

RETROSPECTIVE ANALYSIS OF THE PREDICTORS OF OUTCOME FOLLOWING LOCAL EXCISION FOR T1 RECTAL ADENOCARCINOMA

T. JAYAKRISHNAN¹, S. ABEL², A. REICHSTEIN³, R. FORTUNATO³, S. NOSIK³,
J. MCCORMICK³, G. FINLEY⁴, D. MONGA⁴, A. V. KIRICHENKO², R. E. WEGNER²

¹Department of Internal Medicine, Allegheny Health Network, Pittsburgh, PA, USA

²Division of Radiation Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, PA, USA

³Division of Colorectal Surgery, Allegheny Health Network, Pittsburgh, PA, USA

⁴Division of Medical Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, PA, USA

Abstract – Objective: Early-stage cancers may allow for less radical approaches such as local excision which preserve quality of life without compromising oncologic outcomes. We examined outcomes of patients with early-stage rectal adenocarcinoma treated with Local excision (LE).

Patients and Methods: We queried the NCDB for patients with pT1N0M0 rectal adenocarcinoma treated with local excision alone. Multivariable Cox regression was used to identify predictors of overall survival (OS).

Results: We identified 887 patients eligible for analysis across 2010-2014. The median tumor size was 1.5 cm (IQ range: 0.9-2.5 cm). A minority of patients had grade 3 tumors (5%), lymphovascular invasion - LVI (8%), or perineural invasion PNI (<1%). Median follow up was 36 months (1-83). Predictors of worse survival included: size >4 cm, age >67, higher comorbidity score, and presence of LVI. On Kaplan Meier analysis, 5-year OS was 75% vs. 74% for patients without and with LVI, respectively (p-value=0.0115). In terms of size, the 5-year OS rates were 74% for size <4 cm vs. 51% size >4 cm (p-value=0.0138).

Conclusions: The study demonstrates excellent survival outcomes in patients with early-stage rectal adenocarcinoma treated with LE alone. LVI remains a predictor of outcome, while grade and PNI were not significant.

KEYWORDS: Rectal Cancer, Adenocarcinoma, Local excision, Transanal surgery, Survival Analysis.

LIST OF ABBREVIATIONS: LE Local excision, OS Overall Survival, NCDB National Cancer Database, LVI Lymphovascular invasion, PNI Perineural invasion, NCCN National Comprehensive Cancer Network, IQR Interquartile Range, TEM Transanal Endoscopic Microsurgery, TAMIS Transanal Minimally Invasive Surgery, RATE Robotic Assisted Transanal Excision.

INTRODUCTION

While radical interventions are indicated for more advanced stages of the diseases, early stage cancers may allow for less radical approaches which preserve quality of life without compromising oncologic outcomes^{1,2}. It is thus that the idea of local

excision (LE) as a curative approach was proposed for early stage rectal cancer about 30 years ago³⁻⁵. According to the recent (NCCN) guidelines, appropriately selected early stage rectal cancer patients may be treated with transanal local excision⁶. The criteria restricts this treatment strategy to patients with T1 N0 non-fixed, well to moderately differen-



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tiated tumors that are less than 3 cm in size, occupy less than 30 % of the circumference of the bowel and lie within 8 cm of the anal verge with no evidence of lymphovascular or perineural invasion on imaging^{6,7}. In the present study we sought to use the National Cancer Database (NCDB) to examine outcomes in a large cohort of patients with early stage rectal adenocarcinoma treated with LE alone and to identify as well as confirm predictors of outcome.

PATIENTS AND METHODS

We conducted a retrospective review using de-identified data from the NCDB; therefore, the study was exempt from Institutional Review Board oversight. Jointly maintained by the American Cancer Society and the American College of Surgeons, the National Cancer Database (NCDB) encompasses approximately 70% of newly diagnosed malignancies each year across the United States. We queried the NCDB for patients with pT1N0M0 rectal adenocarcinoma treated with local excision. We excluded patients with TNM stages other than T1N0M0 and those treated with other modalities such as radiation

therapy and chemotherapy. Patients with less than 1 month follow up were excluded to account for immortal time bias. We excluded patients for whom data on lymphovascular invasion and perineural invasion were not available as these were significant predictors of outcomes from previous studies. Figure 1 outlines the patient selection process.

Race was divided into three broad categories including Caucasian, African American, or other. Comorbidity was quantified using the widely accepted Charlson/Deyo comorbidity index. Socioeconomic data in the patients' residence census tract were provided as quartiles of the percentage of persons with less than a high school education and median household income. The facility type was assigned according to the Commission on Cancer accreditation category. Locations were assigned based on data provided by the United States Department of Agriculture Economic Research Service. Insurance status is documented in the NCDB as it appears on the admission page. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

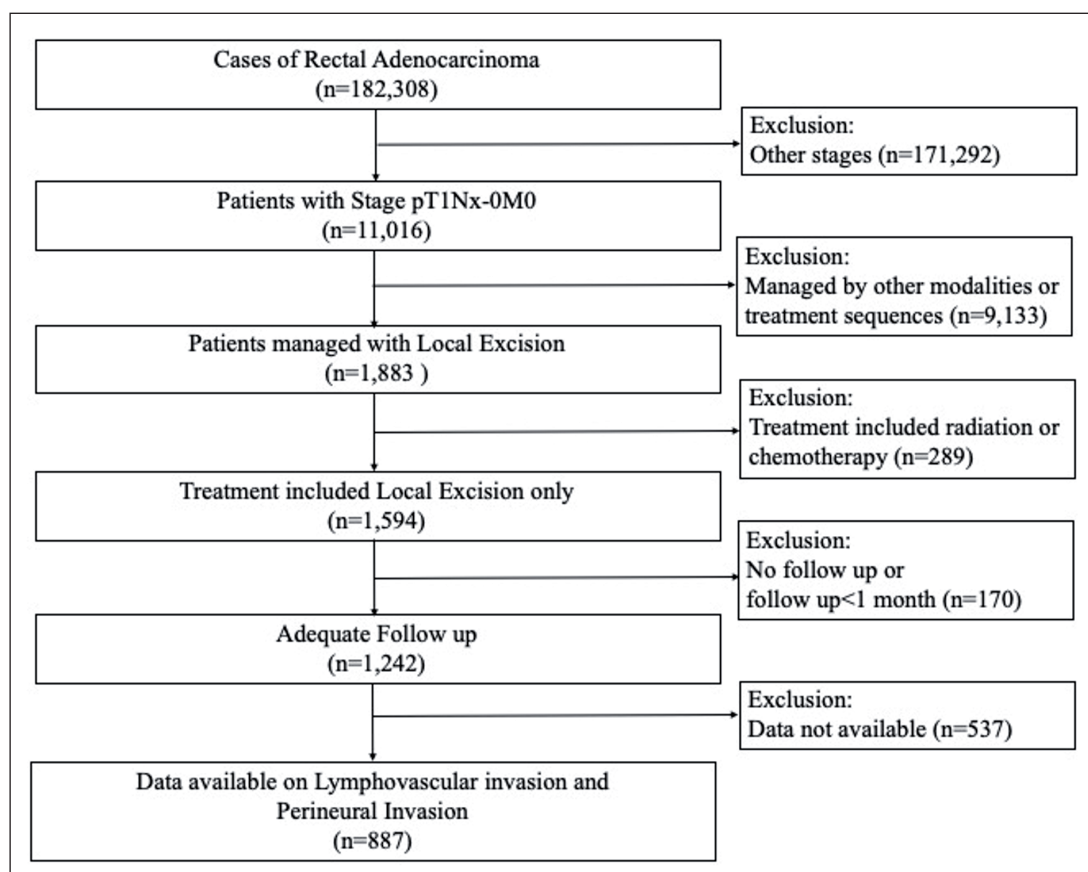


Fig. 1. CONSORT Diagram Outlining the Selection criteria for Study Eligibility.

STATISTICAL ANALYSIS

Data were analyzed using Medcalc Version 18 (Ostend, Belgium). Summary statistics are presented for discrete variables. Baseline characteristics were tabulated and included lymphovascular invasion (LVI), perineural invasion (PNI), grade, and size all of which have been recorded in the NCDB since 2010. Overall survival was calculated in months from time of diagnosis to date of last contact or death as is standard within the NCDB. Kaplan-Meier curves were used to calculate cumulative probability of survival. Log-rank statistics were used to test for significant differences in the cumulative proportions across groups. A Cox proportional hazards model was used for multivariable survival analysis. Due to the large nature of the dataset, factors significant on univariable Cox regression were entered using a stepwise backward elimination process. Adjusted hazard ratios and 95% confidence intervals are reported, using an alpha level of 0.05 to indicate statistical significance.

RESULTS

The dataset included 182,308 rectal adenocarcinoma patients, of which 1,883 patients with pT1Nx-0M0 stage were identified that underwent local excision as part of the treatment. Of these, 887 patients were eligible for analysis across 2010-2014 as per exclusion criteria described earlier (Figure 1).

Table 1 displays patient characteristics associated with the entire cohort. To briefly summarize, the median age was 67 and 57% of patients were male. Most patients were Caucasian (86%), had comorbidity score 0 (76%), had insurance (96%) and were treated at a comprehensive community cancer program or academic program (91%). The median tumor size was 1.5 cm (IQ range: 0.9-2.5 cm) and the vast majority were well to moderately differentiated tumors (83%). A minority of patients had grade 3 tumors (5%), LVI (8%), or PNI (<1%).

Median follow up was 36 months (1-83) and median overall survival was 68 months for all patients (95% CI 65-72 months). On multivariable Cox regression, predictors of worse survival included - size >4 cm, age >67, higher comorbidity score, and presence of lymphovascular invasion (LVI) (Table 2). Interestingly, survival was not related to grade of the disease. There was also no relation noted with gender, race, year of diagnosis, treatment facility, socioeconomic factors of income/insurance/educational status/geographical location. On Kaplan Meier analysis, 5 year OS was 75% vs. 74% for patients without and with LVI respectively, p -value=0.0115 (Figure 2). In terms of size, the 5 year OS rates were 74% for size <4 cm vs. 51% size >4 cm (p -value=0.0138) (Figure 3).

TABLE 1. Clinicopathologic and Treatment Characteristics of Patients Selected for the Study (n=887).

Characteristics	No. (%)
Sex	
Male	508 (57)
Female	379 (43)
Race	
White	770 (87)
African American	67 (8)
Other	50 (6)
Age	
≤67	459 (52)
>67	428(48)
Comorbidity Score	
0	674 (76)
1	159 (18)
≥2	54 (6)
Insurance	
Not Insured	18 (2)
Private Payer	371 (42)
Government	481 (54)
Unrecorded	17 (2)
Education %	
≥29	115 (13)
20 to 28.9	227 (26)
14 to 19.9	277 (31)
<14	268 (30)
Treatment Facility type	
Community cancer program	73 (8)
Comprehensive community cancer program	387 (44)
Academic/research program	423 (48)
Treatment facility location	
Metro	724 (82)
Urban	128 (14)
Rural	15 (2)
Income, US dollars	
<30,000	135 (15)
30,000 to 35,000	194 (22)
35,000 to 45,999	221 (25)
>46,000	336 (38)
Grade	
Well differentiated	166 (19)
Moderately differentiated	574 (65)
Poorly differentiated	43 (5)
Not Recorded	104 (12)

DISCUSSION

The present study reports survival outcomes among a large cohort of patients selected for transanal local excision (TAE) of rectal cancer and followed up for a median of 3 years with a median survival of 68 months. The tumor characteristics considered significant in terms of survival and incorporated into the NCCN selection criteria, namely size of the tumor and lymphovascular invasion (LVI) remain significant factors in the present study as well⁸⁻¹¹. The interaction of tumor size with LVI has been suggested although these factors could independently be associated with survival as well, as in the present study^{11,12}.

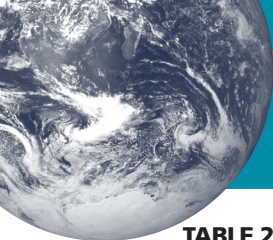
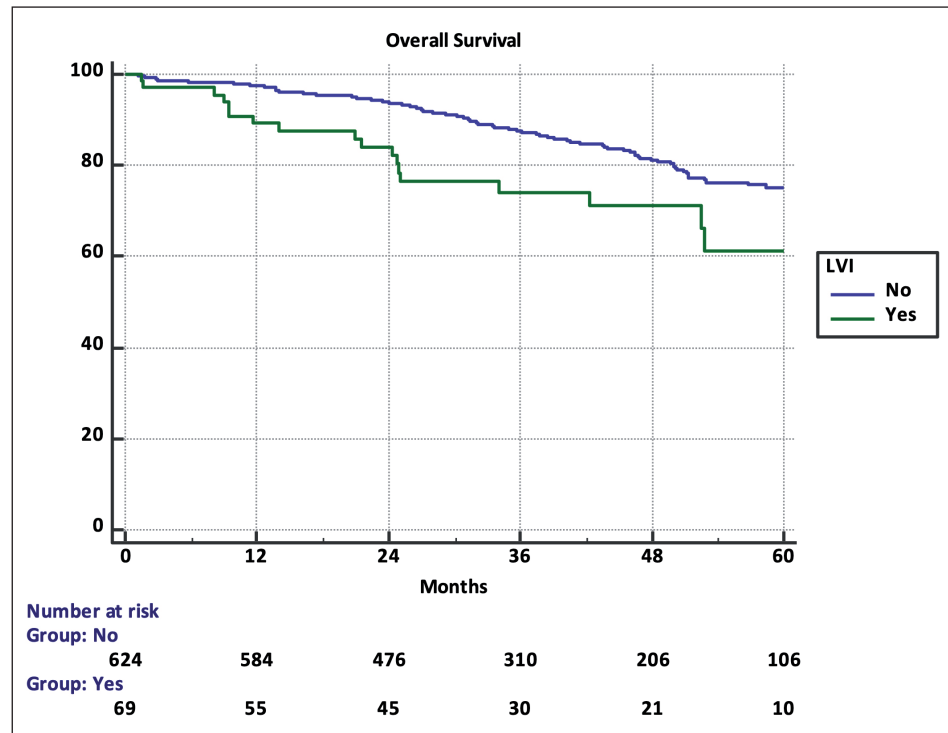


TABLE 2. Multivariate Cox Regression Analysis for Overall Survival.

Characteristic	Hazards Ratio (95% Confidence Interval)	p-value
Age		
≤67	Reference	
>67	2.16 (1.40-3.33)	0.0005
Gender		
Male	Reference	
Female	1.01 (0.72-1.42)	0.9534
Race		
Caucasian	Reference	
African American	1.19 (0.64-2.20)	0.5876
Other	0.35 (0.11-1.10)	0.0726
Grade		
Grade 1	Reference	
Grade 2	0.75 (0.50 – 1.14))	0.1816
Grade 3	1.17 (0.59-2.32)	0.6453
Comorbidity Score		
0	Reference	
1	1.57 (1.06-2.33)	0.0239
≥2	2.97(1.80-4.90)	<0.0001
Facility Type		
Community Cancer Center	Reference	
Comprehensive Community Cancer Center	0.64 (0.36-1.11)	0.1134
Academic/Research Program	0.61 (0.345-1.07)	0.0835
Education, % without high school diploma		
≥29	Reference	
20-28.9	0.79 (0.44-1.41)	0.4286
14-19.9	0.99 (0.54-1.80)	0.9723
<14%	0.84 (0.4301.67)	0.6255
Income, USD		
<30,000	Reference	
30,000-34,999	1.30 (0.74-2.28)	0.3655
35,000-45,999	1.19(0.64-2.24)	0.5819
≥46,000	1.37(0.69-2.70)	0.3691
Insurance		
None	Reference	
Private	0.70 (0.16-3.09)	0.6417
Government	1.19 (0.27-5.29)	0.8155
Others	2.24 (0.38-13.36)	0.3764
Distance		
Distance≤10 miles	Reference	
Distance>10 miles	0.67 (0.47-0.97))	0.0356
Geographical Location		
Metro	Reference	
Urban	1.28 (0.5-2.20)	0.3652
Rural	1.37 (0.41-4.65))	0.3764
Year of Diagnosis		
2010	Reference	
2011	0.95 (0.59-1.52)	0.8250
2012	1.13 (0.70-1.82)	0.6263
2013	0.95 (0.54-1.68)	0.8518
2014	1.70 (0.92-3.13)	0.0881
Size of Tumor (cms)		
0.1-1.0	Reference	
1.1-2.0	1.03 (0.65-1.62)	0.9131
2.1-3.0	1.55 (0.93-2.59)	0.0934
3.1-4.0	1.04 (0.44 – 2.46)	0.9218
>4.0	2.00 (1.07 – 3.71)	0.0288
Lymphovascular Invasion		
No	Reference	
Yes	1.82 (1.07-3.11)	0.0276
Perineural Invasion		
No	Reference	
Yes	1.19 (0.79-1.78)	0.3996

Fig. 2. Kaplan Meier Curve Comparing Survival Outcomes Based on Presence or Absence of Lymphovascular Invasion (LVI).



Perineural invasion (PNI) - another important pathological characteristic associated with poor outcomes for rectal cancer patients, was not significant in the present study, keeping in mind that very few patients had PNI on pathology¹³.

The use of local excision for management T1 rectal carcinoma has increased over the last two decades¹⁴. The tradition technique using operative

anoscopy has been largely supplanted by minimally invasive transanal endoscopic surgical resections such as Transanal Endoscopic Microsurgery (TEM), Transanal Minimally Invasive Surgery (TAMIS) or Robotic Assisted Transanal Excision (RATE). Regardless of approach, oncologically sound principles call for proper patient selection, complete extirpation of tumor, and pathologically

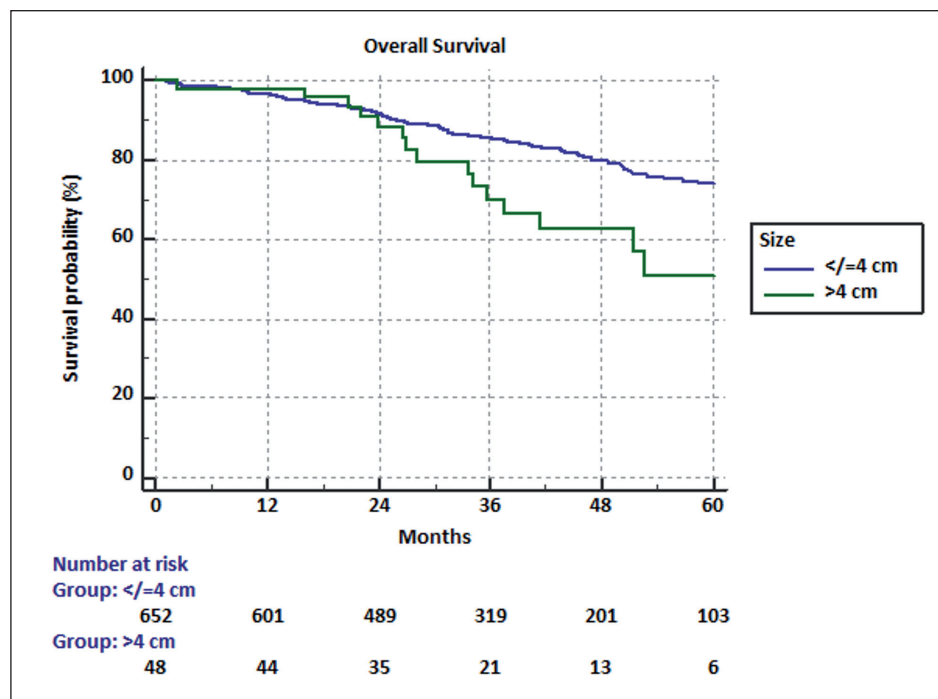
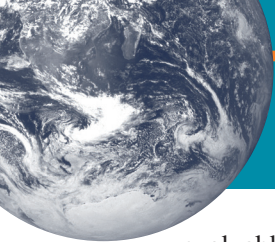


Fig. 3. Kaplan Meier Curve Comparing Survival Outcomes Based on Size of the Tumor.



evaluable specimen. Eligible patients are those with T1 N0 non-fixed, well to moderately differentiated mid- and distal- rectal tumors that are less than 3 cm in size, occupy less than one-third of the circumference of the rectum. In order to be considered oncologically acceptable, the resection must be full thickness into the perirectal fat with negative deep and mucosal margins, avoiding tumor fragmentation⁶. To accomplish this, a one centimeter margin is mapped out around the tumor. Full thickness incision is made perpendicularly through the bowel wall into the perirectal fat (Figure 4). This is carried around the tumor and the tumor retrieved in a single piece. The tumor is oriented and mapped on a board for pathological evaluation (Figure 4). This is required for margin assessment. When feasible, the defect is closed transversely to avoid luminal compromise.

Functional status of the patients with respect to their ability to maintain bowel function, anal continence, and preserving genitourinary functions are important considerations while managing patients with rectal cancer irrespective of the intent of the treatment. Achieving this balance is challenging in rectal cancer patients due to concerns for higher local recurrence when compared to colon cancer¹⁵⁻¹⁸. Naturally, the concerns may be three fold – oncological outcomes in terms of recurrence and overall survival, surgical outcomes in terms of post-operative recovery, and quality of life.

While considering the oncological outcomes, a major concern with TAE is the failure to identify micro metastatic nodal disease that would, otherwise, be resected in the more radical procedures^{19,20}. This is estimated to range between 9-17% and may

play a role in the increased risk for local recurrence even when considering variable durations of follow-ups in different studies (4-20% with local excision vs. 0-7% with radical resection)^{8,10, 19,21-37}. For patients who suffer recurrence, salvage surgery is offered and shown to be effective in most patients in terms of achieving R0 resection and cancer remission^{14,8,27,38,34}. In one study, the risk of recurrence was 19 times with TAE compared to total mesorectal excision (TME), the majority of whom underwent salvage surgery following recurrence⁸. The impact of the recurrence and salvage surgery on overall survival has been variable^{8,19,21-36}. The differences have been attributed to the variability in unfavorable histology between TAE and radical surgery groups (varied 5-12%) as well as differences in ages^{10,22,25}. A meta-analysis consisting of 1 randomized clinical trial and 6 non-randomized studies comparing TEM with TME failed to detect differences in terms of survival³⁹. Therefore, it may be reasonable to assume that although patients undergoing TAE suffer from higher risk for local recurrence and need for salvage surgeries, the overall survival is not compromised.

Considering the high risk of recurrence, a consideration for these patients would be pre and post-surgical treatment with chemotherapy with or without addition of radiation therapy. While it is intuitive to consider adjuvant radiation therapy for high risk patients with pT1 rectal cancer undergoing TAE, improvement in outcomes in terms of recurrence and overall survival has not been consistent^{8,27,37,40-45}. Certainly the addition of chemotherapy and radiation following local excision of T1 rectal adenocarcinomas remains a consideration for those



Fig. 4. Intra-operative image demonstrating (A) Full thickness excision. The mucosa has been mapped. Mesorectal fat can be seen deep to the specimen (B) Specimen is oriented and mapped on a board for accuracy of margins on pathological evaluation^a (Representative specimen from Allegheny Health Network (AHN) Division of Colorectal Surgery).

with poor prognostic features such as deep submucosal invasion and lymphovascular invasion that are associated with lymph node metastasis³⁴. Studies have also demonstrated the promising role of preoperative chemoradiation in patients with T1 rectal cancer prior to TAE and achieving similar outcomes to those undergoing TME after preoperative chemoradiation⁴⁶. There was no significant difference between the matched TAE and TME groups in terms of relapse (5% versus 7%) and 5-year overall survival (96.6% vs. 88.0%). In addition, this study demonstrated curative role of preoperative chemoradiation therapy even in those with metastatic lymph nodes⁴⁶.

An important factor impacting this population is the selection process and ability to determine whether the selection criteria truly capture the patients with early stage disease without dissemination – locally including nodal basis and systemically. The local staging may be challenging, and the two common modalities are Endoscopic Ultrasound (EUS) and Magnetic Resonance Imaging (MRI). NCCN guidelines recommend MRI of pelvis as the primary modality for evaluating the pelvis with EUS reserved for conditions where MRI is contraindicated⁶. In the present study, it does appear that the patients were appropriately selected as only a minority of patients (8%) had positive lymphovascular invasion on the final pathological specimen. It is interesting that although the outcomes were impacted by the presence or absence of LVI in this cohort the absolute difference in survival was only 1% at 5 years. This may be related to the fact that the patient selected for local excision represented a low risk cohort overall.

Local procedures do indeed promise to offer minimal morbidity, sphincter sparing and therefore preservation of continence as well as lower post-operative mortality and early recovery^{15,24}. In two meta-analyses comparing the techniques, the perioperative complication and mortality rates for local excision procedures were less than half of that for radical surgeries^{21,35}. The complications reported are minor with re-operation rates between 0-7%¹⁴. Better outcomes in terms of quality of life and bowel function have also been demonstrated in those undergoing chemoradiation therapy after local excision of high risk lesions in comparison to radical surgery⁴¹. This is pertinent especially in populations that may be unfit for surgery due to medical comorbidities or age. Age is an independent predictor of poor outcome for these patients but the potential for sustaining good outcomes while maintaining quality of life in this group will need further studies.

The limitations of the present study are multiple. While we have been able to estimate the survival outcomes and identify the risk factors for mortality, the data pertaining to recurrence and salvage thera-

pies could not be studied as this data is not available in the database. As demonstrated in previous studies the outcome in these patients is not necessarily one of quantity but involve the quality of life that could not be assessed either. The volume and the multi-institutional nature of the data does, however, provide robustness and generalizability to the results. Our goal for the study was to analyze the outcomes in terms of survival and factors effecting the survival which were fulfilled in the present analysis. Mutations such as BRAF, RAS and MSI (microsatellite instabilities are additional variables of interest in this disease). Unfortunately, in this cohort data pertaining to MSI is reported only in 148 patients (148/887 =>16%), 12 with instability and KRAS is reported in even less - 25 patients (25/887=>3%), 8 with mutation. Therefore, these were not included in the analysis.

Moving forward, local excision in conjunction with preoperative chemoradiotherapy is being investigated as a safe alternative to transabdominal resection in patients with T2N0 cancer (ACOSOG Z6041) and potentially even other stages where patients refuse or are unfit for transabdominal surgeries^{31,48}. Further studies in understanding the biology of the disease and aimed at identifying molecular markers of aggressive disease would be helpful. Use of pre-operative diffusion weighted MRI and making the MRI criteria more stringent may help decrease the false negative for pathological lymph nodes but could come at risk for false positives would be a concern. Impact of socioeconomic disparities on enrollment of patients to these newer treatment paradigms and impact on overall survival also need to be closely monitored. Above all, education of patients selected to undergo local excision, appropriate counselling, and aggressive postoperative surveillance are paramount.

Conclusions

Our large contemporary series demonstrates excellent survival outcomes in patients with early stage rectal adenocarcinoma treated with LE alone. LVI remains a predictor of outcome, while grade and perineural invasion were not significant in this analysis, likely due to a small number of patients with those characteristics.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE:

Study was a retrospective review using de-identified data from the NCDB; therefore, the study was exempt from Institutional Review Board oversight.

CONSENT FOR PUBLICATION:

Not Applicable



AVAILABILITY OF DATA AND MATERIAL:

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

COMPETING INTEREST:

No author present on this article has any conflicts of interest.

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TJ: Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original Draft, Review and Editing, Visualization.

SA, AR, RF, SN, JM, GF, DM, AK: Conceptualization, Writing - Review and Editing.

RW: Conceptualization, Methodology, Formal analysis, Investigation, Software, Resources, Writing – Original Draft, Review and Editing, Visualization, Project Administration. All authors have read and approved the manuscript

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