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Neoadjuvant chemoradiation followed by transanal local excision for T2 rectal cancer confers equivalent survival benefit as traditional transabdominal resection

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A R T I C L E   I N F O

A B S T R A C T

Background: Despite clinical guidelines classifying T2 rectal cancer as a contraindication for transanal local excision attributable to unacceptably high rates of local recurrence, it is a practice that persists clinically. Recent clinical trials have suggested that transanal local excision in addition to neoadjuvant chemoradiation is an acceptable alternative in select patients.
Methods: The 2004–2015 National Cancer Database was queried for patients with clinical stage T2N0M0 rectal adenocarcinoma who underwent surgical intervention. Patients were stratified by treatment with transabdominal resection or transanal local excision, both with and without neoadjuvant chemoradiation. Propensity matching was performed, and, using the Kaplan-Meier and Cox proportional hazard models, survival was compared between the groups.
Results: A total of 12,021 patients met inclusion criteria, including 1,761 and 6,629 patients who underwent transabdominal resection with and without neoadjuvant chemoradiation, respectively, and 695 and 2,936 patients who underwent local transanal excision with and without neoadjuvant chemoradiation, respectively. In unadjusted analysis, patients undergoing induction therapy followed by transabdominal resection or local excision had equivalent survival. Similarly, on multivariate Cox proportional hazard regression after propensity matching, local excision was not an independent predictor of patient mortality compared with transabdominal resection (hazard ratio 0.93, 95% confidence interval 0.75–1.16).
Conclusion: Local transanal excision in addition to neoadjuvant chemoradiation may provide comparable survival benefit to transabdominal resection for patients with clinical stage T2N0M0 rectal cancer. Therefore, patients who refuse or are poor candidates for transabdominal resection should be considered for neoadjuvant therapy followed by transanal local excision.

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Introduction

Despite widespread implementation of screening practices throughout the past several decades, colorectal cancer remains a major cause of significant mortality in the United States and is the third most common cause of cancer death among both men and women.[1,2] The management of patients with primary rectal cancer typically involves a multidisciplinary approach that includes surgical resection, chemotherapy, and radiation therapy contingent on tumor characteristics, overall disease burden, and functional status.[3,4] Patients who are unfit for abdominal surgery owing to social factors or a high comorbidity burden, or those who refuse surgery may benefit from less invasive therapies, including local transanal excision.[5]

Unlike T1 tumors in which local excision is widely accepted, the National Comprehensive Cancer Network (NCCN) has recommended transabdominal resection for T2 rectal tumors that are defined as invading the rectal muscularis propria.[6] This
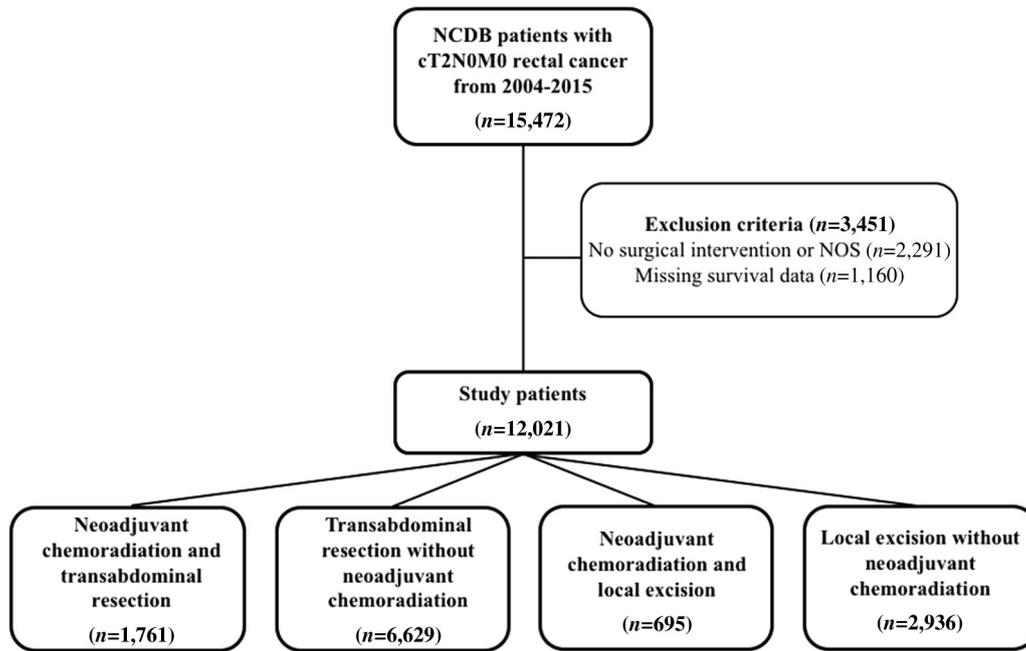
Fig 1. Study population after application of inclusion and exclusion criteria.

Table I
Baseline demographic and clinical characteristics

	Transabdominal resection		Local excision		P value
	Neoadjuvant chemoradiation ($n = 1,761$)	None ($n = 6,629$)	Neoadjuvant chemoradiation ($n = 695$)	None ($n = 2,936$)	
Age, years (median, IQR)	62 (17)	66 (20)	63 (16)	69 (21)	< .001
Sex (female)	37.6% (662)	42.5% (2,818)	36.3% (252)	45.6% (1,340)	< .001
Race					< .001
White	88.6% (1,554)	89.2% (5,858)	89.8% (622)	87.0% (2,524)	
Black	7.6% (134)	6.6% (434)	6.6% (46)	9.8% (283)	
Other	3.8% (66)	4.2% (275)	3.6% (25)	3.3% (95)	
Year of diagnosis, median (IQR)	2010 (4)	2010 (5)	2010 (4)	2009 (6)	< .001
Charlson-Deyo comorbidity index					< .001
0	77.8% (1,370)	73.0% (4,838)	82.4% (573)	75.6% (2,221)	
1	18.1% (318)	20.7% (1,370)	12.4% (86)	18.1% (532)	
2+	4.1% (73)	6.4% (421)	5.2% (36)	6.2% (183)	
Insurance status					< .001
Private	50.3% (874)	44.1% (2,896)	49.2% (338)	38.0% (1,099)	
Government	46.5% (808)	53.8% (3,530)	48.6% (334)	59.8% (1,732)	
None	3.2% (55)	2.0% (134)	2.2% (15)	2.2% (63)	
Facility location					.015
Metro	78.9% (1,351)	81.4% (5,222)	76.9% (513)	82.1% (2,337)	
Urban	18.3% (314)	16.4% (1,055)	20.4% (136)	15.7% (447)	
Rural	2.7% (47)	2.1% (137)	2.7% (18)	2.2% (62)	
Academic/research program	33.4% (562)	34.2% (2,213)	26.4% (178)	31.0% (892)	< .001
Adjuvant therapy					< .001
None	80.2% (1,412)	79.0% (5,237)	82.9% (576)	66.6% (1,956)	
Radiation	0.2% (3)	1.9% (126)	0.4% (3)	5.8% (171)	
Chemotherapy	18.9% (333)	6.8% (451)	16.0% (111)	4.9% (143)	
Chemoradiation	0.7% (13)	12.3% (815)	0.7% (5)	22.7% (666)	

IQR, interquartile range.

recommendation is largely driven by the expected high local-recurrence rates exceeding 20% in patients with T2 rectal tumors after transanal excision.[7] Furthermore, salvage treatment for failure after local excision is quite frequently not feasible or is associated with significant morbidity.[8] On the other hand, there has been limited evidence in recent years supporting the use of local excision in patients with clinical T2 rectal cancer after neoadjuvant therapy.[9–12] As such, the most recent NCCN guidelines suggest that neoadjuvant chemoradiation followed by local excision may be a reasonable alternative for select patients who refuse or are unfit for transabdominal resection, although further investigation is needed, especially regarding long-term outcomes.[13]

The purpose of this study is to identify and characterize the cohort of patients who underwent neoadjuvant chemoradiation followed by local excision for T2 rectal cancer in a large contemporary database and to compare the survival of these patients with those who underwent traditional transabdominal resection. We

Table II
Unadjusted outcomes

	Transabdominal resection		Local excision		P value
	Neoadjuvant chemoradiation ($n = 1{,}761$)	None ($n = 6{,}629$)	Neoadjuvant chemoradiation ($n = 695$)	None ($n = 2{,}936$)	
30-day mortality	0.7% (12)	1.3% (86)	0.7% (5)	0.7% (20)	< .001
90-day mortality	1.6% (29)	2.7% (176)	1.4% (10)	2.1% (62)	< .001
1-year survival[*]	96.6% (1,681)	94.9% (6,128)	97.5% (665)	93.2% (2,654)	—
2-year survival[*]	92.6% (1,498)	90.8% (5,427)	92.2% (589)	87.2% (2,330)	—
5-year survival[*]	79.6% (827)	75.1% (2,817)	77.7% (288)	67.6% (1,207)	—

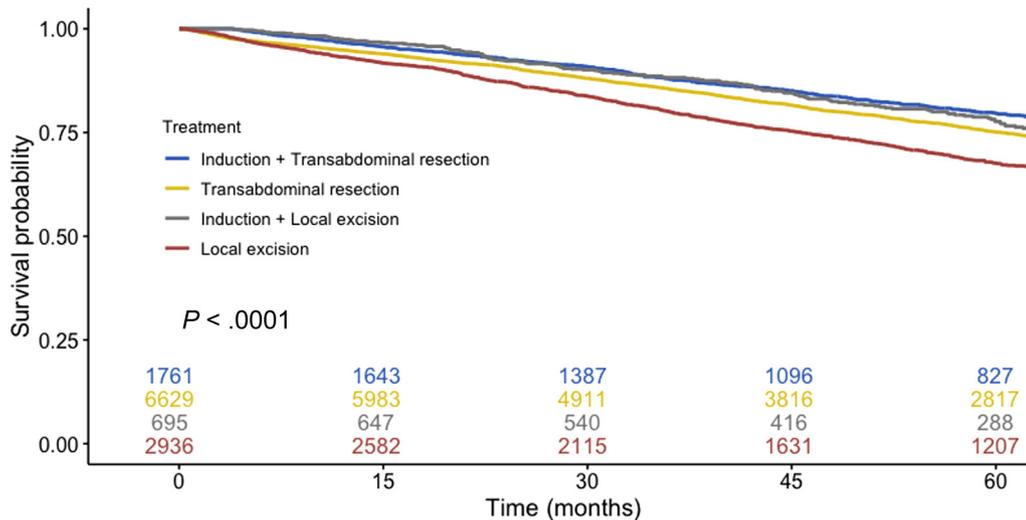[*] From Kaplan-Meier analysis, censored for lack of event occurrence.

Fig 2. Kaplan-Meier analysis of the total population stratified by cohort, irrespective of adjuvant therapy ($P < .0001$).

hypothesize that cT2N0M0 patients who receive induction chemoradiation followed by either transabdominal resection or local transanal excision will have comparable survival postsurgery.

Methods

Data source

This study is a retrospective cohort analysis of the 2004–2015 National Cancer Database (NCDB), which is one of the largest cancer registries in the world and is maintained by the American College of Surgeons Commission on Cancer and the American Cancer Society.[14] In aggregate, the database contains oncology outcomes data from more than 1,500 programs and 34 million discrete hospital records. This study was deemed exempt by Duke University's Institutional Review Board (Durham, NC).

Inclusion criteria

All adult patients (age ≥18 years) with clinical stage T2N0M0 rectal adenocarcinoma—as defined by the American Joint Committee on Cancer (AJCC)—who underwent surgical intervention between the years 2004–2015 were included in the analysis. Subjects were identified by cross referencing International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) topography codes. Patients with missing survival or procedure data were excluded from analysis.

Demographics and outcomes

Patient demographic characteristics included age, sex, race, year of diagnosis, insurance status, facility location and type, and

baseline comorbidities represented by the Charlson-Deyo comorbidity index. Outcome variables in this study included 30-day, 90-day, and overall mortality rates, as well as 1-, 2-, and 5-year survival.

Statistical analysis

Baseline demographic and clinical characteristics between primary study cohorts were compared using the Wilcoxon Mann-Whitney test for continuous variables and the Pearson χ^2 test for categorical variables. Unadjusted overall survival was estimated using the Kaplan-Meier method. To mediate the known selection bias, account for potential confounding variables, and identify independent predictors of survival, Cox proportional hazard models were constructed. Variables from the unadjusted analysis were selected a priori for inclusion in the models based on clinical experience and included age, sex, race, year of diagnosis, comorbidities, insurance status, facility location, and program type. Model diagnostics were assessed. Propensity score matching among patients who received neoadjuvant chemoradiation was performed on the basis of preoperative patient demographics. Statistical analysis was performed using R v 3.5 for Mac (Vienna, Austria).

Results

In total, 12,021 patients met inclusion criteria during the study period. This included 1,761 and 6,629 patients who underwent transabdominal resection with and without neoadjuvant chemoradiation, respectively, and 695 and 2,936 patients who underwent local transanal excision with and without neoadjuvant
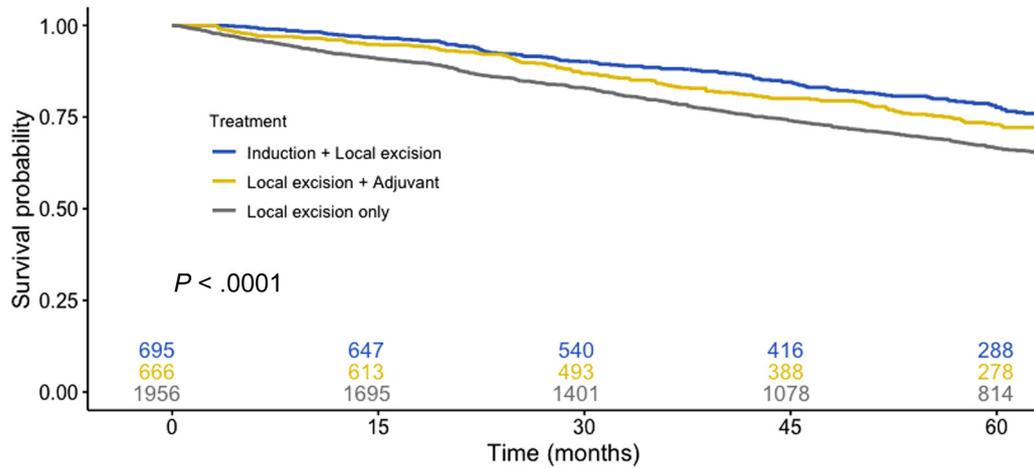
Fig 3. Kaplan-Meier analysis among patients who were treated with local transanal excision, stratified by receipt of neoadjuvant, adjuvant, or no chemoradiation ($P < .0001$; neoadjuvant versus adjuvant chemoradiation $P = .087$).

Table III
Risk of death (Cox proportional hazards)

Predictor	Hazard ratio	95% confidence interval		P value
		Lower	Upper	
Age (per year)	1.05	1.05	1.06	< .001
Sex (female)	0.83	0.77	0.89	< .001
Race				
White	Ref	Ref	Ref	Ref
Black	1.25	1.10	1.42	< .001
Other	0.73	0.59	0.92	.007
Year of diagnosis (per year)	1.01	1.00	1.03	.087
Charlson-Deyo comorbidity index				
0	Ref	Ref	Ref	Ref
1	1.42	1.31	1.54	< .001
2+	2.15	1.92	2.42	< .001
Insurance status				
Private	Ref	Ref	Ref	Ref
Government	1.21	1.20	1.33	< .001
None	1.90	1.47	2.45	< .001
Facility location				
Metro	Ref	Ref	Ref	Ref
Urban	1.06	0.97	1.16	.203
Rural	0.92	0.72	1.17	.481
Academic/research program	0.83	0.77	0.89	< .001
Treatment				
Induction + transabdominal resection[*]	Ref	Ref	Ref	Ref
Transabdominal resection only	0.98	0.87	1.1	.709
Induction + local excision[*]	1.03	0.86	1.25	.728
Local excision only	1.15	1.02	1.3	.023

[*] Induction therapy refers to neoadjuvant chemotherapy and radiation.

Table IV
Baseline demographic and clinical characteristics of propensity-matched cohort

	Induction + transabdominal resection ($n = 639$)	Induction + local excision ($n = 639$)	P value
Age, years (mean, STD)	64 (16)	64 (14.5)	.775
Sex (female)	36.3% (232)	35.8% (229)	.907
Race			.937
White	90.8% (580)	90.3% (577)	
Black	5.5% (35)	5.9% (38)	
Other	3.8% (24)	3.8% (24)	
Year of diagnosis, median (IQR)	2010 (4)	2010 (4)	.785
Charlson-Deyo comorbidity index			.869
0	82.6% (528)	81.8% (523)	
1	12.7% (81)	12.8% (82)	
2+	4.7% (30)	5.3% (34)	
Insurance status			.978
Private	48.0% (307)	48.2% (308)	
Government	49.9% (319)	49.6% (317)	
None	2.0% (13)	2.2% (14)	
Facility location			.923
Metro	77.0% (492)	77.2% (493)	
Urban	20.7% (132)	20.2% (129)	
Rural	2.3% (15)	2.7% (17)	
Academic/research program	24.7% (158)	25.2% (161)	.897
Adjuvant therapy			.337
None	80.6% (515)	83.6% (534)	
Radiation	0.2% (1)	0.5% (3)	
Chemotherapy	18.6% (119)	15.3% (98)	
Chemoradiation	0.6% (4)	0.6% (4)	

IQR, interquartile range.

chemoradiation, respectively (Fig 1). A total of 3,451 patients were excluded from analysis because of missing survival information in the database or ($n = 1,160$) or no indicated surgical intervention ($n = 2,291$). Baseline demographic and clinical characteristics of the complete study population are summarized in Table I. Patients who underwent neoadjuvant chemoradiation followed by local excision were older (median age 63 years vs 62 years) and had fewer comorbidities (Charlson-Deyo comorbidity index >0, 17.6% vs 22.2%) than patients who underwent neoadjuvant chemoradiation followed by transabdominal resection.

In unadjusted outcome analysis (Table II), patients undergoing neoadjuvant chemoradiation followed by transabdominal resection had similar postoperative survival at all time points compared with patients who underwent neoadjuvant chemoradiation followed by

transanal excision (transabdominal resection versus local excision, 1-, 2-, and 5- year survival: 96.6% vs 97.5%, 92.6% vs 92.2%, and 79.6% vs 77.7%, respectively). Patients who did not receive induction therapy but underwent local transanal excision had significantly decreased survival. In Kaplan-Meier survival analysis (Fig 2), a similar percentage of censored cases was present in all studied cohorts. On log-rank testing, the survival distributions for the 4 primary cohorts differed significantly ($P < .001$). When limited to patients who received neoadjuvant chemoradiation, however, survival curves were similar between patients that underwent transabdominal or local resection ($P = .28$). A subgroup analysis was performed among patients who underwent transanal local
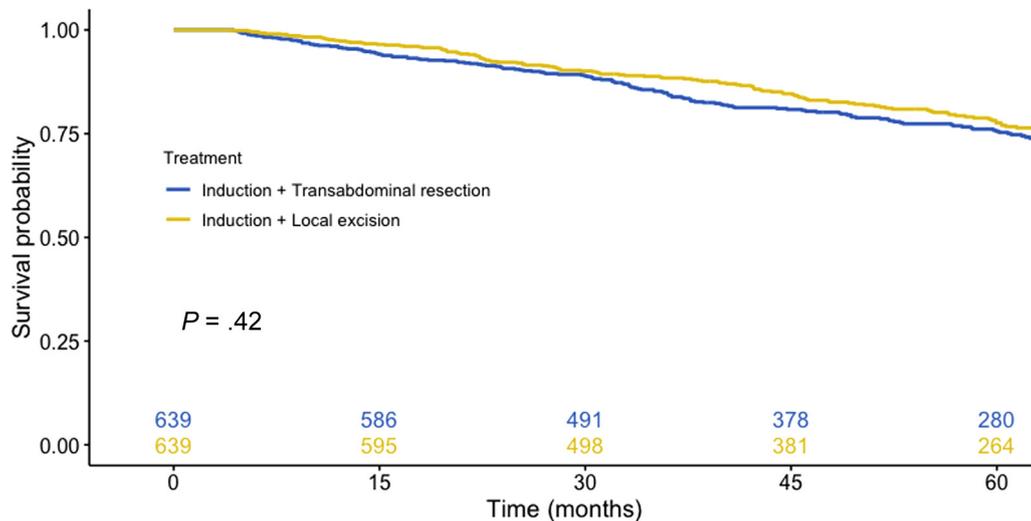
Fig 4. Kaplan-Meier analysis among propensity-matched patients who received neoadjuvant chemoradiation followed by either transabdominal resection or transanal excision ($P = .42$).

Table V
Risk of death (Cox proportional hazards) in propensity-matched cohort

Predictor	Hazard ratio	95% confidence interval		P value
		Lower	Upper	
Age (per year)	1.05	1.04	1.07	< .001
Sex (female)	0.78	0.61	0.98	.034
Race				
White	Ref	Ref	Ref	Ref
Black	1.87	1.25	2.80	.002
Other	0.68	0.30	1.54	.359
Year of diagnosis (per year)	1.00	0.95	1.06	.875
Charlson-Deyo comorbidity index				
0	Ref	Ref	Ref	Ref
1	1.25	0.92	1.69	.147
2+	2.01	1.31	3.07	.001
Insurance status				
Private	Ref	Ref	Ref	Ref
Government	0.94	0.72	1.24	.682
None	1.40	0.65	3.02	.389
Facility location				
Metro	Ref	Ref	Ref	Ref
Urban	1.01	0.78	1.32	.914
Rural	1.02	0.54	1.94	.953
Academic/research program	0.68	0.51	0.9	.006
Treatment				
Induction + transabdominal resection[*]	Ref	Ref	Ref	Ref
Induction + local excision[*]	0.93	0.75	1.16	.539

[*] Induction therapy refers to neoadjuvant chemotherapy and radiation.

excision, stratified by receipt of neoadjuvant chemoradiation, adjuvant chemoradiation only, or no chemoradiation. Compared with neoadjuvant and adjuvant cohorts (Supplemental Table), patients who did not receive chemoradiation were older (median age 70 years vs 63 years and 66 years, $P < .001$), more likely to have a score of 2+ on the Charlson-Deyo comorbidity index (7.0% vs 5.2% and 5.1%, $P < .001$), and were less likely to have private insurance (35.9% vs 49.2% and 43.7%, $P < .001$). On log-rank testing (Fig 3), the survival distributions between the chemoradiation cohorts were similar ($P = .087$); however patients that did not receive chemoradiation had significantly decreased survival ($P < .0001$).

In multivariable analysis, using a Cox proportional hazards model (Table III), significant independent predictors of decreased overall survival included advanced age (hazard ratio [HR] 1.05, 95% confidence interval [CI] 1.05–1.06), greater comorbidities (2+ vs 0, HR 2.15, 95% CI 1.92–2.42), black race (HR 1.25, 95% CI 1.10–1.42), government insurance (HR 1.21, 95% CI 1.20–1.33), or no insurance (HR 1.90, 95% CI 1.47–2.45). Female sex (HR 0.83, 95% CI 0.77–0.89) and surgery at an academic/research program (HR 0.83, 95% CI 0.77–0.89) predicted improved survival. Compared with neoadjuvant chemoradiation followed by transabdominal resection, neoadjuvant chemoradiation followed by local transanal excision was not independently associated with differential postoperative survival (HR 1.03, 95% CI 0.86–1.25). Local excision without induction therapy did, however, predict decreased survival (HR 1.15, 95% CI 1.02–1.3).

A propensity-score matched analysis revealed 639 pairs of matched patients who underwent induction chemoradiation followed by either transabdominal resection or transanal excision. Both cohorts had similar baseline demographic and clinical characteristics (Table IV). On Kaplan-Meier survival analysis, both cohorts had similar rates of unadjusted survival (Fig 4, $P = .42$). On Cox proportional hazards analysis (Table V), neoadjuvant chemoradiation followed by transanal excision was associated with similar survival compared with neoadjuvant chemoradiation and transabdominal resection (HR 0.93, 95% CI 0.75–1.16).

Discussion

This is the largest study, to our knowledge, analyzing the effect of surgical approach, neoadjuvant chemoradiation followed by transabdominal resection versus transanal excision, for patients diagnosed with clinical stage T2N0M0 rectal cancer on postsurgical outcomes. Acknowledging that the literature has historically demonstrated a significant survival advantage for patients undergoing transabdominal resection and, as a result, the majority of current guidelines recommend against transanal approaches, the goal of this study was to compare outcomes among those patients who have been treated with transabdominal resection or transanal excision for T2 rectal cancer in a large modern cohort.

The results of this study indicate that among patients who do receive neoadjuvant chemoradiation, postoperative survival is comparable between those who undergo transabdominal resection or local transanal excision. This finding was observed on both unadjusted and adjusted analyses and after propensity matching. Furthermore, patients who are treated with transanal local excision

without neoadjuvant or adjuvant chemoradiation have decreased survival compared with all other groups.

Current clinical guidelines for the management of T2 rectal cancers, including those of the NCCN, typically involve total mesorectal excision as the cornerstone of therapy because of a higher risk of recurrence and mesorectal lymph node involvement compared with early low grade T1 tumors.[4,6,15] In 2012, Lezoche et al[12] published the results of a prospective randomized clinical trial, demonstrating that in select patients with low cT2N0M0 rectal cancers, undergoing neoadjuvant chemoradiation followed by endoluminal locoregional resection conferred an equivalent survival benefit compared with patients undergoing neoadjuvant therapy followed by traditional transabdominal resection (locoregional versus transabdominal resection, 5-year survival 72% vs 80%, $P = .609$; recurrence or metastasis development 12% vs 10%, $P = .686$).

Similarly, a 2013 randomized clinical trial from Poland by Bujko et al[16] also noted acceptable recurrence and survival rates in patients undergoing neoadjuvant therapy followed by local excision in those patients who were deemed pathologic complete responders or were downstaged after neoadjuvant treatment. Pathologic T2 patients who were poor responders to neoadjuvant chemoradiation had a recurrence rate of 36.4%. A single arm phase 2 trial in 2016 by Garcia-Aguilar et al[17] from the American College of Surgeons Oncology Group also demonstrated acceptable oncologic and quality-of-life outcomes in cT2 rectal cancer patients treated with neoadjuvant chemoradiation before local excision owing to generally positive responses to neoadjuvant treatment and concluded this approach to be reasonable in patients who refused or were poor candidates for transabdominal surgery (3-year disease-free survival of 86.9%). The results of this NCDB analysis are in accordance with these trials, despite recent NCCN guidelines advising against this practice.

Several limitations are inherent to this study and are worth noting. Analysis of a large clinical database such as the NCDB is limited by completeness, data accuracy, and availability of appropriate predictor variables. The NCDB mitigates these limitations with standardization of the data fields and close auditing of data reporting.[18] Some of these biases are further eliminated through the use of a multivariable model and propensity matching; however, the strength of the model is only as good as the quality of associated predictor variables. We were unable to extrapolate the basis of treatment decisions to undergo local excision rather than traditional transabdominal resection, which is uniquely specific to this study, and therefore a potential for selection bias certainly exists. We did control for baseline comorbidities on our multivariable model, however, which will help control for treatment decisions based upon operative risk estimates. In addition, the lack of data granularity pertaining to preoperative functional status, pathologic response to induction therapy, specific chemoradiation regimens, and postoperative complications also limits the analysis. Last, an important potential consequence of transanal excision is local pelvic recurrence, which often requires salvage surgery that is frequently highly morbid, if feasible at all. As such, the lack of information regarding disease recurrence in the NCDB is an important limitation of this study.

Despite these limitations, analyzed in context of the existing literature, the results of this study correlate with recently conducted trials demonstrating that patients with clinical stage T2N0M0 rectal cancer achieve the optimal oncologic and survival benefit through traditional transabdominal mesorectal resection;

however, similar short-term and long-term survival may be observed with neoadjuvant chemoradiation followed by transanal local excision. Therefore, patients who refuse or are poor candidates for transabdominal resection should be considered for neoadjuvant therapy followed by transanal local excision.

Conflict of interest

There are no conflicts of interest.

Funding

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2019.02.005.

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