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Retrospective Cohort Study

Contemporary, national patterns of surgery after preoperative therapy for stage II/III rectal adenocarcinoma

Soriano C *et al.* Rectal cancer surgery after preoperative therapy

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Abstract

BACKGROUND

Contemporary ⁶ treatment of stage II/III rectal cancer combines chemotherapy, chemoradiation, and surgery, though the sequence of surgery with neoadjuvant treatments and benefits of minimally-invasive surgery (MIS) is debated.

AIM

To describe patterns of surgical approach ⁷ for stage II/III rectal cancer in relation to neoadjuvant therapies.

⁹ METHODS

A retrospective cohort was created using the National Cancer Database. Primary outcome was rate of sphincter-sparing surgery after neoadjuvant therapy. Secondary outcomes were surgical approach (open, laparoscopic, or robotic), surgical quality (R0 resection and 12+ lymph nodes), and overall survival.

RESULTS

¹ A total of 38927 patients with clinical stage II or III rectal adenocarcinoma underwent surgical resection from 2010-2016. Clinical stage II patients had neoadjuvant chemoradiation less frequently compared to stage III (75.8% vs 84.7%, $P < 0.001$), but had similar rates of total neoadjuvant therapy (TNT) (27.0% vs 27.2%, $P = 0.697$). Overall rates of total mesorectal excision without sphincter preservation were similar between clinical stage II and III (30.0% vs 30.3%) and similar if preoperative treatment was chemoradiation (31.3%) or TNT (30.2%). Over the study period, proportion of cases approached laparoscopically increased from 24.9% to 32.5% and robotically 5.6% to 30.7% ($P < 0.001$). This cohort showed improved survival for MIS approaches compared to open surgery (laparoscopy ¹ HR 0.85, 95%CI 0.78-0.93, and robotic HR 0.82, 95%CI 0.73-0.92).

CONCLUSION

Sphincter preservation rates are similar across ² stage II and III rectal cancer, regardless of delivery of preoperative chemotherapy, chemoradiation, or both. At a national level, there is a shift to predominantly MIS approaches for rectal cancer, regardless of whether sphincter sparing procedure is performed.

Key Words: Rectal cancer; Total neoadjuvant therapy; Colorectal surgery; Minimally-invasive surgery; Chemotherapy; Radiation

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Core Tip: At a population level, there have been increases in neoadjuvant treatment and minimally-invasive surgical (MIS) approaches for ² stage II and III rectal cancer. These shifts have are not associated with changes in rates of permanent ostomy which

remain about 30%. In contrast to prior trials, this 'real-world' cohort showed an association with higher quality surgical resection and improved survival with MIS.

INTRODUCTION

The management of rectal cancer has evolved, with emphasis on optimizing oncological outcomes and minimizing operative morbidity. Treatment of locally advanced rectal cancer typically involves multimodality therapies and total mesorectal excision (TME)^[1,2]. Neoadjuvant therapy using chemotherapy and/or radiotherapy has several advantages, such as locoregional control and improved overall survival, compared to surgery alone^[3-5]. Additionally, the administration of chemoradiation combined with induction or consolidation chemotherapy, known as total neoadjuvant therapy (TNT), has gained popularity due to increased treatment compliance without compromise of pathologic complete response or complete resection rates^[6-8].

Despite advances in multimodality treatment paradigms, the optimal sequence of surgery in relation to chemotherapy and radiation remains unknown. Recent trials have assessed pre-operative treatment regimens and improved rates of organ preservation, disease free survival, and pathological complete response rates in patients with high risk, locally advanced rectal cancer^[9-11]. Several factors, including anatomic considerations, tumor features, and functional symptoms, can influence decision-making, and treatment is typically individualized. Due to the complexity of rectal cancer care, variation has been described, with differences in curative resection rates, postoperative morbidity and mortality, and long-term oncologic outcomes among both surgeons and hospitals^[12]. Furthermore, practices of how surgery is sequenced with other modalities, especially in the era of minimally invasive surgery (MIS), is not well described.

Therefore, the aim of this study was to characterize surgical resection of locally advanced rectal adenocarcinoma in the setting of multimodal therapy at the national level, with a focus on describing patterns of surgery in sequence with neoadjuvant treatment delivery and shift in surgical approach trends over time. We hypothesized that there would be increases in the delivery of neoadjuvant chemotherapy and chemoradiation, performance of sphincter-sparing resections, and use of minimally invasive surgical approaches.

MATERIALS AND METHODS

This study was exempt from human subjects review by the Benaroya Research Institute Institutional Review Board.

Data/population

A retrospective cohort of ¹ patients with clinical stage II and stage III rectal adenocarcinoma who underwent surgical resection between 2010 and 2016 was created using the ³ National Cancer Database (NCDB). The NCDB is a validated national cancer registry of the ³ American College of Surgeons and American Cancer Society, collected from more than 1500 ⁸ Commission on Cancer-accredited facilities. Stage was defined according to the seventh edition of the American Joint Committee on Cancer's clinical group. ⁹ The cohort was based on clinical stage, rather than pathologic stage, as treatment delivery is established once staging workup is complete. Patients with a diagnosis of multiple cancers and undergoing palliative surgery were excluded (Figure 1).

Outcomes/definitions

To describe patterns of surgical care delivery, ³ the primary outcome was proportion of patients receiving local excision or TME with or without sphincter preservation. The frequency of sphincter preservation was characterized by surgery alone or in sequence with chemotherapy or radiation therapy. Using NCDB definitions, local excision was defined as ¹⁸ conventional trans-anal excision or trans-anal endoscopic microsurgery. TME with sphincter preservation was defined as any rectal resection that included anastomosis [low anterior resection (LAR) and total proctocolectomy and pouch-anal anastomosis]. TME without sphincter preservation was defined as any rectal resection without anastomosis [abdominoperineal resection (APR), LAR with colostomy, and total proctocolectomy with ileostomy]. Surgical approach to TME was subcategorized into open, laparoscopic, and robotic. Conversion to open from laparoscopy and robotics was also reported, but these cases were included in their intended approach categories.

Chemotherapy delivery was defined as single or multi-agent systemic administration before or after surgery. TNT was defined as delivery of both multiagent chemotherapy and radiation therapy prior to surgical date.

Secondary outcomes that were assessed include pathologic stage, quality of surgical resection, and overall survival. Quality of surgical resection included proportion of cases with negative margins, total lymph node harvest and proportion of cases with 12+ lymph nodes harvested. To explore potential variation in care delivery, patient factors (age, sex, insurance status, comorbidities) and location of care (facility information, geographic area) were described and used as covariates in the survival analysis. Comorbidities were defined using the Charlson-Deyo comorbidity index.

Statistical analysis

Categorical and continuous variables based on clinical interest were compared with chi-square and Kruskal Wallis tests, respectively. While the hypothesis did not focus on differences in treatment based on rectal cancer stage, stage-specific data are provided in supplemental text (Supplementary Table 1). Because of the expected uptake of MIS over time we described trends in surgical approach by year. Test for trend of surgical approach were done with Chi-squared test. Univariate and multivariate adjusted overall survival analyses were performed using cox proportional hazards model on a subset of the analysis sample excluding patients with multiple cancers or where treatment and diagnosis were done at different facilities, as per NCDB recommendations. The final survival model was adjusted for age, sex, race, insurance, rurality, geography, facility type, pathologic stage, cancer grade, preoperative radiation, chemotherapy type and sequence, surgery type (LE, TME with or without sphincter preservation), intent of surgical approach (open, laparoscopic, robotic), resection margin status and 12+ lymph nodes resected status. Kaplan Meier survival curves stratified by TME with and without sphincter preservation are shown, by intent of surgical approach (open, laparoscopic, robotic). Statistical significance was determined by $P < 0.05$. Survival and patient characteristics tables were run with Mayo Clinic's SAS

macros^[13] on SAS version 9.4 and JMP Pro Version 15 was also used for graphics and data analysis.

RESULTS

Patient demographics and sequence of treatment

From 2010-2016, a total of 38,927 patients underwent resection of stage II/III rectal cancer (mean age 60.9 ± 12.7 years, and 61% male). Baseline patient and facility characteristics are outlined in Table 1. Sphincter was not preserved in 30.2% ($n = 11748$). Patients with clinical stage III disease represented 55% of the cohort, and stage distribution was similar whether TME with sphincter preservation (55.5%) or not (54.9%) was performed. It was rare to undergo local excision after initially presenting with clinical stage II (5.2%) or clinical stage III (2.5%) rectal cancer.

Sequence of treatment by stage

Patients with clinical stage II disease more frequently had no radiation (16.8% vs 8.7%, $P < 0.001$) or no chemotherapy (14.9% vs 5.9%, $P < 0.001$) compared to clinical stage III patients (Supplementary Table 1). Clinical stage II patients less frequently had neoadjuvant chemoradiation (75.2%, vs 84.1% $P < 0.001$), but had similar rates of TNT (27.0% vs 27.2%, respectively, $P = 0.697$) compared to clinical stage III. Overall rates of TME without sphincter preservation were similar between clinical stage II and III, 30.0% vs 30.3%, respectively, and similar if preoperative treatment was neoadjuvant chemoradiation (31.3%, $n = 9762$ TME without sphincter preservation out of $n = 31160$ that received neoadjuvant chemoradiation) or TNT (30.2%, $n = 1302$ TME without sphincter preservation out of $n = 4302$ that received TNT).

Surgical approach and quality of resection

Rates of open resection in the cohort were approximately 50%, but over the period of the study decreased from 69.4% in 2010 to 36.8% in 2016. There were concomitant rises in laparoscopic resection from 24.9% to 32.5% and robotic resection 5.6% to 30.7% ($P <$

0.001) (Figure 2). Open approach was used for 60% of TME without sphincter preservation compared to 47% of TME with sphincter preservation ($P < 0.001$).

The distribution of surgical approach is described in Table 2. Conversion to an open operation was lower with robotic approach (6.9%) compared to laparoscopy (14.5%). This was maintained regardless of whether sphincter sparing procedure was performed (conversion rate 15% laparoscopic, 6.9% robotic) or not (conversion rate 16.4% laparoscopic, 7.1% robotic), or whether TNT (conversion rate 15.6% laparoscopic, 6.5% robotic) was delivered.

R0 resection was obtained 94.8% of ¹⁰ patients who underwent TME with sphincter preservation, and 90.3% of ¹⁰ patients who underwent TME without sphincter preservation ($P < 0.001$). Twelve or more lymph nodes were examined more frequently in TME with sphincter preservation (71.6%) than without sphincter preservation (68.4%). Rates of R0 resection and 12+ lymph nodes harvested were both lower with open, compared to minimally invasive, approaches.

Overall survival

Table 3 summarizes factors impacting overall survival in this cohort. After adjustment, TME without sphincter preservation ³ was associated with worse survival HR 1.30 (95%CI 1.20-1.40) compared to sphincter preservation. Interestingly, this cohort showed improved survival for minimally invasive approaches compared to open surgery (laparoscopy ¹ HR 0.85, 95%CI 0.78-0.93, and robotic HR 0.82, 95%CI 0.73-0.92). This improved survival in cases approached minimally invasively was sustained after stratification into TME with and without sphincter preservation (Figure 3).

DISCUSSION

This contemporary, nationwide cohort study identified an expected shift towards a minimally invasive surgical approach for stage II/III rectal cancer with high quality surgical outcomes. Most of the patients are getting neoadjuvant radiation, but only a small fraction receives TNT. Neoadjuvant treatment at the population level does not

seem to affect sphincter-sparing rates. Interestingly, this cohort also showed improved survival in cases approached minimally invasively—a finding that is at odds with prior, high-quality randomized control trials, but may reflect important differences between the randomized control trial population and surgeon and patient selection that occur in broader practice.

Contemporary treatment for rectal cancer is multidisciplinary. The most common neoadjuvant regimen utilizes chemoradiotherapy, which has been shown to lower the recurrence rate and is associated with less toxicity than post-operative radiation, with no difference in overall survival^[14]. Additionally, neoadjuvant therapy may promote tumor shrinkage and affect sphincter-sparing rates. Still, despite recommendations in national guidelines describing neoadjuvant treatment for locally advanced rectal cancer or nodal disease^[15,16], variation in radiation delivery is seen^[17,18]. Midura *et al*^[19] identified that factors such as hospital volume and facility type affected delivery of neoadjuvant therapy, including decreased use of neoadjuvant therapy for higher stage rectal cancer at lower-volume, community cancer centers. Furthermore, total neoadjuvant therapy has been increasingly promoted, in which studies have reported local disease control and decreased recurrence rates^[20]. A majority of patients in our cohort underwent some type of neoadjuvant treatment, and sphincter-sparing rates were similar ² in patients with stage II or stage III disease. Prior meta-analysis supports the approximate rate of permanent colostomy to be approximately 30%^[21]. It is important to note that certain clinical features, such as tumor distance from the anal verge or patients' prior continence status, which might influence the decision for a non-sphincter sparing operation, are not available in this dataset. Most decisions about sphincter preservation happen before surgery, and rates of low tumors and incontinence rates are not expected to have meaningfully changed during this time period.

The equivalence of minimally invasive and open approaches for rectal cancer surgery continues to be debated. Laparoscopy and robotic-assisted colorectal surgery have enabled decreased length of hospital stay, better analgesia, and improved visibility and

ergonomics, specifically in the pelvis^[22-24]. However, adoption of MIS for rectal cancer has been controversial, as both the Z6051 and ALaCaRT trials were unable to establish non-inferiority of pathological outcomes for minimally invasive vs open resection in patients with rectal cancer^[25,26]. Follow-up of these trials found no significant difference in survival⁵ between approaches, with Z6051 showing 2-year disease free survival (DFS) of 79.5% in the laparoscopic group and 83.5% in the open group and ALaCaRT showing 2-year DFS of 94% in the laparoscopic group and 93% in the open group^[27,28]. Finally, the ROLARR trial found no significant difference in conversion to open laparotomy between conventional laparoscopy vs robotic-assisted surgery, and concluded no short term benefit of robotic surgery over laparoscopy^[29]. Our findings of improved survival with minimally invasive approaches, even after adjustment for pathological stage, neoadjuvant treatment, and patient/center features, are at odds with these prior, high-quality studies. However, the NCDB has a wider, national representation, and the findings herein may reflect patient- and approach- selection in broader practice, including training, resources, and institutional factors that impact approach outside of randomized trial patients. For example, it is unclear if the improved resection margins and lymph node harvest in the laparoscopic and robotic subgroups are due to the approaches themselves or the cases that lent themselves to be approached minimally invasively (or the surgeons choosing a minimally invasive approach in these cases). Additionally, our findings are limited by the absence of information regarding local recurrence rate. However, it is notable that this effect of surgical approach on survival in this national cohort was maintained even after adjustment for multiple confounders or when stratifying the analysis by the subgroups with and without sphincter preservation. Local excision operations in the setting of stage II/III are controversial and deserve special mention in this cohort. Patients with stage II/III who underwent transanal local excision make up a minority of operations and are not the standard treatment because of the inability to evaluate mesorectal lymph nodes. Still, several studies have shown the feasibility of this approach in the setting of neoadjuvant treatment^[30-33]. In select patients showing tumor response to short course radiotherapy

or chemotherapy, high rates of organ preservation can be achieved. Therefore, patients and their surgeons may opt for this approach if facing a decision about permanent colostomy or if they are poor surgical candidates for the standard TME. Further randomized studies to better assess the feasibility of this approach, and long term follow up for meaningful oncologic outcomes are underway^[34].

This study is further limited by the inability to address the magnitude of treatment response and the impact of treatment response on decisions for sphincter preservation and surgical approach. For instance, we were unable to assess clinical complete responders, which occurs as frequently as 20%-30%^[20], and would not be included unless they underwent resection and pathology confirmed no residual tumor. Patients may avoid resection if they have a complete clinical response but would need an APR, so there is bias in this study such that APR surgery only occurred in those patients that likely did not have good response and still needed resection. This presumably also impacts overall survival estimates. Finally, there is a lack of data available regarding local staging studies that could lead to misclassification of clinical stage. For instance, it has been reported that magnetic resonance imaging, which has become the standard of care, can over-stage rectal cancer as high as 30%^[35-37]. Misclassification of stage could result in undertreatment or overtreatment, and that cannot be determined using this dataset. Despite these limitations, this study provides important information regarding treatment delivery patterns.

CONCLUSION

At a national level, minimally invasive surgery has become the predominant approach for rectal cancer. Sphincter preservation rates, when patients undergo surgical resection, do not vary with delivery of neoadjuvant treatment. In this broad national cohort, both open surgery and non-sphincter sparing operations were associated with worse overall survival for patients with stage II/III rectal adenocarcinoma.

ARTICLE HIGHLIGHTS

Research background

It is not well described whether the contemporary, multi-disciplinary approaches to stage II/III rectal cancer are resulting in meaningful changes in sphincter preservation, surgical quality, or overall survival.

Research motivation

While we push to individualize treatment decisions, it is important to recognize whether contemporary patterns to increase minimally-invasive surgery (MIS) and neoadjuvant treatment offer meaningful change the expected outcome of locally advanced rectal cancer.

Research objectives

Describe broad uptake in sphincter preservation, minimally-invasive approaches to rectal cancer, and the associated surgical outcomes of resection margins, lymph node harvest, and overall survival.

Research methods

Retrospective 'real-world' cohort of National Cancer Database (NCDB) sites, limited to stage II/III surgically treated rectal cancer.

Research results

Neither stage nor neoadjuvant treatment made a meaningful impact on rates of permanent colostomy, which was about 30% across all subgroups. From 2010 to 2016, there was a broad shift to MIS (laparoscopic and robotic) approaches to rectal cancer. These MIS approaches were associated with more frequent negative margins, better lymph node harvest, and improved overall survival after adjustment.

Research conclusions

There has been a shift to MIS approaches to locally advanced rectal cancer. Sphincter preservation rates remain similar in contemporary years, despite increasing neoadjuvant therapy. In recent years, more cases at NCDB sites are done MIS, which associate with better surgical quality and improved overall survival in this study.

Research perspectives

The findings of improved surgical quality and overall survival in this cohort are in contrast to randomized trial data that preceded this study. This may highlight the difference between randomized patients are 'real-world' practices or call into question the need for more contemporary, and pragmatic, trials for locally advanced rectal cancer surgery.

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