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ORIGINAL ARTICLE

Retrospective Cohort Study

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

Celine Soriano, Henry T Bahnson, Jennifer A Kaplan, Bruce Lin, Ravi Moonka, Huong T Pham, Hagen F Kennecke, Vlad Simianu

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Abstract

BACKGROUND

Contemporary 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 for stage II/III rectal cancer in relation to neoadjuvant therapies.

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

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 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 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

Core Tip: At a population level, there have been increases in neoadjuvant treatment and minimally-invasive surgical (MIS) approaches for 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.

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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 determined to be exempt from human subjects review by the Benaroya Research Institute Institutional Review Board.

Data/population

A retrospective cohort of patients with clinical stage II and stage III rectal adenocarcinoma who underwent surgical resection between 2010 and 2016 was created using the National Cancer Database (NCDB). The NCDB is a validated national cancer registry of the American College of Surgeons and American Cancer Society, collected from more than 1500 Commission on Cancer-accredited facilities. Stage was defined according to the seventh edition of the American Joint Committee on Cancer's clinical group. 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, 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 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.

Table 1 Patient and facility demographics of patients with clinical stage II/III rectal cancer, stratified total mesorectal excision and sphincter preservation

	Local excision (*n* = 1442)	TME with sphincter preservation (*n* = 25737)	TME without sphincter preservation (*n* = 11748)	Total (*n* = 38927)	*P* value
Age at diagnosis					< 0.001[1]
mean ± SD	66.2 ± 14.13	60.3 ± 12.47	61.6 ± 12.72	60.9 ± 12.67	
Sex					< 0.001[2]
Male	787 (54.6%)	15810 (61.4%)	7251 (61.7%)	23848 (61.3%)	
Charleson Comorbidity Score					< 0.001[2]
0	1057 (73.3%)	19828 (77.0%)	8828 (75.1%)	29713 (76.3%)	
1	278 (19.3%)	4486 (17.4%)	2206 (18.8%)	6970 (17.9%)	
2+	107 (7.4%)	1423 (5.5%)	714 (6.1%)	2244 (5.8%)	
Race[3]					< 0.001[2]
Black	185 (12.8%)	2006 (7.8%)	1108 (9.4%)	3299 (8.5%)	
Other	61 (4.2%)	1501 (5.8%)	562 (4.8%)	2124 (5.5%)	
White	1183 (82.0%)	22054 (85.7%)	10012 (85.2%)	33249 (85.4%)	
Insurance status[3]					< 0.001[2]
Medicare/medicaid/other government	852 (59.1%)	11308 (43.9%)	5825 (49.6%)	17985 (46.2%)	
Not insured	38 (2.6%)	1019 (4.0%)	663 (5.6%)	1720 (4.4%)	
Private insurance/managed care	518 (35.9%)	13117 (51.0%)	5066 (43.1%)	18701 (48.0%)	
Living location[3]					< 0.001[2]
Metropolitan	1164 (83.2%)	20618 (82.2%)	9142 (79.4%)	30924 (81.4%)	
Rural	30 (2.1%)	548 (2.2%)	295 (2.6%)	873 (2.3%)	
Urban	205 (14.7%)	3916 (15.6%)	2083 (18.1%)	6204 (16.3%)	
Facility type[3]					< 0.001[2]
Academic/research program	540 (37.4%)	9852 (38.3%)	4536 (38.6%)	14928 (38.3%)	
Community cancer program	95 (6.6%)	1453 (5.6%)	711 (6.1%)	2259 (5.8%)	
Comprehensive community cancer program	562 (39.0%)	9593 (37.3%)	4538 (38.6%)	14693 (37.7%)	
Integrated network cancer program	193 (13.4%)	3689 (14.3%)	1451 (12.4%)	5333 (13.7%)	
Facility geographic region[3]					< 0.001[2]
Midwest	343 (24.7%)	6883 (28.0%)	3528 (31.4%)	10754 (28.9%)	
Northeast	313 (22.5%)	5040 (20.5%)	2027 (18.0%)	7380 (19.8%)	
South	533 (38.3%)	8522 (34.7%)	3983 (35.4%)	13038 (35.0%)	
West	201 (14.5%)	4142 (16.8%)	1698 (15.1%)	6041 (16.2%)	

[1]Kruskal Wallis.
[2]Chi-Square.
[3]Race unknown for 255 patients; Insurance unknown for 521 patients; Living location unknown for 926 patients; Facility type and geographic region unknown for 1714 locations.
TME: Total mesorectal excision.

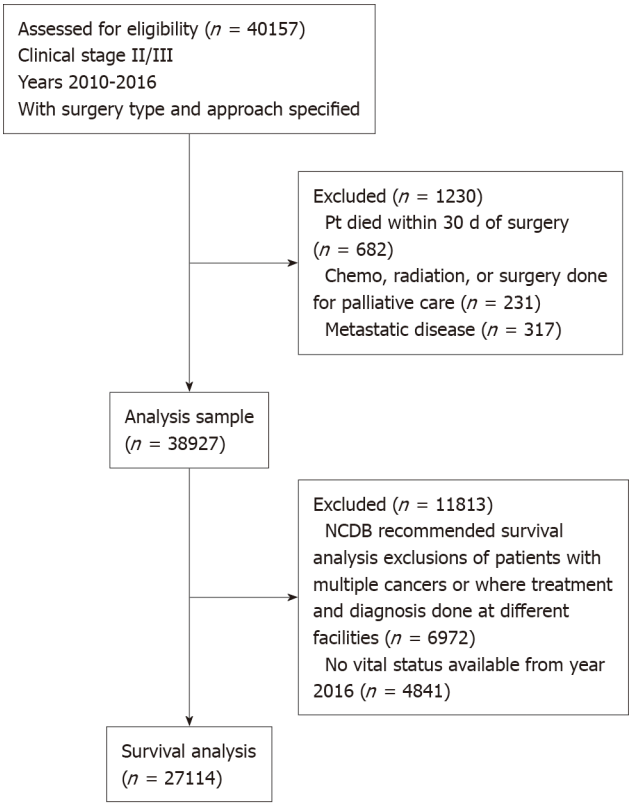

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Figure 1 CONSORT diagram of inclusion and exclusion criteria for cohort creation and survival analysis.

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 patients who underwent TME with sphincter preservation, and 90.3% of 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

Table 2 Tumor characteristics and surgical quality by surgical approach

	Open (*n* = 19830)	Laparoscopic (*n* = 12144)	Robotic (*n* = 6953)	Total (*n* = 38927)	*P* value
Clinical stage					< 0.001[1]
II	9286 (46.8%)	5477 (45.1%)	2906 (41.8%)	17669 (45.4%)	
III	10544 (53.2%)	6667 (54.9%)	4047 (58.2%)	21258 (54.6%)	
Pathological stage					< 0.001[1]
0	508 (3.2%)	323 (3.4%)	222 (3.9%)	1053 (3.4%)	
1	3801 (23.8%)	2736 (28.7%)	1669 (29.6%)	8206 (26.3%)	
2	5416 (33.9%)	2941 (30.8%)	1669 (29.6%)	10026 (32.2%)	
3	6107 (38.2%)	3480 (36.5%)	2044 (36.3%)	11631 (37.3%)	
4	152 (1.0%)	57 (0.6%)	29 (0.5%)	238 (0.8%)	
Chemotherapy sequence					< 0.001[1]
No chemotherapy	2031 (10.2%)	1397 (11.5%)	459 (6.6%)	3887 (10.0%)	
Chemotherapy after surgery	1864 (9.4%)	1210 (10.0%)	421 (6.1%)	3495 (9.0%)	
Chemotherapy before and after surgery	5435 (27.4%)	3691 (30.4%)	2256 (32.4%)	11382 (29.2%)	
Chemotherapy before surgery	10481 (52.9%)	5840 (48.1%)	3810 (54.8%)	20131 (51.7%)	
Radiation sequence					< 0.001[1]
No radiation	2449 (12.3%)	1713 (14.1%)	651 (9.4%)	4813 (12.4%)	
Radiation after surgery	1470 (7.4%)	911 (7.5%)	315 (4.5%)	2696 (6.9%)	
Radiation before surgery	15911 (80.2%)	9515 (78.4%)	5987 (86.1%)	31418 (80.7%)	
Total neoadjuvant therapy	2194 (28.1%)	1262 (25.1%)	846 (28.0%)	4302 (27.1%)	< 0.001[1]
Surgery type					< 0.001[1]
TME with sphincter preservation	12118 (61.1%)	8633 (71.1%)	4986 (71.7%)	25737 (66.1%)	
TME without sphincter preservation	7061 (35.6%)	2760 (22.7%)	1927 (27.7%)	11748 (30.2%)	
Conversion to open	0 (0.0%)	1760 (14.5%)	480 (6.9%)	2240 (11.7%)	< 0.001[1]
Residual tumor					< 0.001[1]
R0	18012 (91.9%)	11174 (93.6%)	6568 (95.1%)	35754 (93.0%)	
R1	806 (4.1%)	413 (3.5%)	193 (2.8%)	1412 (3.7%)	
R2	782 (4.0%)	352 (2.9%)	148 (2.1%)	1282 (3.3%)	
Number of lymph nodes examined (mean ± SD)	14.7 ± 9.7	14.8 ± 9.8	15.7 ± 9.0	14.9 ± 9.6	< 0.001[1]
12 or more lymph nodes examined	13198 (67.1%)	8148 (67.7%)	5088 (73.6%)	26434 (68.4%)	< 0.001[1]

[1]Chi-Square.
TME: Total mesorectal excision.

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 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 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).

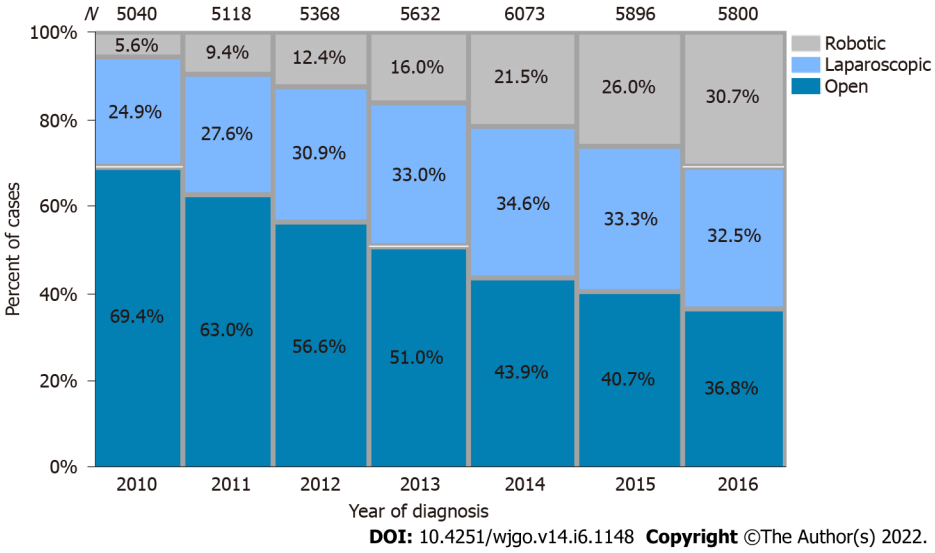
Table 3 Unadjusted (univariate) and adjusted (multivariate) factors associated with overall survival

Variable	*n*	Events	5-yr survival% (95%CI)	Cox univariate HR (95%CI)	Cox univariate score *P* value	Cox multivariate HR (95%CI)	Cox multivariate likelihood ratio *P* value (*n* = 15618)
Age at diagnosis	27114	5281 (19%)	73.3 (72.6, 74.0)	1.03 (1.03, 1.04)	< 0.0001	1.02 (1.02, 1.02)	< 0.0001
Sex					< 0.0001		< 0.0001
Female	10502	1869 (18%)	75.5 (74.4, 76.6)				
Male	16612	3412 (21%)	71.9 (70.9, 72.8)	1.19 (1.13, 1.26)		1.23 (1.14, 1.32)	
Charleson comorbidity score					< 0.0001		< 0.0001
0	20949	3656 (17%)	75.7 (74.9, 76.5)				
1	4792	1202 (25%)	67.4 (65.6, 69.1)	1.43 (1.34, 1.53)		1.25 (1.14, 1.36)	
2+	1373	423 (31%)	58.5 (55.0, 62.0)	2.00 (1.81, 2.22)		1.59 (1.38, 1.82)	
Race					< 0.0001		0.3372
Black	2307	508 (22%)	69.7 (67.1, 72.2)	1.18 (1.08, 1.29)		1.04 (0.92, 1.19)	
Other	1542	246 (16%)	76.6 (73.6, 79.5)	0.85 (0.74, 0.96)		1.01 (0.85, 1.20)	
White	23091	4498 (19%)	73.4 (72.7, 74.2)				
Insurance status					< 0.0001		< 0.0001
Insurance status unknown	382	64 (17%)	71.8 (64.8, 78.8)	1.46 (1.14, 1.88)		0.93 (0.62, 1.39)	
Medicare/medicaid/other government	11607	3039 (26%)	64.8 (63.6, 66.0)	2.12 (2.01, 2.25)		1.33 (1.22, 1.46)	
Not insured	1357	294 (22%)	71.1 (67.9, 74.2)	1.61 (1.42, 1.82)		1.14 (0.97, 1.33)	
Private insurance/managed care	13768	1884 (14%)	80.8 (79.9, 81.7)				
Living location					0.0407		0.3867
Metropolitan	21521	4134 (19%)	73.7 (72.9, 74.5)				
Rural	611	117 (19%)	72.9 (68.2, 77.6)	1.01 (0.84, 1.22)		0.85 (0.67, 1.08)	
Urban	4344	900 (21%)	71.7 (69.9, 73.5)	1.10 (1.02, 1.18)		0.98 (0.89, 1.08)	
Facility type					< 0.0001		0.5531
Academic/research program	10235	1850 (18%)	75.4 (74.2, 76.5)				
Community cancer program	1624	384 (24%)	67.4 (64.4, 70.5)	1.37 (1.22, 1.53)		1.00 (0.86, 1.17)	
Comprehensive community cancer program	10158	2097 (21%)	71.6 (70.4, 72.8)	1.17 (1.10, 1.25)		1.06 (0.98, 1.15)	
Integrated network cancer program	3719	761 (20%)	72.2 (70.2, 74.1)	1.17 (1.07, 1.27)		1.04 (0.93, 1.16)	
Facility geographic region					0.0008		0.0971
Midwest	7378	1455 (20%)	73.6 (72.2, 74.9)	0.91 (0.85, 0.97)		0.926 (0.846, 1.014)	
Northeast	5058	967	74.1 (72.4, 75.7)	0.87 (0.80, 0.94)		0.912 (0.820, 1.014)	

		(19%)					
South	9090	1885 (21%)	71.2 (69.9, 72.4)				
West	4210	785 (19%)	74.0 (72.2, 75.8)	0.89 (0.82, 0.97)		0.878 (0.783, 0.986)	
Pathological stage					< 0.0001		< 0.0001
0	782	66 (8%)	89.2 (86.4, 92.1)				
1	5631	604 (11%)	84.8 (83.5, 86.1)	1.277 (0.990, 1.646)		1.11 (0.84, 1.46)	
2	6861	1399 (20%)	72.1 (70.6, 73.5)	2.48 (1.94, 3.17)		1.97 (1.50, 2.57)	
3	8247	2338 (28%)	61.6 (60.2, 63.1)	3.74 (2.93, 4.77)		3.32 (2.55, 4.33)	
4	136	82 (60%)	25.1 (15.6, 34.6)	10.93 (7.90, 15.11)		8.70 (5.97, 12.67)	
Chemotherapy (multi or single agent)					< 0.0001		0.001
Multiagent chemotherapy	10043	1616 (16%)	77.9 (76.8, 79.0)				
Single-agent chemotherapy	12445	2467 (20%)	72.6 (71.5, 73.6)	1.31 (1.23, 1.39)		1.14 (1.06, 1.24)	
Chemotherapy sequence					< 0.0001		< 0.0001
Chemotherapy after surgery	2387	543 (23%)	71.7 (69.4, 74.0)	1.12 (1.02, 1.23)		0.89 (0.75, 1.06)	
Chemotherapy before surgery	14351	2849 (20%)	72.6 (71.6, 73.6)				
Chemotherapy before and after surgery	8128	1134 (14%)	79.7 (78.5, 80.9)	0.67 (0.63, 0.72)		0.73 (0.67, 0.79)	
Radiation sequence					< 0.0001		0.3489
Radiation after surgery	1934	463 (24%)	70.5 (68.0, 73.1)	1.30 (1.18, 1.43)		0.92 (0.77, 1.10)	
Radiation before surgery	22529	4054 (18%)	75.0 (74.2, 75.7)				
Surgery type					< 0.0001		< 0.0001
Local excision	953	249 (26%)	65.0 (61.0, 69.1)	1.62 (1.42, 1.84)		1.26 (0.94, 1.68)	
TME with sphincter preservation	18237	3107 (17%)	76.4 (75.6, 77.2)				
TME without sphincter preservation	7924	1925 (24%)	67.5 (66.1, 68.8)	1.44 (1.36, 1.53)		1.30 (1.20, 1.40)	
Surgical approach					< 0.0001		< 0.0001
Laparoscopic	8510	1400 (16%)	76.8 (75.5, 78.0)	0.77 (0.72, 0.82)		0.85 (0.78, 0.93)	
Open	14207	3300 (23%)	70.7 (69.8, 71.7)				
Robotic	4397	581 (13%)	75.7 (73.5, 77.8)	0.72 (0.66, 0.79)		0.82 (0.73, 0.92)	
Tumor grade					< 0.0001		< 0.0001
Other (ND/UNK/NA/high grade dysplasia)	3918	594 (15%)	77.3 (75.5, 79.2)	0.87 (0.80, 0.95)		0.99 (0.88, 1.11)	
Poor/undifferentiated	3023	1004 (33%)	58.9 (56.7, 61.1)	1.97 (1.84, 2.11)		1.67 (1.52, 1.83)	
Well/moderate differentiation	20173	3683 (18%)	74.8 (74.0, 75.6)				

Residual tumor					< 0.0001		< 0.0001
R0	24991	4432 (18%)	75.5 (74.8, 76.2)				
R1	932	414 (44%)	44.5 (40.4, 48.6)	3.03 (2.74, 3.36)		2.23 (1.96, 2.54)	
R2	869	347 (40%)	46.5 (42.2, 50.9)	2.76 (2.47, 3.08)		1.99 (1.71, 2.30)	
12 or more lymph nodes examined					< 0.0001		< 0.0001
No	8705	1919 (22%)	70.9 (69.6, 72.1)	1.19 (1.12, 1.25)		1.26 (1.17, 1.36)	
Yes	18176	3317 (18%)	74.5 (73.6, 75.4)				

TME: Total mesorectal excision.



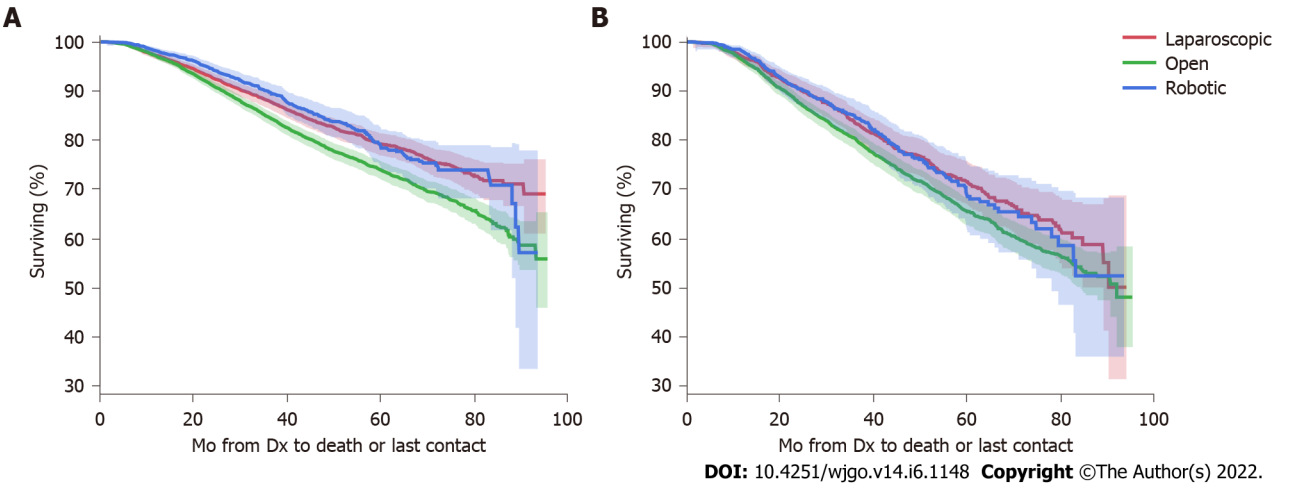
DOI: 10.4251/wjgo.v14.i6.1148

Figure 2 Distribution of surgical approach for stage II/III rectal cancer by year of diagnosis.

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 in patients with stage II or stage III disease. A 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



DOI: 10.4251/wjgo.v14.i6.1148

Figure 3 Kaplan-Meier curves of overall survival, stratified by surgical approach for total mesorectal excision with and without sphincter preservation. A: With sphincter preservation; B: Without sphincter preservation. Shaded areas represent pointwise 95%CIs.

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 survival 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.

FOOTNOTES

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