179 (99)	85 (97)	84 (94)	109 (100)	188 (99)	0.499
Open surgery (n = 278)	276 (99)	121 (100)	47 (98)	19 (100)	33 (100)	56 (98)	0.415
MIS (n = 379)	369 (97.0)	58 (97)	38 (95)	64 (93)	76 (100)	132 (99)	0.053

Abbreviations: NT, neoadjuvant therapy; cCR, clinical complete response; pCR, pathologic complete response; LN, lymph nodes; IQR, interquartile range; CRM, circumferential resection margin; MIS, minimally invasive surgery; DRM, distal resection margin.

*Patients who underwent initial assessment at Memorial Sloan Kettering between June 1, 2009, and March 1, 2015.

[†]Chi-square test for trend.

[‡]Surgical patients with pCR and nonsurgical patients with cCR at 12 months.

[§]Including pCR. Data were available for 642 of the 657 surgery patients.

[#]≤1 mm.