의 학 석 사 학 위 논 문

ypT0-1기 직장암 환자 치료에서 국소 절제와 광범위 절제 간 임상병리학적 인자 및 종양학적 결과 비교분석

A comparison between local excision and radical resection for the treatment of rectal cancer in ypT0-1 patients: analysis of clinicopathological factors and survival rate

울산대학교 대학원

의학과

오수영

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지 도 교 수 박 인 자

이 논문을 의학 석사학위 논문으로 제출함

2021년 2월

울산대학교 대학원

의학과

오수영

오수영의 의학 석사학위 논문을 인준함

심사위원 박진홍 인

심사위원 박인자 인

심사위원 김찬욱 인

울산대학교 대학원

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국문 초록

수술 전 항암 방사선 치료의 도입은 직장암의 국소 재발율 감소와 생존율 향상을 가져왔다. 그리고 수술 전 항암 방사선 치료에 좋은 반응을 보이는 경우 예후가 좋다는 것이 밝혀지면서 완전 관해를 보인 환자에서 직장을 보존하는 방법들이 고안되기 시작하였다. 광범위한 절제로 인해 발생할 수 있는 합병증을 피하면서도 종양학적으로는 광범위 절제와 비슷한 결과를 보여 국소 절제는 많은 관심을 얻고 있다.

본 연구에서는 2005년부터 2014년 동안 직장암으로 진단되어 수술 전 항암 방사선 치료를 받은 후 광범위 절제(Radical resection) 혹은 국소 절제(Local excision)를 시행 받고 ypT0-1 병기로 진단된 환자들이 포함되었다. 그 중 78명의 환자에서 국소 절제를 시행하였고 442명의 환자에서 광범위 절제를 시행하였다. 각 군에 대한 임상 병리학적 특징, 무재발 생존율(Recurrence free survival), 전체 생존율(Overall survival)을 분석하였다.

국소 절제를 시행 받은 군과 광범위 절제를 시행 받은 군 간 무재발 생존율 및 전체 생존율에서 통계적으로 유의미한 차이는 없었으며, 다기관 데이터를 이용한 무재발 생존율 분석에서도 유의미한 차이가 없었다. 광범위 절제를 시행한 군에서 시행한 하위 집단 분석에서는 림프절 양성율이 무재발 생존율과 전체 생존율 모두와 의미 있는 연관성을 보였다.

본 연구 결과 수술 전 항암 방사선 치료에 완전 관해를 보인 직장암에서 국소 절제의 시행은 타당한 치료가 될 수 있음을 확인할 수 있었다. 하지만 림프절 평가의 방법과 수술적 절제 후 치료적 중재에 대한 합의는 아직 부족하다. 본 연구를 비롯한 여러 연구결과에서 국소 절제가 광범위 절제와 비교할 만한 수준의 종양학적 치료 결과를 보였다. 때문에 수술을 시행하지 않고 지켜보는 방법 (Watch and wait)을 포함하여, 직장암 치료에 있어 장기를 보존하는 전략들(Organ preserving strategies)에 대한 치료 방법의 표준화가 필요하다. 또한 수술 전 평가 방법들의 정확도가 높아지고 있는 만큼 국소 절제의 치료 결과에 대한 연구들도 지속적으로 갱신되어야 할 것이다.

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Introduction

Preoperative chemoradiation therapy (PCRT) led to a new era of treatment in rectal cancer. While conventional surgery alone resulted in a high local recurrence rate leading to poor survival outcomes, randomized controlled trials emerged showing a significant reduction in local recurrence and improvement in overall survival (OS) in patients who underwent PCRT [1-3]. Especially in locally advanced rectal cancer, delivering chemoradiotherapy preoperatively was superior to delivering it postoperatively. Along with significant improvements in local control, patients show better compliance with the regimen when it is given before the major surgery, and the chance to preserve the anal sphincter is greatly increased in patients with low-lying tumors by downstaging the tumor instead of subjecting them to abdominoperineal resection. Irradiation seems to be more effective when tumor oxygenation is better before radical surgery [4], and preoperative treatment reduces the acute and long-term toxic effects of chemoradiation [5]. Therefore, PCRT followed by radical resection (RR) is currently the mainstay of treatment for locally advanced rectal cancer.

The response to PCRT varies from complete response to no response, and the degree of regression of the tumor is determined by the proportion of the lesion replaced by fibrous or fibro-inflammatory tissues [6, 7]. Chari et al. reported that patients with good response to PCRT or rectal cancer had better long-term outcomes than those with poor response [8, 9]. Further studies showed a higher 5-year disease-free rate and OS in the group with pathologic complete response (ypCR) [10, 11] and 5-year recurrence-free survival (RFS) and less distant metastasis rate, confirming a strong positive prognostic value of downgraded tumor after PCRT [6].The explanation is that the intrinsic radiosensitivity of tumors with good response to PCRT is indicative of a prognostically favorable tumor profile, meaning less tendency for local recurrence or distant metastasis.

Currently, RR of the rectum with total mesorectal excision is a standardized way to fully evaluate the final pathologic stage of rectal cancer, including profiling sufficient lymph nodes during staging. However, surgical resection of the rectum is associated with significant morbidity, both immediate and late. A considerable proportion of patients require permanent stoma and report sexual dysfunction and bowel and bladder dysfunction or low anterior syndrome, which affects long-term quality of life

[12-14]. Moreover, preoperative radiation therapy increases the rate of complications [15].

The higher complication rate of RR after PCRT led surgeons to consider organ preservation as an alternative strategy for patients with good PCRT response who can potentially avoid being exposed to postoperative risks, such as bleeding, anastomosis leakage, and pelvic nerve damage.

Favorable oncologic outcomes in patients with pCR raised interest in rectum-sparing strategies for patients with good responses to PCRT by suggesting local excision (LE) or a watch-and-wait (WW) approach [16-19]. As downstaging of the tumor to achieve clinical response or pathologic response is observed in 10% to 30% of patients [18, 20-22], these patients can be candidates for an organ-preserving strategy. Since favorable oncologic outcomes in patients with good response to PCRT have been reported, further studies [16, 23] comparing oncologic outcomes between transanal excision and RR in patients with good response to PCRT also reported no significant difference between the two excisional strategies. Similar findings were observed in studies conducted in patients with early [24, 25] and locally advanced [16, 26, 27] rectal cancer, especially in ypT0 tumors, showing comparable local recurrence rates, disease-free survival rates, pelvic RFS, and OS.

In an oncologically negative perspective regarding LE, however, despite gaining T stage, limited evaluation of mesorectal lymph nodes still precludes definitive tumor staging. Moreover, in the case of recurrence after LE, local recurrence in the previously resected site is difficult to manage, and salvage surgery after recurrence often shows R1 resection [28, 29].

However appealing LE is as an alternative organ-sparing strategy to surgeons, there is no standardization of patient selection, surgical methods, and follow-up protocol. Therefore, some studies point out that LE is performed under significant variability, neglecting the standard total mesorectal excision (TME) procedure proven to be oncologically safe [30]. In addition, although continuously developing, clinical staging to confirm the indication of LE using imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), endorectal ultrasonography (EUS), and positron emission tomography (PET), have limited use of evaluation, especially in tissues with radiation-induced fibrosis, and it is particularly worse in accuracy of nodal staging in the setting of T1 and T2 cancers [31-34]. The risk of residual positive lymph nodes in the irradiated mesorectum

is reported to vary between 0% and 17% even with pCR of the primary tumor, which leaves the need for evaluation of mesorectal lymph nodes [35].

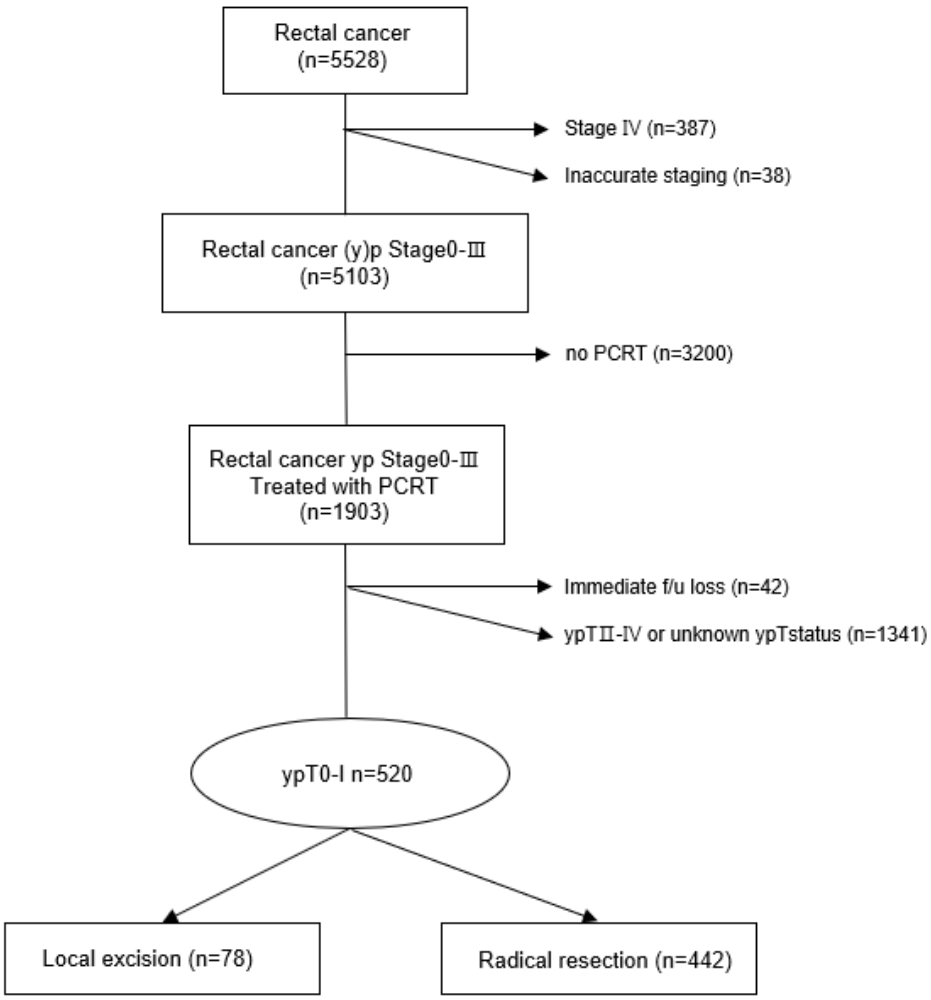
No certain surgical principle for LE in patients with good response after PCRT has been established. Therefore, this study aimed to compare the oncologic outcome between LE and RR in ypT0-1 patients and provide a valid surgery principle by analyzing the prognostic factors of the strategies.

1. Methods

1.1 Patients

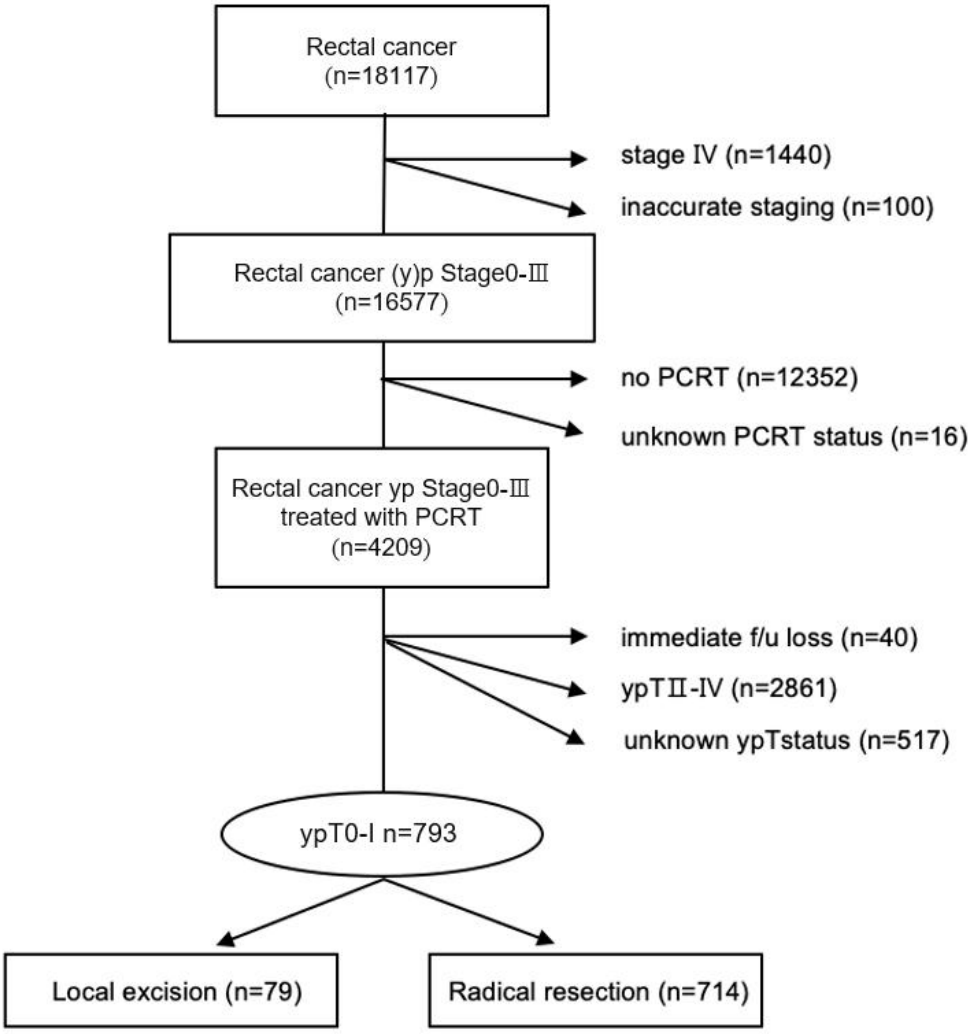
Patients with primary rectal cancer diagnosed as ypT0-1 after being treated with PCRT followed by either RR or LE at Asan Medical Center between 2005 and 2014 were included in this study. Among the 5528 patients diagnosed with rectal cancer regardless of tumor size, those diagnosed with clinical stage 4 disease or with synchronous metastatic disease (n = 387) and those with inaccurate staging (n = 38) were excluded. Patients who did not undergo PCRT (n = 3200) were also excluded from the study. Although 1903 patients completed all cycles of PCRT, patients who were immediately lost to follow-up (n = 42) and patients diagnosed with ypT2-4 or with unknown ypT status (n = 1341) were excluded. A total of 520 patients were diagnosed with ypT0-1, and among the 520 patients, 442 patients received RR and 78 patients underwent LE (Figure 1).

Figure 1. ASAN cohort patient selection algorithm



For verification of the results, we used a multicenter cohort. For this, we identified patients with rectal cancer from the Colorectal Cancer Database of the Korean Society of Coloproctology from 2005 through 2012. In the multicenter cohort, 18117 patients were diagnosed with rectal cancer. A total of 1440 patients were diagnosed clinically as stage 4, and 100 patients with inaccurate staging were excluded. Patients with no PCRT treatment or unknown PCRT status were also excluded, and among ypT0-3 rectal cancer patients, 793 patients were diagnosed with ypT0-1. Finally, 714patients received RR and 79 patients underwent LE, and the data of these patients were analyzed to verify the outcomes (Figure 2).

Figure 2. Multicenter cohort patient selection algorithm



1.2 Treatment

Initial evaluation of the tumor included a complete history, physical examination, and laboratory tests, including serum carcinoembryonic antigen level assessment and colonoscopy with biopsy. T and N stages were assumed by rectal MRI and EUS. CT and 18F-fluorodeoxyglucose PET-CT were used to rule out distant metastases. The more advanced stage was chosen in the case of discrepancy between the work-up modalities.

Rectal cancers diagnosed with clinical T3 stage, T4 stage, and node-positive tumors that showed a threatened circumferential resection margin on MRI underwent PCRT. Tumors that seemed locally unresectable and patients who were medically inoperable were also candidates for PCRT. Patients with less advanced disease, however, were given PCRT for sphincter preservation in cases of low

rectal cancer and in case of the presence of severe medical comorbidities or were reluctant to undergo upfront surgery.

Patients received a total dose of 50.0–50.4 Gy radiotherapy five times a week for 5 weeks with 23 to 25 fractions of local irradiation to the pelvis, 1.8–2.0 Gy each, and a boost dose 4.0–5.4 Gy radiation to the primary tumor over 3 days. Concurrent chemotherapy consisted of either two cycles of an intravenous bolus injection of 5-fluorouracil (5-FU, 375 mg/m^2/day) and leucovorin (20 mg/m^2/day) (FL) for 3 days during the 1st and 5th week of radiotherapy or oral administration of capecitabine (825 mg/m^2) twice daily. Oxaliplatin was used as a combined regimen in some patients.

After completing 4–6 weeks of PCRT, all patients were reevaluated by physical examination, abdominopelvic CT, chest CT, rectal MRI, EUS (optional), and sigmoidoscopy. The response was determined based on the findings of rectal examination, sigmoidoscopy, and MRI. A 5-tier MRI tumor regression grading (mrTRG) system (mrTRG 1, complete regression [absence of tumor signal and barely visible treatment-related scar]; mrTRG 2, good regression [predominant low signal intensity fibrosis with no obvious residual tumor signal]; mrTRG 3, moderate regression [low signal intensity fibrosis predominates but there are obvious areas of intermediate signal intensity]; mrTRG 4, slight regression [little areas of low signal intensity fibrosis or mucin but mostly tumor]; and mrTRG 5, no regression [intermediate signal intensity, same appearances as the original tumor]) was used for post-PCRT response evaluation. Tumors were graded as complete response (CR) when lesions were noted only with the flat scar lesions without ulceration or nodularity in endoscopy.

Resection of the tumor was performed 6–8 weeks after completion of PCRT. Among patients with good response to PCRT for both T and N stages showing CR or near CR, the surgical method of LE or RR was determined by the surgeon and patients depending on factors such as age, medical condition, and socioeconomic circumstances. Patients were informed of the pros and cons of each procedure. Patients reluctant to form a temporary or permanent stoma were likely to choose LE, and surgeons offered LE to patients at elevated risk for longer general anesthesia and postoperative complications due to medical comorbidities. Radical surgical resection was performed according to TME. For LE, transanal local excision and transanal minimally invasive surgery and/or full-thickness excision was

done.

Tumor response was assessed by a pathologist specializing in colorectal malignancy pathology. A tumor regression grade system was used to determine the response of the primary tumor according to the proportion of tumor cells and fibrosis in resected specimens, as suggested by the Gastrointestinal Pathology Study Group of the Korean Society of Pathologists [36]. Pathologic staging after RR was determined according to the 7th American Joint Committee on Cancer Staging System. Patients with an indeterminate tumor regression grade or inability to confirm recurrence status were excluded from the study. Immediate salvage RR was strongly recommended to patients diagnosed with ≥ypT2 stage after LE. Patients with deep submucosa invasion, lymphovascular invasion, perineural invasion, tumor budding, and margin involvement were also recommended to undergo salvage operations.

All medically fit patients underwent adjuvant chemotherapy after RR with PCRT. Adjuvant chemotherapy consisted of four cycles of FL monthly or six cycles of capecitabine. Oxaliplatin regimens were delivered with discrete monitoring, attended by a physician.

1.3 Postoperative surveillance and recurrence

Patients in the LE group were followed up every 3 months for the first postoperative year and every 6 months thereafter. Physical examination with a digital rectal examination, checkup of laboratory test results, and sigmoidoscopy were done every 3 months for the first 1–2 years and every 6 months for the next 3–4 years. Full colonoscopy was performed every 2–3 years. CT scan of the abdominopelvic and chest regions was done every 6 months for 5 years. Those in the RR group underwent physical examination, laboratory tests, abdominopelvic and chest CT scans, and sigmoidoscopy every 6 months for 5 years, while a full colonoscopy was done every 2–3 years.

Clinical, radiologic, or endoscopic evidence of intraluminal tumor in contiguous areas to the primary resection site was defined as local regrowth—tumor within the mesorectum or rectal wall after excision was defined as local recurrence. Distant metastasis was defined as dissemination to the peritoneal surface or tumor presence in a distant organ.

1.4 Statistical analysis

Analyses of clinicopathologic characteristics of categorical variables were conducted using chi-square

test and t-test for continuous variables. The Kaplan-Meier method with the log-rank test was used to determine RFS and OS. RFS was measured from the day of resection to the date of the first identification of recurrence. Multivariable analysis with the Cox proportional hazards model was used to compare risk factors associated with RFS and OS. P-values of less than 0.05 were considered statistically significant, and all analyses were conducted using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA).

2. Results

2.1 Clinicopathologic characteristics

Clinicopathological features are shown in Table 1. Among the 520 patients, 78 patients underwent LE and 442 underwent RR. The mean age was 62.9 years in the LE group and 58.5 years in the RR group. For concurrent chemotherapeutic regimens during PCRT, FL was more frequently used in the LE group. In the LE and the RR groups, 26 (33.3%) and 196 (44.3%) patients, respectively, were treated with capecitabine, and 49 (62.8%) and 198 (44.8%) patients, respectively, with FL. Patients with stage 3 or 4 disease underwent more RR than LE; 55 (70.5%) patients were diagnosed with cT1-2 stage in the LE group, while 76 (17.2%) patients were diagnosed with cT1-2 stage in the RR group. Clinical lymph node metastasis was higher in the RR group than the LE group [384 (86.9%) and 37 (47.4%), respectively].

The sphincter was preserved in 348 (78.7%) patients in the RR group. Patients who underwent LE had more ypT0 disease (69.2%) than those in the RR group (55.2%). Lymph nodes (LN) in RR after PCRT were pathologically negative in 409 (92.5%) patients and positive in 33 (7.5%) patients. More patients in the RR group underwent adjuvant chemotherapy (CTx) after surgery [LE group, 35 (44.9%) patients; RR group, 378 (85.5%) patients]. Among patients in the RR group with positive LN, 26 lymph nodes were excised, and 1.92 lymph nodes were malignancy positive among resected lymph nodes on average. Although not shown, lymphovascular invasion (LVI) was identified in four patients, and perineural invasion (PNI) in 28 patients. Circumferential margin (CRM) was negative in 349 patients, positive in one patient, and unidentified in 92 patients (data not shown). In the LE group, 45

patients had no LVI and no PNI, while 33 had unknown LVI and PNI status. CRM was positive in two patients, both in the deep resection margin.

Table 1. Clinicopathological characteristics of ASAN cohort

Characteristics	Local excision (n=78)	Radical resection (n=442)	P-value*
Sex (%)			0.557
Male	44 (56.4)	265 (60.0)	
Female	34 (34.6)	177 (40.0)	
Age, year, mean ± SD	62.9 ± 11.3	58.5 ± 10.2	0.001
Concurrent chemotherapeutic regimen (%)			0.02
Capecitabine	26 (33.3)	196 (44.3)	
FL	49 (62.8)	198 (44.8)	
Others	1 (1.3)	22 (5.0)	
unknown	2 (2.6)	26 (5.9)	
cT stage (%)			<0.001
1-2	55 (70.5)	76 (17.2)	
3-4	23 (29.5)	366 (82.8)	
cN stage (%)			<0.001
cN (-)	41 (52.6)	58 (13.1)	
cN (+)	37 (47.4)	384 (86.9)	
Operation			
TAE	61 (78.2)		
TAMIS	17 (21.8)		
LAR		73 (16.5)	
ULAR		269 (60.9)	
APR		94 (21.3)	
ISR		6 (1.3)	
Sphincter saving resection*		348 (78.7)	
ypT stage			
ypT0	54 (69.2)	307 (55.2)	
ypTis	16 (20.5)	103 (23.3)	
ypT1	8 (10.3)	32 (7.2)	
ypN stage*			
ypN(-)	N/A	409 (96.9)	

ypN(+)	N/A	22 (3.1)	
Adjuvant chemotherapy			<0.001
No	43 (55.1)	64 (14.5)	
Yes	35 (44.9)	378 (85.5)	
Follow-up duration (mo)	66.9 ± 28.7	71.7 ± 33.2	0.244

SD standard deviation, IV intravenous, FL 5-Fluorouracil and leucovorin, TAE transanal excision, TAMIS transanal minimally invasive surgery, LAR low anterior resection, ULAR ultra-low anterior resection, APR abdominoperineal resection, ISR intersphincteric resection

P-values were calculated using x^2 and t- test as appropriate, from non-missing data.

Values are presented as number (%) or mean ± standard deviation unless otherwise indicated.

*Only evaluated in the radical resection group

2.2 Oncologic outcomes: recurrence and survival

In the LE group, seven (8.9%) patients experienced recurrence, three (42.9%) showed local recurrence and four (57.1%) showed recurrence in distant LN (1 patient, 14.3%) and lung (3 patients, 42.9%). In the RR group, 43 (9.7%) patients experienced recurrence, 3 (7.0%) with local recurrence and 40 (93.0%) with distant recurrence. Single-organ distant metastasis was detected in 37 patients in the lung (20 patients, 46.5%), liver (8 patients, 18.6%), bone (4 patients, 9.3%), and distant LN (4 patients, 9.3%). Multiple organ metastasis was found in three patients: brain and lung (1 patient, 2.3%), distant LN and liver (1 patient, 2.3%), and distant LN and lung (1 patient, 2.3%) (Table 2). Recurrence was noted in LN, lung, liver, bone, brain, and ovary in the RR group. The recurrence-free period was 92.72 ± 45.37 months in the LE group and 72.48 ± 15.67 months in the RR group. Patients with recurrence in the LE group all underwent adjuvant CTx, and one patient underwent additional transanal excision.

Table 2. Recurrence site in ypT0-1 rectal cancer treated with preoperative chemoradiotherapy according to the surgical method

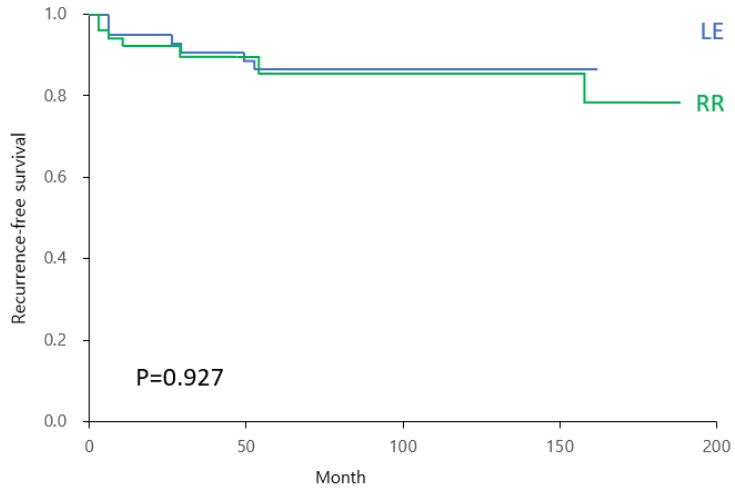
Recurrence site	Group		P value
	Local excision (%)	Radical resection (%)	
Local recurrence	3 (42.9)	3 (7.0)	0.029

Distant recurrence	4 (57.1)	40 (93.0)	
Total	7	43	
Single organ	7 (100.0)	40 (93.0)	
Multiple organ	0 (0.0)	3 (7.0)	0.630
Total	7	40	

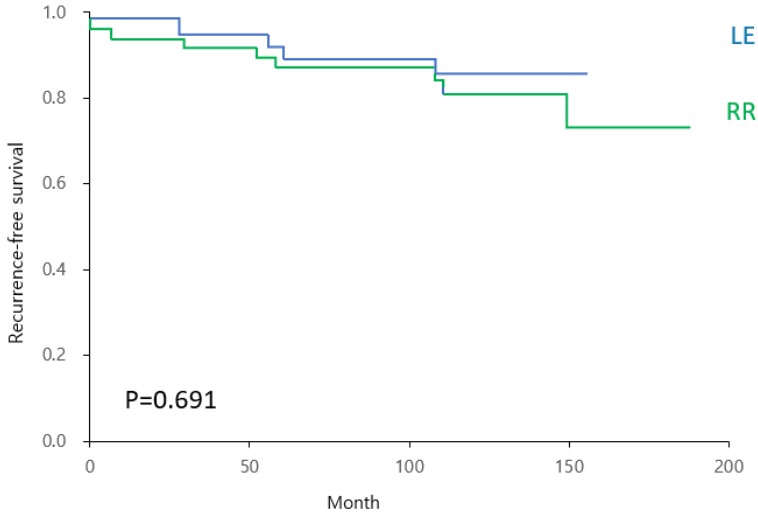
The p-values of each columns are analyzed by Fisher's exact test.

Oncologic outcomes between the two groups were not different. The 5-year RFS was higher in the RR group (94.7%) than in the LE group (98.0 %), but it was not statistically significant ($P = 0.927$). The 5-year OS was higher in the LE group (94.9%) than in the RR group (93.7%), but it was also was not statistically significant ($P = 0.691$) (Figure 3).

Figure 3. Oncologic outcomes according to surgical treatment of ypT0-1 rectal cancer after preoperative chemoradiotherapy. Recurrence-free survival (A) and overall survival (B). RR radical resection, LE local excision.



Recurrence-free survival (A)



Overall survival (B)

There were no factors associated with RFS in ypT0-1 cancer except for the cT stage before PCRT (Table 3).

Table 3. Factors associated with recurrence free survival in ypT0-1 rectal cancer treated with preoperative chemoradiotherapy in ASAN cohort

Variable	Hazard ratio	95% CI	*P*-value
Adjuvant CTx	1.231	0.536-2.827	0.624
ypT stage			0.672
ypT0	0.943	0.471-1.889	0.868
ypTis-1	0.523	0.125-2.183	0.374
cT stage	2.869	1.111-7.407	0.029*
cN stage	0.530	0.256-1.097	0.087
Concurrent CTx			0.616
Capecitabine,	0.769	0.422-1.401	0.390
FL	0.664	0.157-2.804	0.578
Others	0.295	0.341-0.046	0.295

Sex	1.189	0.671-2.109	0.553
Resection group	0.697	0.264-1.841	0.467
Local Excision	1		
Radical Resection			

CI, confidence interval; CTx, chemotherapy; FL, fluorouracil-leucovorin

*Statistically significant

When subgroup analysis was done in the RR group, LN metastasis was the only factor associated with RFS (Table 4).

Table 4. Factors associated with recurrence free survival in ypT0-1 rectal cancer treated radical resection after preoperative chemoradiotherapy in ASAN cohort

Variable	Hazard ratio	95% CI	*P*-value
Adjuvant CTx	0.796	0.233-2.723	0.716
ypT stage			0.776
ypT0	0.726	0.283-1.863	0.506
ypTis-1	0.778	0.178-3.396	0.738
cT stage	2.136	0.612-7.455	0.234
cN stage	0.711	0.291-1.733	0.453
Concurrent CTx			0.835
Capecitabine	0.760	0.363-1.559	0.466
FL	0.592	0.136-2.571	0.484
Others	0.000	0.000-7.672	0.971
Sex	1.269	0.633-2.545	0.501
Lymph node metastasis	4.444	1.974-10.006	<0.001
Lymphovascular invasion			0.840
Yes	1.990	0.202-19.631	0.556

Indeterminated	1.036	0.236-4.552	0.963
			1.0
I	0		0.995
	0		0.986

CI, confidence interval; CTx, chemotherapy; FL, fluorouracil-leucovorin

None of the factors showed a statistically significant association with OS (Table 5).

Table 5. Factors associated with overall survival in ypT0-1 rectal cancer treated with preoperative chemoradiotherapy in ASAN cohort

Variable	Hazard ratio	95% CI	*P*-value
Adjuvant CTx	0.614	0.316-1.195	0.151
ypT stage			0.569
ypT0	0.942	0.506-1.754	0.850
ypTis-1	0.462	0.110-1.928	0.289
cT stage	1.717	0.741-3.980	0.208
cN stage	1.124	0.507-2.494	0.774
ConcurrentCTx			0.741
Capecitabine	0.864	0.490-1.522	0.613
FL	0.348	0.047-2.564	0.300
Others	0.834	0.247-2.823	0.774
Sex	0.715	0.405-1.264	0.249
Resection Group	1.013	0.382-2.690	0.979
Local Excision	1		
Radical Resection			

CI, confidence interval; CTx, chemotherapy; FL, fluorouracil-leucovorin

However, in the subgroup analysis of RR, adjuvant CTx, LN metastasis, and age were significantly associated with OS (Table 6).

Table 6. Factors associated with overall survival in ypT0-1 rectal cancer treated radical resection after preoperative chemoradiotherapy in ASAN cohort

Variable	Hazard ratio	95% CI	P-value
Adjuvant CTx	0.404	0.177-0.922	0.031*
ypT stage			0.679
ypT(0	0.755	0.346-1.651	0.482
ypTis-1	0.623	0.141-2.753	0.532
cT stage	1.579	0.586-4.258	0.366
cN stage	1.219	0.460-3.233	0.690
Concurrent CTx			0.640
Capecitabine	0.730	0.366-1.453	0.370
FL	0.391	0.052-2.961	0.363
Others	0.617	0.162-2.352	0.479
Sex	0.744	0.389-1.424	0.373
Lymph node metastasis	4.067	1.891-8.747	<0.00*
Lymphovascular invasion			0.804
Yes	1.624	0.185-14.248	0.662
Indeterminated	1.364	0.403-4.621	0.618
			1.0
	0		0.995
	0		0.977
Age	1.050	1.016-1.086	0.004*

CI, confidence interval; CTx, chemotherapy; FL, fluorouracil-leucovorin

*Statistically significant

2.3 Oncologic outcomes verified in the multicenter database

The clinicopathologic features of the multicenter cohort are shown in Table 7.

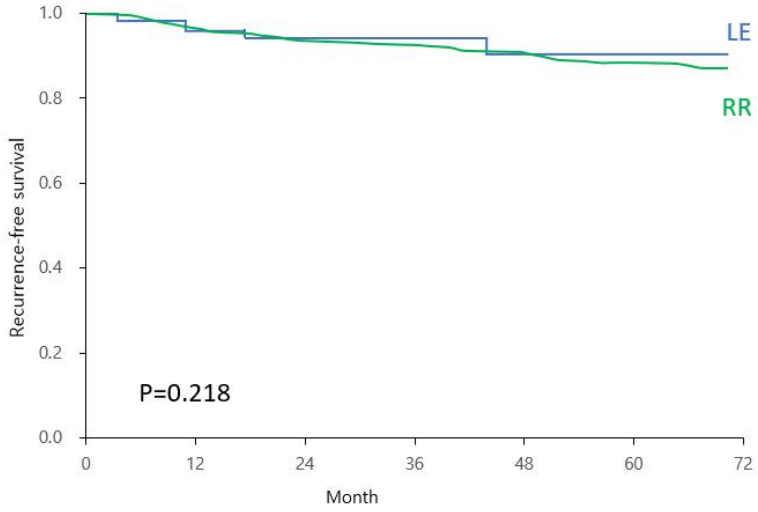
Table 7. Clinicopathological characteristics of multicenter cohort

Characteristics	Local excision (n=79)	Radical resection (n=714)
Sex		
Male	39(49.4)	430 (60.2)
Female	40 (50.6)	284 (39.8)
Age , year, mean ± SD	60.8 ± 11.9	58.8 ± 11.1
Pretreatment CEA, ng/dL, mean ± SD	1.9 ± 1.1	4.4 ± 13.4
cT stage		
1-2	35 (44.3)	133 (18.7)
3-4	20 (25.3)	447 (62.6)
Unknonwn	24(30.4)	134 (18.7)
cN stage		
cN (-)	35 (44.3)	147 (20.6)
cN (+)	22 (27.8)	437 (60.7)
Unknown	22 (27.8)	130 (18.2)
Sphincter preserving resection	-	616 (86.3)
Synchronous colon cancer	0	13 (2.2)
ypT stage		
ypT0	34 (43.0)	394 (55.2)
ypT1is	16 (20.3)	132 (18.5)
ypT1	29 (36.7)	188 (26.3)
ypN stage*		
ypN(-)	N/A	646 (90.5)
ypN(+)		55 (7.7)
Adjuvant chemotherapy		
No	37 (59.7)	94 (13.9)
Yes	23 (37.1)	555 (82.3)
Unknown	2 (3.2)	25 (3.7)

Values are presented as number (%) or mean ± standard deviation unless otherwise indicated.

Overall, clinicopathological features were similar to those of the Asan cohort. More patients with clinical advanced stage (cT3-4) were included in the RR group compared to the LE group. The sphincter was preserved in 86.3% of the RR group. Adjuvant chemotherapy was administered more in the RR group (82.3%) than in the LE group (37.1%). RFS was higher in the LE group overall, but it was not statistically significant ($P = 0.218$) (Figure 4).

Figure 4. Recurrence-free survival according to surgical treatment of ypT0-1 rectal cancer after preoperative chemoradiotherapy in multicenter study



There were no factors associated with RFS in the uni-/multivariable analysis (Table 8). Excision strategies were not associated with RFS in the multicenter cohort.

Table 8. Factors associated with recurrence free survival in ypT0-1 rectal cancer after preoperative chemoradiotherapy in multicenter cohort

Variable	Hazard ratio	95% CI	*P*-value
ypT stage			0.716
ypT0	1		
ypT1	0.847	0.460-1.557	0.592

ypTis	1.143	0.636-2.056	0.655
Sex			0.621
Male	1		
Female	1.127	0.702-1.809	
Group			0.671
Local excision	1		
Radical resection	1.301	0.386-4.381	
cT stage			0.430
cT0-2	1		
cT3-4	1.134	0.567-2.265	0.722
Unknown	0.442	0.100-1.959	0.283
cN stage			0.225
cN(-)	1		
cN(+)	0.944	0.483-1.845	0.867
Unknown	3.112	0.746-12.979	0.119
Adjuvant CTx			0.215
No	1		
Yes	1.929	0.812-4.583	0.137
Unknown	0.897	0.179-4.487	0.894
Age	1.005	0.983-1.027	0.65
Pre-PCRT CEA	1.003	0.991-1.016	0.588

OR odds ratio; CI, confidence interval

3. Discussion

We identified that the RFS and OS were not different according to the resection extent, categorized into local and radical excision, in patients with ypT0-1 after preoperative chemoradiotherapy in this study. We then verified the results of a single-center study in a multicenter cohort. Although lymph node metastasis was a significant factor associated with RFS and OS in the RR group, we could not find any risk factors for RFS and OS in the overall cohort.

The downstaging effect of PCRT led patients and surgeons to consider a less invasive way to sufficiently treat rectal cancer with better function postoperatively, without compromising oncologic outcomes. Organ-preserving strategies, such as LE of the tumor or closely monitoring the disease progression without any intervention (WW approach) could be applied for rectal cancer patients with complete or near CR to PCRT. Concerning the patient's postoperative quality of life, patients can live without transient/permanent stoma and avoid a higher rate of surgical complications, including anastomosis, leakage, or wound complications, and do not suffer from dysfunctional problems of pelvic organs (bladder and sex organs) [12-14]. In a study with a median follow-up of 61 months, 88.2% of patients who underwent LE were stoma-free, and the rectal preservation rate is reported to be around 64% to 70% and even up to 78.5% with strict patient selection [37-39].

As regards oncologic aspect, many studies demonstrated superior prognostic outcomes of rectal cancer with good response to PCRT [6, 8, 10, 11]. A study reported the cumulative incidence of disease free survival (DFS) and distant metastasis for 10 years as 89.5% and 10.5% when rectal cancer showed complete regression after PCRT [9]. DFS and distant metastasis rates in the intermediate regression group were 73.6% and 29.3%, and in the poor regression group were 63% and 39.6%, respectively. Patients having good response to PCRT showed higher DFS and lower metastasis, independent of other clinicopathologic parameters. Pathological staging after chemoradiation therapy (CRT) is reported to be the strongest prognostic factor, closely related to local recurrence [37]. A study [17] showed 0% of local recurrence in ypT0, 2% in ypT1, while ypT2 ranged from 6–20% and up to 43% of local failure risk in ypT3 patients with no pathological response. It is also reported that the risk of nodal metastasis is closely

related to ypT status [40, 41]. Many studies report on the prognostic significance of tumor regression, especially after the concept of tumor regression grade was introduced. This enabled surgeons were able to select less invasive options in patients with good response to PCRT [42].

Long-term oncologic outcomes between LE and RR were shown to have no statistically significant difference in prior studies when the tumor showed good response to PCRT. A case-matched study with LE and RR reported 5-year local recurrence rates of 91.8% and 97.6%, 5-year disease-free survival rates of 86.7% and 86.4%, and 5-year OS of 85% and 90%, none being statistically significant [37]. Our study also showed consistent results when comparing LE and RR in 5-year RFS and OS, showing 98.0% vs. 94.7% and 94.9% vs. 93.7%, respectively, with no statistical significance. Multicenter-based data also confirmed that there was no significant difference in RFS between the LE and RR groups. Therefore, by undergoing LE instead of RR, patients can potentially avoid unnecessary radical surgery and its associated morbidity and mortality with comparable long-term treatment results to RR.

For the successful application of LE in rectal cancer with good response to PCRT, proper patient selection is critical. The treatment strategy is determined by clinical staging dependent on imaging modalities, and strict selection of patients to perform LE is known to reduce LR of the tumor by clinical examination, endoscopy, and MRI [43]. Careful reevaluation is done with state-of-the-art MRI, but it is inevitably less accurate than pathologic staging [44]. Even with rectal MRI, which is considered superior to EUS, limitations remain in predicting T stage and the relationship of the tumor with mesorectal fascia [45]. Especially after PCRT, it becomes harder to differentiate fibrosis from residual viable tumors. Studies report a poor correlation of post-PCRT imaging and pathologic results, showing an accuracy of 47–52% in T stage and 64–68% in N stage, with overall accuracy reported to be around 68–72% in DWI [32, 46, 47]. Additionally, with PET-CT, although it is known to be able to confirm regression of the tumor by detecting the mean difference of 12.21% higher RI ($P < 0.001$) when compared to non-responders, studies evaluating the tumor that showed CR to PCRT are lacking [48].

Detecting reduction of metabolism of the tumor after PCRT is continuously studied to predict the pathologic response of the treatment by establishing a response predictive model with PET-CT [49], but

the accuracy in confirming the clinical response is reported to be only 44% [47]. At the molecular level, efforts are being made to predict response to chemoradiation by figuring out factors such as pretreatment apoptotic index, p53, Ki-67, EGFR, P21, EGFR, Bax/bcl-2; furthermore, microarray studies of genetic profiles were also run [50, 51]. However, although promising, definite predictive factors of tumor markers are lacking at present. Therefore, further development in response evaluation modality is essential to select patients with rectal cancer who are indicated for organ-preserving strategies after PCRT suitably.

As the reasons for potential treatment failure after LE are related to remnant mesorectum and pelvic lymph node status, it is crucial to identify evidence of recurrence in time; therefore, we conducted more intense and shorter-term follow-up in the LE group–laboratory tests and sigmoidoscopy done every 3 months for the first 2 years and then every 6 months for 5 years. All reevaluation exams were thoroughly reviewed by specialists of each modality.

Although PCRT significantly improved oncologic outcomes in treating rectal cancer by reducing local recurrence and prolonging OS, TME is still considered the gold standard for sufficient lymph node retrieval and complete excision of the tumor. A study compared patients with node-positive and node-negative rectal cancer at pretreatment clinical stage, both treated non-operatively after achieving complete clinical response, and the two groups had a similar rate of pathologic nodal metastases at the time of recurrence [52]. The 5-year surgery-free rate of node-positive and node-negative groups was 39.7% and 46.8% ($P = 0.2$), respectively, distant metastasis-free survival was 77.5% and 80.5% ($P = 0.49$), respectively, and none of them showed a statistically significant difference. This study showed that even when rectal cancer was node positive at the pretreatment clinical stage, a good response to PCRT was seen; patients are not at increased risk for local recurrence or developing recurrence in more advanced disease.

Taken together, the results of this study showed that LN metastasis is the strongest associated factor with RFS, even in patients who showed good response to PCRT. About 5% of patients with ypT0 are reported to have positive lymph nodes at pathological examination [9, 21]. In our study, 7% (28 patients

among 361 RR patients) of ypT0 patients were noted to have LN metastases in the final pathology. Lack of an accurate modality to evaluate LN status in patients undergoing locally excision leaves an incomplete understanding of the oncologic outcome of LE, and studies are still ongoing in this regard.

Performing adjuvant therapy in patients with CR using PCRT also lacks consensus. In our study, patients underwent chemotherapy based on treatment guidelines with some modifications according to the patient's general condition and physician's preference. Whether to undergo adjuvant chemotherapy was determined according to the initial clinical tumor stage regardless of the final pathologic state. However, much fewer patients treated with LE received adjuvant chemotherapy compared with those in the RR group. The LE group included more patients reluctant to undergo aggressive treatment, and this might have influenced the adjuvant chemotherapy receipt rate. Although the number of patients who received adjuvant chemotherapy was significantly less in the LE group, RFS was not different between the two groups. Long-term oncologic outcomes and standard treatment guidelines on adjuvant chemotherapy in ypT0 are scarce. However, recent studies report no significant benefit of adjuvant chemotherapy in rectal cancer with good response to PCRT. Several studies in patients with ypT0-2N0 rectal cancer treated with adjuvant chemotherapy showed no influence on RFS [53-55]. In our study, adjuvant chemotherapy in ypT0 patients had no statistical significance in RFS and OS in both groups. However, further prospective randomized studies with a larger sample size are needed to validate whether there are no additional oncologic benefits.

Additionally, the organ-preservation strategy is evolving and becoming more common than LE. The WW strategy is actively being introduced. Although LE is considered to have minimal morbidity compared to RR, considerable rates of anorectal pain, wound dehiscence, and readmission to hospitals are reported, and it is worse after undergoing PCRT [29, 56]. Significant worsening of anorectal function is observed after LE, and given that the sole potential benefit of LE may be the pathologic confirmation of ypT0 status compared to WW strategy, avoiding LE in patients that show CR to PCRT can be a safer option, avoiding any surgical complications [57]. Clinical assessment strategies for tumors is constantly

developing, and accuracy in the selection of patients who can be suitable candidates for less invasive treatment is improving. Endoscopic appearance alone showed excellent specificity [58], and tumor regression grade assessed by MRI is increasingly included in routine evaluation, accumulating data with higher accuracy [59].

It is already more than 15 years since the organ-preserving strategy was introduced, but there have been no standard treatment guidelines for LE. Clinicians can often be hesitant because of the remaining risk of underevaluating the cancer, which leads to irreversible detrimental results. However, it is undeniable that more conservative ways are gaining popularity to preserve organs and lessen complications. Delaying the establishment of a standardized protocol of LE or WW strategy will worsen the variation of patient selection and evaluation of long-term treatment goals such as follow-up methods or period and further treatment strategies, including adjuvant chemotherapy and salvage surgery after local recurrence.

There are some limitations to this study. First, it was a retrospective study using a single-center database with heterogeneous patient features. It was inevitable that the group who underwent RR had more patients with advanced disease who underwent adjuvant chemotherapy. Additionally, as patients with poor general condition or with more comorbidities are considered to undergo less invasive treatment, the average age of the patients was higher in the LE group. However, none of the factors showed statistical significance in analyzing RFS and OS. In addition, we utilized multicenter-based data to confirm statistical significance, which showed consistent results with our study. Second, due to the extended period of the study, inter-observer variability in the interpretation of imaging and differences in chemotherapy regimens could have been present, but diagnostic modalities in our center have always been up to date and treatment was in line with standardized guidelines. Despite the limitations, this study included many patients who underwent PCRT with standardized surgery at a qualified institution with more than 10 years of follow-up time and will sufficiently serve as reference data for further studies. In addition, by verifying the single-center cohort results with the multicenter cohort data, we tried to mitigate the study's limitation as a single-center retrospective study. A prospective study with a large

sample size with refined treatment protocols will better elucidate the best way forward for organ-preserving strategies.

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Abstract

Background and Objectives: Preoperative chemoradiation therapy (PCRT) led to a significant reduction in local recurrence and improved overall survival (OS) in patients with advanced rectal cancer. Tumors with good response to PCRT have a favorable prognosis, and these findings raise interest in rectum-sparing strategies.

Methods: Patients with primary rectal cancer diagnosed with ypT0-1 after PCRT followed by either radical resection (RR) or local excision (LE) between 2005 and 2014 were included in this study (LE = 78 and RR = 442). Clinicopathologic features, recurrence-free survival (RFS), and OS were analyzed.

Results: There was no statistically significant difference in RFS and OS between the LE and RR groups. Additionally, there was no significant difference in RFS. Lymph node (LN) positivity in the final pathology was the only factor associated with RFS and OS showing a statistically significant difference.

Conclusions: This study confirms the feasibility of LE in rectal cancer showing complete response to PCRT. Comparable oncologic outcomes between LE and RR groups further raises the need for standardization in organ-preserving strategies, including watch-and-wait treatment, necessary for patients' follow-up. Additionally, careful patient selection with higher accuracy modalities should be updated to improve treatment outcomes of LE.