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Therapeutic strategies for ypT1 rectal cancer after neoadjuvant chemoradiotherapy: a retrospective cohort study

Yibo Cai[1] · Lai Jiang[1] · Haixing Ju[1] · Yuping Zhu[1] · Zhuo Liu[1]

Abstract

Purpose The optimal treatment of ypT1 rectal cancer after neoadjuvant chemoradiotherapy (nCRT) remains controversial. This study aimed to determine whether local excision is non-inferior to radical surgery and whether adjuvant chemotherapy (ACT) would improve survival in patients with ypT1 rectal cancer after nCRT.

Methods We enrolled 1212 and 91 patients with ypT1 rectal cancer underwent nCRT followed by radical surgery from the SEER database (2004–2018) and the Zhejiang Cancer Hospital (ZJCH) (2010–2022), respectively. Another 62 patients underwent LE were also identified from SEER registries. Propensity score matching was performed to balance baseline characteristics between patients in different treatment groups.

Results Regional nodal metastasis was histopathologically detected in 257 patients (20.7%) within the SEER cohort, showing a significant association with poor cancer-specific survival (CSS) and overall survival (OS). Consistent findings were also observed in the ZJCH cohort. After 1:1 propensity score matching (60 pairs), no significant differences were observed between the extended resection and local excision groups in CSS (hazard ratio [HR] 0.88, $P = 0.785$) and OS (HR 0.81, $P = 0.450$). Patients with regional nodal metastases were more likely to receive ACT, while no apparent survival benefit was observed with additional ACT after PSM adjusting (187 pairs). Notwithstanding, for individuals younger than 50 years, ACT might provide a survival benefit in CSS (HR 0.25, $P = 0.033$) and OS (HR 0.30, $P = 0.022$).

Conclusion Although patients with ypT1 rectal cancer have a non-negligible risk for nodal metastasis, oncologic outcomes of local excision following nCRT seem to be comparable to radical surgery. ACT could not effectively improve prognosis in patients with ypT1 tumors, except for those younger than 50 years of age.

Keywords ypT1 rectal cancer · Local excision · Adjuvant chemotherapy · Survival outcome · SEER

Introduction

Colorectal cancer (CRC) is one of the most common fatal malignancies worldwide, with approximately one-third of these cases originating from the rectum [1]. Despite steady decline in the overall incidence of CRC in Western countries during the past three decades, the incidence of rectal cancer in younger adults has been exponentially increasing [2, 3]. Notably, the determination of an individual treatment strategy for patients with rectal cancer is a complex and multifaceted process. According to the National Comprehensive Cancer Network (NCCN) guideline, the current standard therapy for locally advanced rectal cancer (LARC) includes neoadjuvant chemoradiotherapy (nCRT), surgery, and adjuvant chemotherapy (ACT) [4]. nCRT was recommended with the goal of tumor downstaging, increasing organ preservation rate and decreasing locoregional relapse [5]. In the German CAO/ARO/AIO-94 trial, approximately 6% of patients with LARC were reported to downstage to the ypT1 stage after receiving nCRT, which maybe higher in the future because of the widespread promotion of total neoadjuvant therapy (TNT) [6, 7].

The presence of lymph node (LN) metastasis in rectal cancer portends a poor prognosis, which has been used to guide local and systemic treatment decisions. The rarity of ypT1 rectal cancer poses challenges in determining the risk of regional nodal metastasis and identifying optimal

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treatment strategies, which still remain inconclusive and controversial. For pT1 rectal cancer with low risk of LN metastasis, local excision is the preferred minimally invasive procedure, owing to a similar long-term survival but higher organ preservation rate compared with conventional radical surgery [4, 8]. However, these advantages from the local excision remain dubious for patients with ypT1 rectal cancer. Small retrospective studies included patients with ypT0-1 rectal cancer pointed out that local excision could yield similar oncologic outcomes compared with the total mesorectal excision, but a lower postoperative morbidity and better anal sphincter function [9, 10]. However, some investigators recommended against local excision for patients with ypT1 rectal cancer because of relatively high rates of LN metastasis and local recurrence [11]. Furthermore, the role of ACT for patients with ypT1 rectal cancer also continues to be controversial. The application of ACT is supported by the accumulating evidence from several landmark studies focused on colon cancer. However, up to now, all of completed randomized controlled trials (RCTs) failed to demonstrate any statistical efficacy of fluorouracil-based ACT in LARC after neoadjuvant chemoradiation and surgery [12–14]. Consequently, the clinical guidelines offer discordant recommendations for the postoperative treatment of LARC patients who respond well to nRCT [15]. Given the favorable therapeutic effects with standard nRCT among patients with ypT1 disease, there is insufficient evidence to support the routine use of ACT, even in the node-positive patients.

Here, we designed this first real-world study using a large national database to explore the risk of LN metastasis and the feasibility of local excision in patients with ypT1 rectal cancer after nCRT. Beyond that, particular attention was also paid to exploring the precise role of ACT in ypT1 rectal cancer.

Materials and methods

Data source and patient selection

The Surveillance, Epidemiology and End Results (SEER) program, a population-based cancer registry, is sponsored by the National Cancer Institute and aggregates cancer incidence and survival clinical data from 18 registries covering approximately 34.6% of the US population [16]. In this retrospective study, data on patients diagnosed with ypT1 rectal cancer after nCRT from 2004 to 2018 were obtained from the SEER 18 Registries using the SEER*Stat software (version 8.4.0). The selection criteria of eligible patients were set as follows: (1) the International Classification of Disease for Oncology, Third Edition code, ICD-O-3, topography code: C209; (2) ICD-O-3 histological type/behavior code:

9140/3, 9480/3,9490/3; (3) Rx Summary-Surgery/Radiation Sequence code: Radiation before surgery; and (4) all patients were restaged and ypT1 stage was defined according to the 8th American Joint Committee on Cancer (AJCC) TNM staging system. Patients with distant metastasis and those with unknown surgery status or TNM stage were excluded from this study. For each eligible patient, information pertaining to age at diagnosis, preoperative carcinoembryonic antigen (CEA) level, surgical procedures, LN harvest, LN metastasis, as well as ACT were determined. According to the surgical procedure codes, patients were classified into two treatment groups: underwent local excision only (local excision group, SEER site-specific surgery codes: 10–29) and underwent proctectomy plus regional LN dissection (extended resection group, SEER site-specific surgery codes: 30–80).

In addition, between 2010 and 2022, we enrolled another 91 consecutive ypT1 patients underwent nCRT followed by radical resection from the Zhejiang Cancer Hospital as the ZJCH cohort. For the adequate LN harvest, we focused on participants underwent extended resection in both SEER and ZJCH cohorts to facilitate further analyses of the frequency of LN metastasis.

Statistical analysis

Baseline demographics and clinical characteristics between nodal positive and nodal negative groups were described as percentages for categorical variables and compared with the Pearson chi-square test or Fisher's exact test. A binomial logistic regression model was fitted to test the categorical associations between pathological LN metastasis and age at diagnosis, race, gender, year of diagnosis, number of LN examined, clinical N stage, and perineural invasion. Cancer-specific survival (CSS) and Overall survival (OS) were calculated from the date of diagnosis to the date of death from rectal cancer and any cause, respectively. Relapse-free survival (RFS) was calculated from the date of surgery to the date of recurrence or last follow-up. Survival outcomes were evaluated using the Kaplan–Meier method with the log-rank test for univariate comparisons. To improve the accuracy of our results, patients with unknown survival status and those suffering from at least two malignant tumors were excluded from survival analysis. After checking the proportional hazards assumption, hazard ratios (HR) and 95% CIs were estimated using multivariate-adjusted Cox proportional hazards regression model. To minimize a treatment selection bias in the SEER cohort, propensity score matching (PSM) was performed using a 1:1 matching protocol with a nearest neighbor-matching algorithm and a caliper of 0.01. All statistical analysis was performed using SPSS statistical software version 22.0 (SPSS Inc., IBM Corporation, Chicago,

IL). A two-tailed *P* value < 0.05 was considered statistically significant for all analyses.

Results

Patient characteristics in ypT1 rectal cancer after nCRT stratified by LN status

We identified 1303 patients with ypT1 rectal cancer who underwent nCRT followed by extended resection, 1212 patients from the SEER database (SEER cohort) and 91 patients from the Zhejiang Cancer Hospital (ZJCH cohort). Demographic and clinicopathological characteristics of the participants stratified by LN status are summarized in Table 1. Regional LN metastasis was observed in 257 patients (20.7%) in the SEER cohort and 15 patients (16.4%) in the ZJCH cohort, respectively. In the SEER cohort, a close correlation was found between age and LN metastasis ($P < 0.001$). Compared with patients ≥ 70 years, the rate of LN metastasis was twofold higher in patients younger than 50 years (12.8% vs 26.1%). The proportions of nodal metastasis gradually increased along the years of diagnosis, from 15.4 (2004–2008) to 28.5% (2014–2018) ($P < 0.001$). LN harvest and perineural invasion were astonishingly connected with LN metastasis (both $P < 0.001$). There was no association between preoperative CEA level and LN metastasis. The agreement of the clinical diagnosis with pathology were 43.4% and 66.7% for LN metastasis in the SEER and ZJCH cohorts, respectively. Patients with pathologically positive nodes in both cohorts were more likely to receive ACT, especially in the ZJCH cohort (93.3% vs 36.8% in the SEER cohort) (Table 1).

Preoperative predictors and prognostic value of LN metastasis in ypT1 rectal cancer

In the SEER cohort, a higher risk of pathologically confirmed LN involvement was associated with age at diagnosis, numbers of retrieved LNs, clinical LN metastasis, and perineural invasion status instead of gender, race/ethnicity, or the year of diagnosis (Table 2). The odds of LN metastasis in patients older than 70 years were 0.43 times lower than the odds in patients younger than 50 (odds ratio (OR) 0.43, 95% CI 0.26–0.73, $P < 0.001$). Patients with 12 or more LNs retrieved (OR 1.95, 95% CI 1.38–2.75, $P < 0.001$) and perineural invasion (OR 4.58, 95% CI 1.00–20.89, $P = 0.050$) were more likely to have regional LN involvement. Consistent with finding from the SEER cohort, clinical LN metastasis remain significant preoperative predictors of pathological LN metastasis in the ZJCH cohort (OR 8.80, 95% CI 2.37–32.61, $P = 0.001$). One hundred and ninety-three deaths were caused by ypT1 rectal cancer in the SEER

cohort, and the 10-year CSS and OS rates were 77.5% and 63.5%, respectively. LN metastasis increased the risk of cancer-specific mortality (HR 1.86, 95% CI 1.32–2.62, $P < 0.001$, Fig. 1A) and all-cause mortality (HR 1.35, 95% CI 1.02–1.81, $P = 0.039$, Fig. 1B). During follow-up, 12 of the 91 patients (13.2%) experienced local recurrence or distant metastasis in the ZJCH cohort. Among 78 patients, all 8 deaths were related to tumor progression and the cumulative 10-year CSS rate was 80.2%. LN metastasis appeared to be associated with poor CSS (HR 4.38, 95% CI 0.91–21.04, $P = 0.065$, Fig. 1C) and RFS (HR 4.67, 95% CI 1.27–17.12, $P = 0.020$, Fig. 1D) in patients with ypT1 rectal cancer following nCRT.

Extended resection versus local excision for ypT1 rectal cancer

In the SEER cohort, we identified another 62 patients with ypT1 rectal cancer underwent nCRT followed by local excision from 2004 to 2018. After PSM, a total of 120 patients (60 patients in each group) were analyzed and the baseline characteristics were well-balanced between the local excision and extended resection groups (Supplemental Table 2). For multivariable survival analysis, additional LN dissection was not significantly associated with favorable CSS (HR 0.81, 95% CI 0.35–2.20, $P = 0.785$, Fig. 2A) or OS (HR 0.81, 95% CI 0.48–1.39, $P = 0.450$, Fig. 2B).

The role of ACT in patients with ypT1 rectal cancer after nCRT

After nCRT with subsequent regional lymphadenectomy, 209 patients (17.2%) in the SEER cohort and 67 patients (73.6%) in the ZJCH cohort received ACT (Table 1). However, for multivariable Cox regression analysis in the SEER cohort, ACT did not provide apparent survival benefit in patients with ypT1 rectal cancer (CSS: HR 0.99, 95% CI 0.55–1.50, $P = 0.746$; OS: HR 0.95, 95% CI 0.68–1.34, $P = 0.784$, Supplemental Table 1). PSM in ypT1 rectal cancer with and without ACT resulted in the selection of 187 matched pairs of patients. Supplemental Table 3 summarizes the baseline characteristics of the entire unmatched and propensity score-matched cohorts. Regrettably, as shown in Fig. 3, ACT was not associated with additional survival benefit after performing PSM in terms of CSS (HR 0.77, 95% CI 0.47–1.26, $P = 0.304$) and OS (HR 0.78, 95% CI 0.51–1.18, $P = 0.231$). Subgroup analysis evaluated gender, CEA level, and number of LN examined without revealing any good evidence of improved survival in any subgroup. Of note, no related survival benefit was observed for either node-positive or node-negative patients (Supplemental Figs. 1 and 2). However, for patients younger than 50 years, ACT was shown to be significant associated with improved CSS (HR

Table 1 Clinicopathologic characteristics of patients with ypT1 rectal cancer after neoadjuvant chemoradiotherapy stratified by LN status

Variable	SEER cohort ($n=1212$)			ZJCH cohort ($n=91$)		
	LN positive (%)	LN negative (%)	$P^{\dagger}$	LN positive (%)	LN negative (%)	$P^{\dagger}$
Total patients	251 (20.7)	961 (79.3)		15 (16.4)	76 (83.6)	
Age at diagnose (years)			<0.001			$0.672^{\ddagger}$
<50	58 (23.1)	164 (17.1)		4 (26.7)	13 (13.1)	
50–69	150 (59.8)	505 (52.5)		9 (60.0)	49 (64.5)	
≥70	43 (17.1)	292 (30.4)		2 (13.3)	14 (18.4)	
Gender			0.043			0.260
Male	147 (58.6)	629 (65.5)		8 (53.3)	52 (68.4)	
Female	104 (41.4)	332 (34.5)		7 (46.7)	24 (31.6)	
Race			$0.019^{\ddagger}$	NA		
White	202 (80.5)	798 (83.0)				
Black	21 (8.4)	79 (8.2)				
Asian/PI/AI	25 (10.0)	84 (8.7)				
Unknown	3 (1.2)	0 (0.0)				
Year of diagnosis			<0.001	NA		
2004–2008	88 (35.1)	484 (50.4)				
2009–2013	100 (39.8)	319 (33.2)				
2014–2018	63 (25.1)	158 (16.4)				
Grade			0.873			$0.139^{\ddagger}$
Well/moderately differentiated	183 (72.9)	712 (74.1)		9 (60.0)	55 (72.4)	
Poorly differentiated/undifferentiated	22 (8.8)	75 (7.8)		3 (20.0)	3 (3.9)	
Unknown	46 (18.3)	174 (18.1)		3 (20.0)	18 (23.7)	
Histologic type			$0.1780^{\ddagger}$			$0.083^{\ddagger}$
Adenocarcinoma	237 (94.4)	932 (97.0)		12 (80.0)	72 (94.7)	
Mucinous adenocarcinoma	11 (4.4)	22 (2.3)		3 (20.0)	4 (5.3)	
Signet ring cell carcinoma	3 (1.2)	7 (0.7)		-	-	
CEA level			0.321			$0.990^{\ddagger}$
Normal	106 (42.2)	356 (37.0)		14 (93.3)	71 (93.4)	
Elevated	46 (18.3)	194 (20.2)		1 (6.7)	5 (6.6)	
Borderline/unknown	99 (39.4)	411 (42.8)		-	-	
No. of LN examined			$<0.001^{\ddagger}$			0.744
LN <12	104 (41.4)	605 (63)		8 (53.3)	42 (55.3)	
LN ≥12	144 (57.4)	342 (35.6)		7 (46.7)	34 (44.7)	
Unknown	3 (1.2)	14 (1.5)		-	-	
Clinical LN metastasis			<0.001			<0.001
Negative	43 (17.1)	465 (48.4)		5 (33.3)	61 (80.3)	
Positive	109 (43.4)	40 (4.2)		10 (66.7)	15 (19.7)	
Unknown	99 (39.4)	456 (47.5)		-	-	
Perineural invasion			<0.001	NA		
No	107 (42.6)	296 (30.8)				
Yes	6 (2.4)	5 (0.5)				
Unknown	138 (55.0)	660 (68.7)				
Adjuvant chemotherapy			<0.001			$0.035^{\ddagger}$
No	132 (52.6)	608 (63.3)		1 (6.7)	23 (30.2)	
Yes	77 (30.7)	132 (13.7)		14 (93.3)	53 (69.7)	
Unknown	42 (16.7)	221 (23.0)		-	-	

LN lymph node, *PI* Pacific Islander, *AI* American Indian, *NA* not available, *CEA* carcinoembryonic antigen

†Pearson chi-square test

‡Fisher's exact test

Table 2 Multivariable logistic regression analysis of potential factors associated with LN metastasis in patients with ypT1 rectal cancer after neoadjuvant chemoradiotherapy

Variable	SEER cohort ($n=1212$)		ZJCH cohort ($n=91$)	
	OR (95% CI)	**P**	OR (95% CI)	**P**
Age at diagnose (years)				
< 50	1 (reference)		1 (reference)	
50–69	0.89 (0.58–1.34)	0.565	0.66 (0.14–3.13)	0.602
≥ 70	0.43 (0.26–0.72)	0.001	0.54 (0.07–4.28)	0.557
Gender				
Male	1 (reference)		1 (reference)	
Female	1.20 (0.85–1.68)	0.299	1.55 (0.42–5.64)	0.509
Race			NA	
White	1 (reference)			
Black	0.90 (0.49–1.64)	0.731		
Asian/PI/AI	1.25 (0.73–2.16)	0.414		
Year of diagnosis			NA	
2004–2008	1 (reference)			
2009–2013	1.55 (0.90–2.66)	0.117		
2014–2018	1.48 (0.81–2.69)	0.201		
CEA level				
Normal	1 (reference)		1 (reference)	
Elevated	0.77 (0.48–1.22)	0.263	0.65 (0.05–7.74)	0.731
No. of LN examined				
LN < 12	1 (reference)		1 (reference)	
LN ≥ 12	1.95 (1.38–2.75)	< 0.001	1.22 (0.33–4.52)	0.770
Clinical LN metastasis				
Negative	1 (reference)		1 (reference)	
Positive	28.10 (17.11–46.17)	< 0.001	8.80 (2.37–32.61)	0.001
Perineural invasion			NA	
No	1 (reference)			
Yes	4.58 (1.00–20.89)	0.050		

LN lymph node, *OR* odds ratio, *CI* confidence interval, *PI* Pacific Islander, *AI* American Indian, *NA* not available, *CEA* carcinoembryonic antigen

0.25, 95% CI 0.07–0.89, $P=0.033$, Supplemental Fig. 1) and OS (HR 0.30, 95% CI 0.10–0.84, $P=0.022$, Supplemental Fig. 2).

Discussion

Currently, nCRT is the standard therapy for patients with LARC to downstage disease and reduce locoregional recurrence. Pathologic downstaging to ypT1 stage after nCRT is relatively uncommon, which means a favorable response to preoperative therapy. Given its relative rarity and the lack of prospective randomized trials, the optimal sequential treatment strategies of ypT1 patients have not been established. Thus, we designed this first and largest population-based study with long-term follow-up to shed light on the therapeutic value of local excision and ACT in patients with ypT1 rectal cancer after nCRT.

Despite patients with ypT1 rectal cancer are considered to have a good therapeutic response to nCRT, the risk of regional LN involvement cannot be ignored and approximately 12.0–20.0% of these patients presented with nodal metastasis after LN sampling [17–19]. In our study, the pathologic node-positive rates were 20.7% in the SEER cohort and 16.4% in the ZJCH cohort, respectively. Further, multivariate Cox regression analysis demonstrated that LN involvement was an independent negative prognostic factor in ypT1 rectal cancer, associated with poor CSS (HR 1.86, 95% CI 1.32–2.62, $P<0.001$) and OS (HR 1.35, 95% CI 1.02–1.81, $P=0.039$), in tandem with previous findings from a meta-analysis [18]. The optimal surgical approach for patients with ypT1 rectal cancer is still controversial and the role of local excision among these individuals who respond well to nCRT has not been clearly elucidated. Previously, several small retrospective studies demonstrated that local excision seems to offer a better evacuation and continence function after surgery and comparable oncological outcomes
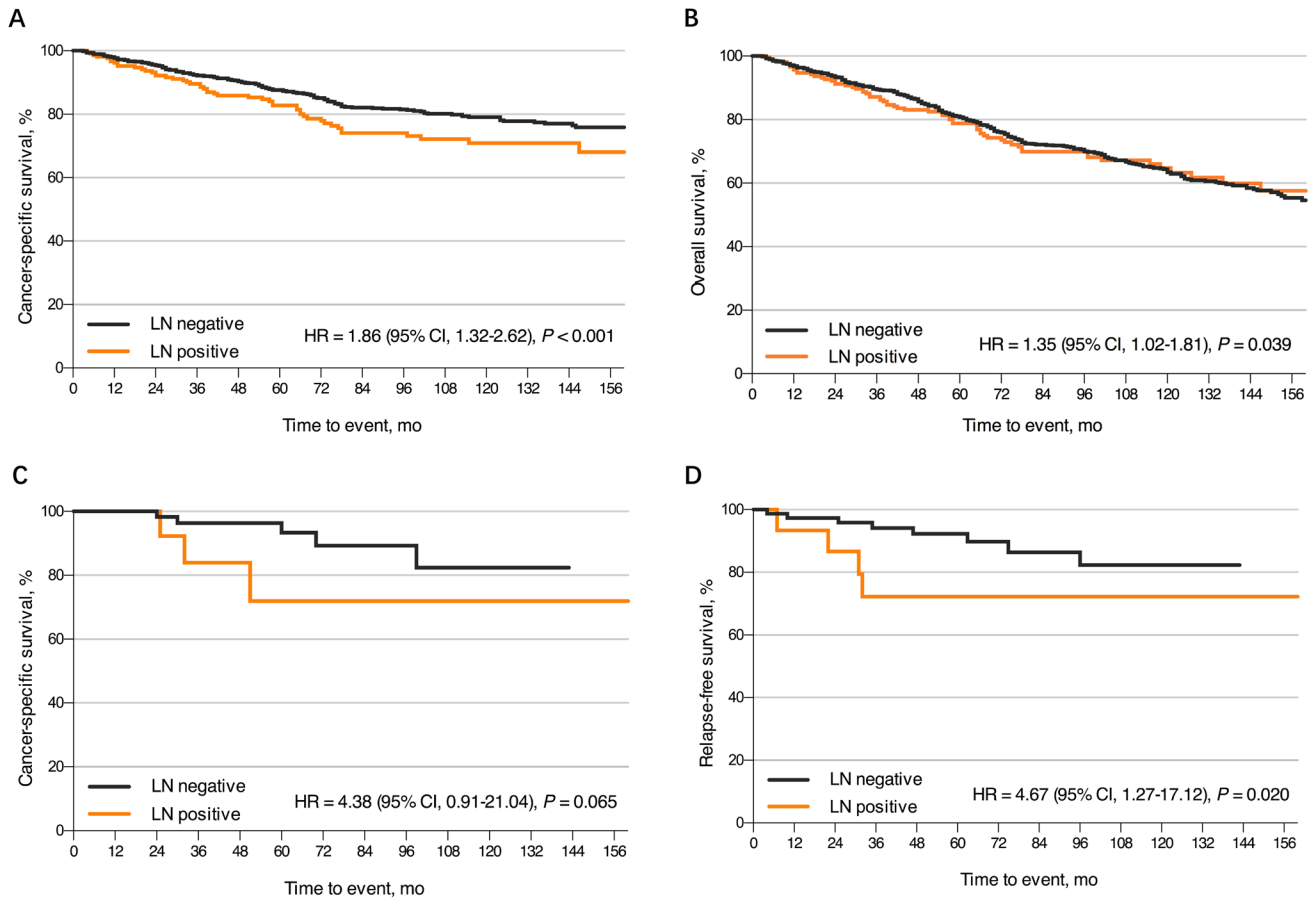
Fig. 1 Kaplan–Meier survival curves for patients with ypT1 rectal cancer after nCRT stratified by LN status. **A** CSS in the SEER cohort. **B** OS in the SEER cohort. **C** CSS in the ZJCH cohort. **D** RFS in the ZJCH cohort. nCRT, neoadjuvant chemoradiotherapy; LN, lymph node; CSS, cancer-specific survival; OS, overall survival; RFS, relapse-free survival
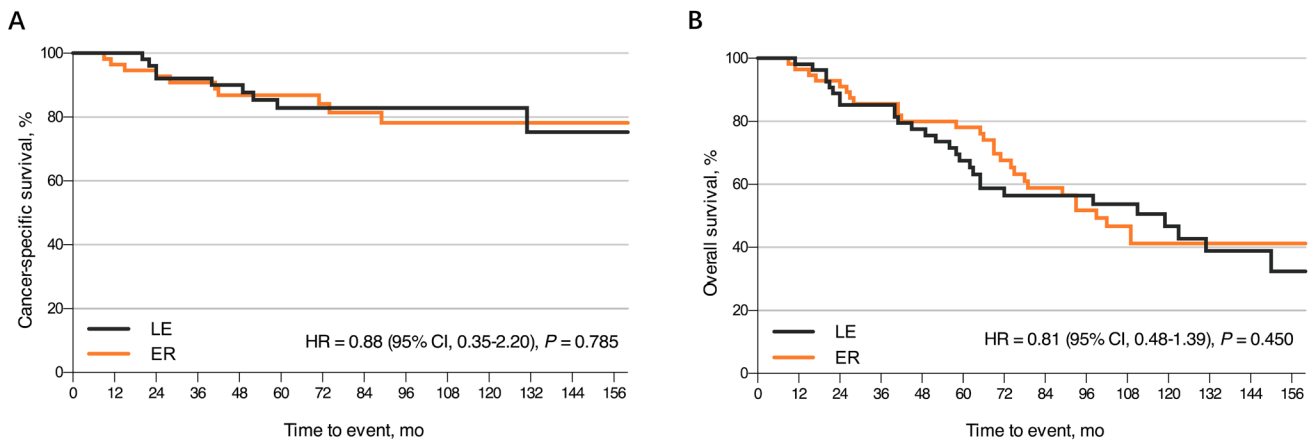

Fig. 2 Kaplan–Meier survival curves for patients with ypT1 rectal cancer after nCRT according to the surgical approaches. **A** CSS comparison between ER and LE. **B** OS comparison between ER and LE. nCRT, neoadjuvant chemoradiotherapy; CSS, cancer-specific survival; ER, extended resection; LE, local excision; OS, overall survival
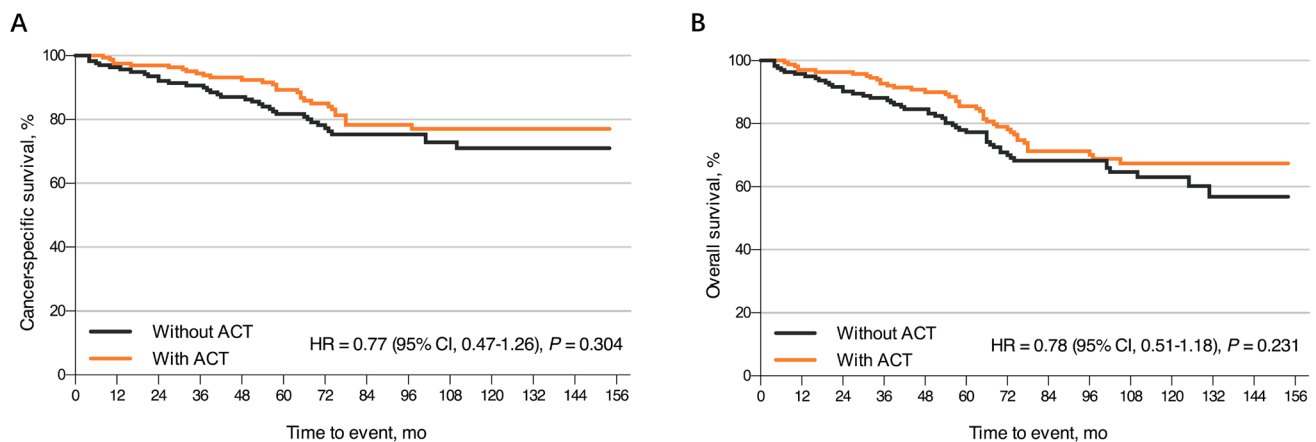
Fig. 3 Kaplan–Meier survival curves for ypT1 rectal cancer patients with or without ACT. **A** CSS comparison between the ACT and observation groups. **B** OS comparison between the ACT and observa-tion groups. ACT, adjuvant chemotherapy; CSS, cancer-specific sur-vival; OS, overall survival

for ypT0-1 rectal cancer after nCRT [20, 21]. However, Hal-lam et al. [22] reported the rates of local recurrence and median disease-free survival for patients with ypT1 or higher tumors were 21.9% and 68.0%. They emphasized that local excision after nRCT could be regarded as a cura-tive treatment only when pathological complete response was confirmed. In our study, radical surgery was still the mainstream treatment for ypT1 rectal cancer according to the NCCN guideline. However, consistent with previous findings [20, 21], additional regional LN dissection was not found to improve oncologic outcomes after a longer period of follow-up (CSS: HR 0.88, 95% CI 0.35–2.20, $P = 0.785$; OS: HR 0.81, 95% CI 0.48–1.39, $P = 0.450$). Compared to radical surgery, local excision seems to be a promising minimally invasive approach with a lower incidence of post-operative complications and better anal sphincter function [20, 21]. However, given the non-negligible propensity of LN metastasis, the recommendation of an organ-sparing approach by local excision for ypT1 rectal cancer may still require some caution. A strict patient selection criteria and close follow-up is needed to minimize the risk of recurrence and metastasis, which posed by a non-radical surgery. The clinicopathological predictors of residual nodal disease in ypT1 rectal cancer such as age, the distance of the tumor margin to the anal verge, tumor grade, residual tumor diam-eter, and clinical LN status, should to be taken into account when formulating a surgical decision-making [20, 23, 24].

In fact, the adjuvant treatment of LARC still refer to the regimens of ACT for colon cancer, which are supported by several landmark clinical trials. The clinical significance of ACT following nCRT and surgery in patients with LARC remains controversial and the clinical guidelines offer dis-cordant recommendations of adjuvant treatment for patients with a good therapeutic response to nRCT [15]. In our study,

we found that ACT did not appear to provide survival ben-efit in ypT1 rectal cancer, regardless of whether LN status, grade, number of LN examined, and CEA level varied. For node-negative patients, most of the previous studies were performed with a small sample size and indicated that ACT seems not to be required for patients with yp stage I rectal cancer downstaged by nCRT, which was consistent with our study [25, 26]. More high-level evidence is required to validate this finding, and a RCT of ACT for patients with pathologic complete response or yp stage I is currently ongo-ing [27]. Also, it is worth noting that no survival benefit of ACT was found for node-positive patients in our population-based propensity score analysis, which seems to be different from the expectation. Indeed, there is insufficient evidence to support the routine use of ACT for yp stage III rectal cancer. Up to now, it is disappointing that all of randomized phase III trials (CHRONICLE, I-CNR-RT, PROCTOR-SCRIPT) aimed at demonstrating the effects of fluorouracil-based ACT following nRCT and surgery in LARC have failed [12–14]. A meta-analysis of RCTs similarly reported that additional ACT was not associated with a survival benefit in yp stage III rectal cancer [28]. To our knowledge, this is the first study to perform a subgroup analysis by age in the SEER cohort. A key finding in our study was that patients younger than 50 years seemed to benefit from ACT, whereas those older than 50 years did not. The possible explanation of this difference in efficacy is the heterogeneity of poten-tial for tolerating chemotherapy-related toxicities. For elder patients, the survival benefit from ACT might be counter-acted by chemotherapy-induced adverse events. Recently, for patients with LARC, NCCN guidelines have shifted the attention from adjuvant treatment to total neoadjuvant treat-ment (TNT) [4]. ACT does not significantly improve long-term survival but increased risk of chemotherapy-related

toxicities. The RAPIDO and STELLAR trials support that TNT was associated with a significant improvement in pathologic complete response rate, disease-free survival, and OS as opposed to ACT [29, 30]. Therefore, the TNT strategy can be considered as an alternative to standard treatment in LARC and may facilitate "watch-and-wait" strategy aimed at organ preservation.

Although this study had a large sample size of consecutive patients and long follow-up, there are several limitations that warrant consideration because of its retrospective nature and intrinsic limitations in the SEER database. Firstly, pathological parameters such as tumor budding, depth of submucosal invasion, lymphovascular, and vascular invasions, have been identified as possible risk factors for LN metastasis. Unfortunately, these pathological characteristics have not been publicly released by the SEER cancer registries so far. Secondly, our analyses of ypT1 rectal cancer with local excision may have been underpowered due to insufficient sample size. Moreover, we were unable to evaluate the therapeutic value of local excision combined with ACT, which appears to show a similar efficacy compared with radical surgery in high-risk pT1 rectal cancer [31]. Thirdly, the SEER database does not provide detailed information regarding baseline comorbidities, postoperative complications, specific ACT regimens, or toxicity. Therefore, we are unable to determine if these factors might impact our results. Finally, The SEER dataset lacks data on recurrences, meaning that we could not evaluate the impact of different therapeutic strategies on local recurrence, distant metastasis, or RFS.

Conclusions

In conclusion, our population-based study yielded an unexpectedly high rate of LN metastasis in patients with ypT1 rectal cancer after nCRT. However, regional LN dissection does not seem to confer additional survival benefit. Local excision following nCRT may provide comparable long-term oncologic outcomes to radical surgery. Moreover, the application of additional ACT did not effectively improve the prognosis in patients with ypT1 rectal cancer, except for those younger than 50 years of age. Further multicenter randomized clinical trials are warranted to evaluate the true role of local excision and ACT in the management of ypT1 rectal cancer after nCRT.

Authors contributions Conceptualization: Yibo Cai, Yuping Zhu, Zhuo Liu; Methodology: Yibo Cai, Lai Jiang, Haixing Ju, Zhuo Liu; Formal analysis: Yibo Cai, Lai Jiang, Zhuo Li; Data curation: Yibo Cai, Lai Jiang; Investigation: Haixing Ju, Yuping Zhu, Zhuo Liu; Writing—original draft preparation: Yibo Cai, Zhuo Liu; Writing—review and editing: Haixing Ju,Yuping Zhu, Zhuo Liu; Supervision: Haixing Ju,Yuping Zhu, Zhuo Liu.

Declarations

Competing interests The authors declare no competing interests.

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