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Dentate line invasion is a risk factor for locoregional recurrence and distant metastasis following abdominoperineal resection in rectal cancer: a single-centre retrospective cohort study based on 1854 cases

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Abstract

Background In the context of surgical treatment for rectal cancer, the dentate line is acknowledged as a critical anatomical landmark. However, the prognostic implications of dentate line invasion (DLI) remain elusive and warrant further investigation. This study aims to evaluate and compare the outcomes of patients with rectal cancer who underwent abdominoperineal resection (APR), distinguishing between those with and without DLI.

Materials and methods Between January 2006 and December 2017, this study enrolled 1854 patients with rectal cancer who underwent APR. The cohort was divided into two groups, namely the DLI group ($n=340$) and the non-DLI group ($n=1514$). The primary endpoints were distant relapse-free survival (DRFS) and local recurrence-free survival (LRFS). Univariate and multivariate analyses were conducted to assess the impact of DLI on DRFS, LRFS, overall survival (OS), and disease-free survival (DFS).

Results The median follow-up duration for the patients was 92.9 months, with a 5-year OS rate of 92.0% for the entire cohort. Compared to the non-DLI group, patients in the DLI group showed significantly poorer outcomes, with 5-year DRFS at 57.4% vs. 73.9% ($P<0.001$), DFS at 51.2% vs. 70.7% ($P<0.001$), and LRFS at 71.7% vs. 88.5% ($P=0.018$). OS was the only metric that showed no significant difference(89.0% vs. 92.6%, $P=0.064$). Multivariate analysis demonstrated that DLI negatively impacted DRFS (hazard ratio HR 1.319, $P=0.029$), LRFS (HR 2.059, $P<0.001$), and DFS (HR 1.563,

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$P < 0.001$) as an independent prognostic factor. Furthermore, distant metastasis occurred more frequently in the DLI group (30.0% vs. 23.1%, $P = 0.002$), along with a higher rate of locoregional recurrence. (16.8% vs. 8.3%, $P < 0.001$).

Conclusions DLI correlates with a heightened likelihood of locoregional recurrence and distant metastasis among rectal cancer patients treated with APR. This association underscores the significance of DLI as a crucial prognostic factor that should be considered when developing clinical management strategies.

Keywords Rectal cancer, Dentate line invasion, Abdominoperineal resection, Recurrence, Metastasis

Introduction

Abdominoperineal resection (APR) involves the complete removal of the anal canal structures, resulting in the creation of a permanent colostomy [1]. Although there is an increasing preference for conventional anus-conserving surgeries, such as low (or ultralow) anterior resection and standard coloanal anastomosis, for treating low rectal cancer, APR is typically performed for tumours located near the anus or in cases of anal canal malignancies [2]. Previous studies have reported inferior oncological outcomes following APR compared to anus-conserving procedures, with significant differences in local recurrence and overall survival (OS) rates [2–4]. Additionally, it has been observed that the survival outcomes for patients with lower rectal cancer are generally poorer compared to those with mid- and upper-rectal cancer [5, 6]. This discrepancy is partly due to the increased surgical complexity associated with the confined anatomy of the distal pelvis. Recent research has further elucidated that low rectal cancer has a higher propensity for metastasis to distant lymphatic stations and a greater incidence of distant organ metastases [7, 8]. Moreover, several studies have identified a higher local recurrence rate in cases of dentate line invasion (DLI) compared to non-DLI cases [9, 10]. These findings suggest that DLI might exhibit distinct clinical behaviour, necessitating more rigorous follow-up and surveillance.

The dentate line demarcates the anatomical transition zone where the mucosa changes from squamous to columnar epithelium, thereby delineating the upper and lower anal canal. Theoretically, neoplasms from different regions of the dentate line are expected to exhibit distinct clinical behaviours. Moderate clinical evidence supports this hypothesis, although research remains limited [8, 10]. Notably, there are no prospective randomised controlled trials comparing the prognosis of patients with and without DLI. Consequently, the potential risks associated with DLI are often overlooked, and decisions regarding therapeutic interventions or follow-up protocols are frequently made empirically, based on institutional practices rather than objective parameters.

Given the potential risks associated with DLI, the largest real-world cohort study to date was conducted to determine the specific impact of DLI on survival rates and failure patterns in patients with rectal cancer who underwent APR.

Materials and methods

Study design

Informed consent was obtained from all participants, and the procedures followed adhered to the ethical standards of the World Medical Association Declaration of Helsinki. The studies involving human participants were reviewed and approved by The National Cancer Center's Institute Research Medical Ethics Committee (23/180–3922, 11 May 2023). This study included 1854 patients with rectal cancer who underwent APR at the National Cancer Centre between January 2006 and December 2017. The intent-to-treat principle was applied, including patients who required conversion to an open procedure in the laparoscopic APR (LAPR) group. Inclusion criteria required pathological confirmation of adenocarcinoma, mucinous adenocarcinoma, or signet-ring carcinoma of the rectum (≤7 cm from the anal verge). Patients with other gastrointestinal diseases requiring surgical intervention, previous malignant tumours, or distal metastasis were excluded. Additionally, patients with missing or unreported data on circumferential resection margin (CRM), clinical and pathological tumour stage, DLI, and tumour site were excluded. A 6–8 week interval between surgery and neoadjuvant chemoradiotherapy (NCRT) was maintained. All abdominoperineal procedures were performed according to the standard total mesorectal excision principles. In our cohort, standard APR with TME included dissection of regional lymph nodes (mesorectal, and internal iliac lymph nodes). Lateral pelvic lymph nodes (e.g., external iliac, obturator) and inguinal lymph nodes were not routinely dissected unless preoperative imaging (MRI/CT) or intraoperative assessment indicated suspected metastasis.

All patients enrolled in the study underwent routine follow-up 2 weeks after surgery, followed by scheduled visits every 3 months during the first year, every 6 months in the second year, and annually thereafter. NCRT was indicated for patients with clinically staged T3/T4 tumors, node-positive disease, or threatened mesorectal fascia based on preoperative MRI and multidisciplinary team evaluation, as per the National Comprehensive Cancer Network guidelines. Additionally, patients with

low-lying tumors or suspected extramural vascular invasion on imaging were prioritized for NCRT.

Main outcome measures

Baseline characteristics and perioperative outcomes of the patients were retrospectively collected. These data included sex, age, body mass index (BMI), previous abdominal surgeries, preoperative comorbidities, American Society of Anaesthesiologists (ASA) class, NCRT, adjuvant chemotherapy, tumour size, lymphovascular invasion, perineural invasion, number of nodes examined, DLI, CRM positivity, operative time, blood loss, surgical technique, pathological type, degree of differentiation, and pathologic stage (according to the eighth edition of the American Joint Committee on Cancer staging). Oncological outcomes assessed included survival data, disease-free survival rates, local and distant recurrence rates and time to recurrence. Our team defined "DLI" as the condition where the lower edge of tumours, confirmed by postoperative pathology, involves or crosses the dentate line. By using computed tomography or pelvic magnetic resonance imaging, locoregional recurrence sites were classified into four categories: (1) central—pertaining to perineal recurrence; (2) anterior—encompassing the seminal vesicles, prostate, vagina, uterus, or urinary bladder; (3) posterior—involving the coccyx and sacrum; and (4) lateral—impacting the bony pelvic sidewall or associated structures, such as the lateral lymph nodes, pelvic autonomic nerves, internal iliac vessels, pelvic ureters, and sidewall musculature [11].

Statistical analysis

Categorical variables were compared using the chi-square test and Fisher's exact test. Survival analyses, including local recurrence-free survival (LRFS), distant relapse-free survival (DRFS), disease-free survival (DFS), and overall survival (OS), were conducted using the Kaplan–Meier estimator and assessed with the log-rank test. Endpoint-specific cohorts were defined based on data completeness. Patients missing critical follow-up data for a given endpoint were excluded from the corresponding analysis. Proportional hazards (PH) assumptions were assessed for all univariate Cox models using Schoenfeld residuals. Variables with significant time-dependent effects ($p < 0.1$ in global tests) would have been excluded, but all covariates met the PH assumption ($p > 0.1$).

Univariate logistic regression and Cox proportional hazards models were employed to evaluate the influence of covariates and identify significant risk factors. Statistically significant covariates ($P < 0.1$) in the univariate analysis were included in the multivariate regression analysis. Variables selected for multivariate analysis underwent variance inflation factor (VIF) screening. A threshold of VIF > 5 was used to eliminate collinear variables through backward stepwise selection. The impact of each variable was quantified using hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs). Statistical significance was set at $P < 0.05$.

Data analysis was performed using SPSS Statistics version 26 (IBM, Armonk, NY, USA). The survival analyses were conducted using R (version 4.3.2, R Development Core Team, Vienna, Austria).

Results

Baseline characteristics

A total of 2186 individuals with rectal cancer were included in our study. After excluding 332 patients, such as 68 with previous malignant tumors, 53 with distal metastasis, 111 with other gastrointestinal diseases requiring surgical intervention, and 100 patients with missing or unreported important data, 1854 individuals were ultimately incorporated into this investigation. Among the cohort, DLI was present in 18.3% (340/1854) of patients, while the non-DLI group comprised 81.7% (1514/1854) of patients. Between these groups, there were no notable differences observed in terms of sex, age, BMI, previous abdominal surgeries, preoperative comorbidities, ASA class, NCRT, adjuvant chemotherapy, tumour size, DLI, operative time, blood loss, surgical technique, pathological type, degree of differentiation, pathologic stage, and postoperative complications. However, patients with DLI exhibited a higher rate of CRM positivity (10.0% vs. 3.0%, $P < 0.001$). Additionally, there was a greater prevalence of lymphovascular invasion (22.9% vs. 13.4%, $P < 0.001$) and perineural invasion (28.8% vs. 17.6%, $P < 0.001$) among patients with DLI. Furthermore, DLI patients had a reduced number of nodes examined compared to those without DLI (17.1 ± 9.7 vs. 19.0 ± 13.4, $P = 0.015$)(Table 1).

Recurrence and survival analysis

Patients were followed up for a median duration of 92.9 months (Table 2). The 5-year LRFS rate for the entire cohort was 85.8%. Specifically, the DLI group exhibited a rate of 71.7%, whereas the non-DLI group showed a rate of 88.5% ($P = 0.018$; Fig. 1A). The 5-year DRFS rate for all patients was 71.2%, with rates of 57.4% in the DLI group and 73.9% in the non-DLI group ($P < 0.001$; Fig. 1B). The 5-year DFS rate for the cohort was 67.3%, with rates of 51.2% and 70.7% in the DLI and non-DLI groups, respectively ($P < 0.001$; Fig. 1C). The 5-year OS for the cohort was 92.0%, with no notable differences in survival rates between the DLI and non-DLI groups. ($P = 0.064$; Fig. 1D).

Univariate and multivariate Cox regression analyses

In the univariate analysis of DFS, statistically significant factors included tumour size, NCRT, grade of

Table 1 Baseline characteristics

Variable	Total ($n=1854$)	DLI($n=340$)	Non-DLI($n=1514$)	*p* value
Sex: male, n (%)	1203(64.9%)	206(60.6%)	997(65.9%)	0.066
Age, y, mean (SD)	57.4 ± 11.2	57.2 ± 11.0	57.5 ± 11.2	0.694
Comorbidity, n (%)	976(52.6%)	183(53.8%)	7 93(52.4%)	0.629
BMI, mean (SD)	24.4 ± 3.4	24.2 ± 3.4	24.4 ± 3.4	0.567
Previous abdominal operation, n (%)	361(19.5%)	76(22.4%)	285(18.8%)	0.138
Tumor size	3.6 ± 1.6	3.7 ± 1.7	3.6 ± 1.6	0.526
Neoadjuvant chemoradiotherapy, n (%)	452(24.4%)	76(22.4%)	376(24.8%)	0.335
ASA score, n (%)				0.447
1	139(7.5%)	28(8.2%)	111(7.3%)	
2	1480(79.8%)	272(80.0%)	1208(79.8%)	
3	232(12.5%)	40(11.8%)	192(12.7%)	
4	2(0.1%)	0(0.0%)	2(0.1%)	
5	1(0.1%)	0(0.0%)	1(0.1%)	
Histology, n (%)				0.766
Adenocarcinoma	1682(90.7%)	305(89.7%)	1377(91.0%)	
Mucinous adenocarcinoma	163(8.8%)	33(9.7%)	130(8.6%)	
Signet-ring cell carcinoma	9(0.5%)	2(0.6%)	7(0.5%)	
Differentiation degree, n (%)				0.903
Low	416(22.4%)	79(23.2%)	337(22.3%)	
Moderate	1335(72.0%)	240(70.6%)	1095(72.3%)	
High	103(5.6%)	21(6.2%)	82(5.4%)	
pT category, n (%)				0.130
pT0	69(3.7%)	10(2.9%)	59(3.9%)	
pT1	87(4.7%)	14(4.1%)	73(4.8%)	
pT2	590(31.8%)	105(30.9%)	485(32.0%)	
pT3	961(51.8%)	176(51.8%)	785(51.8%)	
pT4	147(7.9%)	35(10.3%)	112(7.4%)	
pN category, n (%)				0.087
pN0	1053(56.8%)	179(52.2%)	874(57.7%)	
pN+	801(43.2%)	161(47.4%)	640(42.3%)	
Stage, n (%)				0.073
0	61(3.3%)	8(2.4%)	53(3.5%)	
1	513(27.7%)	87(25.6%)	426(28.1%)	
2	479(25.8%)	84(24.7%)	395(26.1%)	
3	801(43.2%)	161(47.4%)	640(42.3%)	
Lymphovascular invasion, n (%)	281(15.2%)	78(22.9%)	203(13.4%)	<0.001*
Perineural invasion, n (%)	365(19.7%)	98(28.8%)	267(17.6%)	<0.001*
Surgical technique, n (%)				0.559
Open surgery	640(34.5%)	122(35.9%)	518(34.2%)	
Laparoscopic surgery	1214(65.5%)	218(64.1%)	996(65.8%)	
Operative time, min, mean (SD)	206.1 ± 68.6	202.1 ± 65.6	207.0 ± 69.3	0.233
Estimated blood loss, ml, mean (SD)	204.2 ± 258.5	246.5 ± 245.0	238.8 ± 261.5	0.620
Number of lymph nodes examined in the surgery, mean (SD)	18.7 ± 12.8	17.1 ± 9.7	19.0 ± 13.4	0.015*
CRM: positive, n (%)	79(4.3%)	34(10.0%)	45(3.0%)	<0.001*
Adjuvant chemotherapy, n (%)				0.085
Yes	914(49.3%)	166(48.8%)	748(49.4%)	
No	476(25.7%)	75(22.1%)	401(26.5%)	
NA	464(25.0%)	99(29.1%)	365(24.1%)	

DLI = dentate line invasion, BMI = Body mass index, ASA = American Society of Anesthesiologists, CRM = Circumferential resection margin

Missing data were only present for adjuvant chemotherapy. Other variables had no missing values due to pre-screening exclusion of cases with incomplete data

Table 2 Oncological results

Variable	Total ($n=1854$)	DLI($n=336$)	Non-DLI($n=1518$)	*p* value
Follow-up in months, mean (SD)	92.9 ± 51.5	89.59 ± 53.7	93.7 ± 51.0	0.209
5-year overall survival, %	92.0% (90.5 – 93.4%)	89.0% (85.0 – 93.0%)	92.6% (91.1 – 94.2%)	0.064
5-year disease-free survival, %	67.3% (64.7 – 69.9%)	51.2% (44.4 – 57.9%)	70.7% (67.9 – 73.5%)	<0.001*
5-year distant relapse-free survival, %	71.2% (68.5 – 73.8%)	57.4% (50.3 – 64.5%)	73.9% (71.1 -76.6%)	<0.001*
5-year local recurrence-free survival, %	85.8% (83.6 – 88.0%)	71.7% (64.5 – 79.0%)	88.5% (86.3 – 90.7%)	0.018*

DLI = dentate line invasion

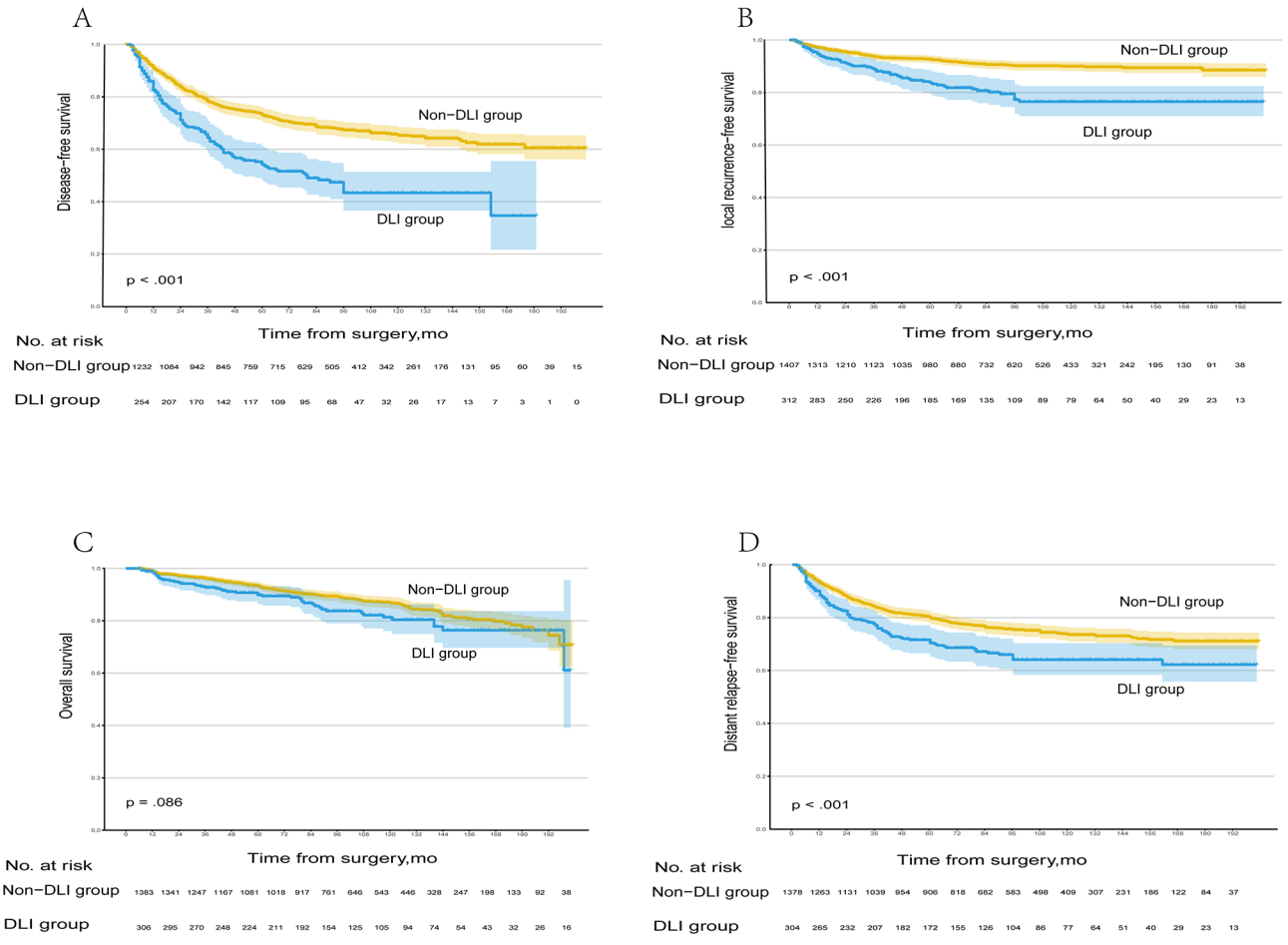

Fig. 1 Kaplan–Meier survival curves of Disease-free survival, Local recurrence-free survival, Overall survival and Distant relapse-free survival

differentiation, DLI, pathological tumour (pT) category, pathological node (pN) category, lymphovascular invasion, perineural invasion, CRM positivity, and adjuvant chemotherapy. Multivariate analysis identified independent adverse prognostic factors for DFS, which included DLI at the lower edge of the tumour (HR 1.563, 95% CI 1.245–1.962, $P<0.001$), NCRT (HR 1.245, 95% CI 1.003–1.545, $P=0.047$), pT category ($P=0.028$), pN category (HR 1.540, 95% CI 1.248–1.901, $P<0.001$), lymphovascular invasion (HR 1.631, 95% CI 1.260–2.110, $P<0.001$), and positive CRM (HR 2.035, 95% CI 1.442–2.871, $P<0.001$) (Table 3).

In multivariate analysis, DLI emerged as an independent prognostic factor significantly associated with decreased DRFS (HR 1.319, 95% CI 1.029–1.691, $P=0.029$) (Table 4) and LRFS (HR 2.059, 95% CI 1.453–2.916, $P < 0.001$) (Table 5). However, DLI did not predict OS significantly (HR 1.204, 95% CI 0.858–1.691, $P=0.283$) (Table 6).

Table 3 Univariate and multivariate analysis of risk factors for DFS

Variable	Univariate analysis		multivariate analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Sex(female/male)	0.990(0.823–1.191)	0.912		
Age	0.995(0.987–1.003)	0.182		
Comorbidity(yes/no)	1.024(0.857–1.223)	0.796		
BMI	1.009(0.983–1.035)	0.506		
Previous abdominal operation(yes/no)	1.032(0.824–1.292)	0.785		
Tumor size	1.066(1.015–1.118)	0.010*	1.041(0.988–1.096)	0.133
Neoadjuvant chemoradiotherapy(yes/no)	1.276(1.049–1.552)	0.015*	1.245(1.003–1.545)	0.047*
ASA score(1 ~ 2/3 ~ 6)	1.031(0.798–1.332)	0.814		
Histology		0.888		
Adenocarcinoma	Reference	Reference		
Mucinous adenocarcinoma	1.037(0.751–1.433)	0.825		
Signet-ring cell carcinoma	0.649(0.091–4.618)	0.666		
Differentiation degree		<0.001*		0.791
Low	Reference	Reference	Reference	Reference
Moderate	0.775(0.630–0.953)	0.016*	1.066(0.843–1.347)	0.595
High	0.507(0.305–0.842)	0.009	0.940(0.541–1.635)	0.828
Lower edge of tumors with the dentate line invasion(yes/no)	1.500(1.208–1.863)	<0.001*	1.563(1.245–1.962)	<0.001*
pT category		<0.001*		0.028
pT0	Reference	Reference	Reference	Reference
pT1	0.469(0.213–1.033)	0.060	0.646(0.281–1.487)	0.304
pT2	0.894(0.514–1.556)	0.693	0.953(0.516–1.759)	0.877
pT3	1.568(0.917–2.681)	0.100	1.290(0.707–2.353)	0.407
pT4	2.196(1.217–3.962)	0.009*	1.478(0.760–2.873)	0.249
pN category(pN+/pN0)	1.996(1.671–2.385)	<0.001*	1.540(1.248–1.901)	<0.001*
Lymphovascular invasion(yes/no)	2.091(1.684–2.595)	<0.001*	1.631(1.260–2.110)	<0.001*
Perineural invasion(yes/no)	1.697(1.385–2.080)	<0.001*	0.969(0.757–1.239)	0.799
CRM(yes/no)	3.233(2.352–4.443)	<0.001*	2.035(1.442–2.871)	<0.001*
Surgical approach(OAPR/LAPR)	1.039(0.860–1.254)	0.694		
Adjuvant chemotherapy(yes/no)	1.552(1.256–1.918)	<0.001*	1.057(0.836–1.337)	0.641

DLI = dentate line invasion, BMI = Body mass index, ASA = American Society of Anesthesiologists, CRM = Circumferential resection margin, LAPR = Laparoscopic abdominoperineal resection, OAPR = Open abdominoperineal resection

The failure patterns

In the entire cohort, the incidence of distant metastasis was 23.6% (437/1854), with the most common sites being the lungs (13.4%), followed by the liver (6.8%) and bones (2.3%). Patients with DLI experienced a markedly increased incidence of distant metastasis (30.0% vs. 23.1%, $P = 0.002$) compared to non-DLI patients, particularly involving the inguinal, common iliac lymph nodes, lungs and bones. Within the DLI group, distant relapse was observed in 55 patients (30.2%) during the first year, 36 (19.7%) in the second year, 50 (27.5%) between the third and fifth years, and 41 patients (22.5%) after five years. The overall locoregional recurrence rate for the cohort was 9.8% (182/1854), with the most common sites being the lateral pelvic (3.9%) and central (3.0%) regions, followed by the anterior (1.5%) and posterior (1.2%) regions. The locoregional recurrence rates for the DLI and non-DLI groups were 16.8% (57/336) and 8.3% (125/1518), respectively ($P < 0.001$), with significant differences observed in the central, anterior, and lateral regions. Table 7 presents a comprehensive overview of failure patterns before matching.

Discussion

The dentate line is a crucial anatomical landmark in APR, yet the prognostic implications of DLI remain ambiguous. In our cohort study based on real-world data, the specific impact of DLI on survival outcomes and failure patterns among patients undergoing APR for rectal cancer was comprehensively explored. Our findings revealed that DLI at the inferior aspect of the tumour significantly influenced both local recurrence and distant metastasis rates. Patients with DLI experienced considerably higher incidences of distant metastasis and locoregional recurrence compared to those without DLI. These results will provide crucial insights for guiding clinical decision-making in treating rectal cancer.

Patients with rectal cancer who undergo APR face variable survival outcomes influenced by multiple factors, among which DLI has received limited investigation. To

Table 4 Univariate and multivariate analysis of risk factors for DRFS

Variable	Univariate analysis		multivariate analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Sex(female/male)	0.943(0.771–1.154)	0.572		
Age	0.991(0.983-1.000)	0.047*	0.996(0.986–1.005)	0.343
Comorbidity(yes/no)	1.011(0.834–1.226)	0.910		
BMI	1.011(0.983–1.039)	0.453		
Previous abdominal operation(yes/no)	1.001(0.786–1.276)	0.991		
Tumor size	1.035(0.978–1.095)	0.229		
Neoadjuvant chemoradiotherapy(yes/no)	1.610(1.308–1.982)	<0.001*	1.490(1.179–1.883)	0.001*
ASA score(1 ~ 2/3 ~ 6)	0.966(0.727–1.283)	0.811		
Histology		0.751		
Adenocarcinoma	Reference	Reference		
Mucinous adenocarcinoma	1.023(0.727–1.440)	0.895		
Signet-ring cell carcinoma	0.475(0.067–3.384)	0.458		
Differentiation degree		0.063		0.382
Low	Reference	Reference	Reference	Reference
Moderate	0.839(0.669–1.052)	0.128	1.192(0.924–1.537)	0.176
High	0.555(0.327–0.940)	0.029*	1.064(0.597–1.897)	0.833
Lower edge of tumors with the dentate line invasion(yes/no)	1.486(1.184–1.865)	0.001*	1.319(1.029–1.691)	0.029*
pT category		<0.001*		0.620
pT0	Reference	Reference	Reference	Reference
pT1	0.574(0.262–1.259)	0.166	0.928(0.404–2.130)	0.860
pT2	0.902(0.508–1.602)	0.725	1.148(0.607–2.169)	0.671
pT3	1.267(0.725–2.214)	0.406	1.263(0.676–2.361)	0.464
pT4	1.637(0.882–3.040)	0.119	1.462(0.728–2.933)	0.286
pN category(pN+/pN0)	1.798(1.483–2.179)	<0.001*	1.537(1.222–2.933)	<0.001*
Lymphovascular invasion(yes/no)	1.990(1.571–2.523)	<0.001*	1.570(1.186–2.078)	0.002*
Perineural invasion(yes/no)	1.852(1.480–2.317)	<0.001*	1.161(0.884–1.525)	0.283
CRM(yes/no)	3.027(2.108–4.347)	<0.001*	1.898(1.285–2.803)	0.001*
Surgical approach(OAPR/LAPR)	0.801(0.653–0.983)	0.034*	1.150(0.903–1.466)	0.257
Adjuvant chemotherapy(yes/no)	1.448(1.155–1.817)	0.001*	1.031(0.800–1.330)	0.812

DLI = dentate line invasion, BMI = Body mass index, ASA = American Society of Anesthesiologists, CRM = Circumferential resection margin, LAPR = Laparoscopic abdominoperineal resection, OAPR = Open abdominoperineal resection

our knowledge, our study represents the largest single-centre real-world analysis conducted to date. Our findings indicate that DLI independently serves as a negative prognostic factor affecting DRFS, LRFS, and DFS; however, it does not significantly affect OS in these patients. A previous Japanese study reported a higher rate of local recurrence and poorer OS among patients with DLI, though it did not employ Cox proportional hazards models for multivariate survival analysis, particularly for DRFS or DFS [12]. In contrast, a meta-analysis by Zeng et al. found a significantly higher local recurrence rate in patients with DLI compared to those without DLI. However, this study exclusively included patients who underwent endoscopic submucosal dissection for rectal tumours [10]. Similarly, Song et al. demonstrated that DLI independently predicts worse DRFS and DFS outcomes, without significant associations with LRFS or OS in patients with rectal cancer. However, their study was restricted to patients with locally advanced lower rectal cancer [8]. Conversely, Shiratori et al. concluded that DLI was not associated with survival [13]. Discrepancies in these findings can be attributed to various factors, including heterogeneity in study populations, small sample sizes, confounding group biases, and perioperative treatment protocol variations, particularly in earlier research periods. In our study, by including a larger cohort of patients with rectal cancer who underwent APR, the risk of bias related to unknown variables was minimised due to reduced clinical heterogeneity.

In our study, a significantly higher incidence of distant metastasis and local recurrence was observed among patients with DLI compared to those without DLI. The notable increase in both distant metastasis and local recurrence within the DLI cohort is likely influenced by various interconnected factors. Regarding distant metastasis, patients in the DLI group exhibited a higher incidence of metastatic spread to the lungs, bones, inguinal lymph nodes, and common iliac lymph nodes. This observed pattern of metastatic involvement might be explained by several anatomical considerations. First,

Table 5 Univariate and multivariate analysis of risk factors for LRFS

Variable	Univariate analysis		multivariate analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Sex(female/male)	1.261(0.935–1.702)	0.128		
Age	0.990(0.977–1.003)	0.133		
Comorbidity(yes/no)	0.913(0.680–1.227)	0.546		
BMI	0.996(0.954–1.040)	0.866		
Previous abdominal operation(yes/no)	1.065(0.738–1.535)	0.738		
Tumor size	1.075(0.992–1.166)	0.079	1.074(0.992–1.162)	0.079
Neoadjuvant chemoradiotherapy(yes/no)	1.546(1.123–2.128)	0.007*	1.363(0.950–1.956)	0.093
ASA score(1 ~ 2/3 ~ 6)	1.347(0.910–1.995)	0.137		
Histology		0.943		
Adenocarcinoma	Reference	Reference		
Mucinous adenocarcinoma	0.922(0.534–1.592)	0.771		
Signet-ring cell carcinoma	1.187(0.166–8.483)	0.864		
Differentiation degree		0.056		0.663
Low	Reference	Reference	Reference	Reference
Moderate	0.741(0.530–1.037)	0.080	0.875(0.603–1.270)	0.482
High	0.381(0.152–0.959)	0.040*	0.686(0.261–1.804)	0.445
Lower edge of tumors with the dentate line invasion(yes/no)	1.733(1.241–2.419)	0.001*	2.059(1.453–2.916)	<0.001*
pT category		0.002*		0.090
pT0	Reference	Reference		
pT1	0.315(0.058–1.720)	0.182	0.405(0.072–2.279)	0.305
pT2	1.075(0.385–3.002)	0.890	1.109(0.377–3.262)	0.851
pT3	1.904(0.702–5.162)	0.206	1.732(0.603–4.974)	0.307
pT4	2.114(0.715–6.247)	0.176	1.435(0.440–4.674)	0.594
pN category(pN+/pN0)	1.667(1.241–2.240)	0.001*	1.292(0.910–4.674)	0.152
Lymphovascular invasion(yes/no)	2.014(1.405–2.886)	<0.001*	1.503(0.980–2.305)	0.062
Perineural invasion(yes/no)	1.691(1.197–2.389)	0.003*	0.815(0.535–1.240)	0.339
CRM(yes/no)	3.894(2.386–6.353)	<0.001*	1.804(1.034–3.147)	0.038*
Surgical approach(OAPR/LAPR)	0.686(0.497–0.949)	0.023*	0.911(0.627–1.325)	0.626
Adjuvant chemotherapy(yes/no)	1.503(1.055–2.142)	0.024*	0.995(0.672–1.474)	0.981

DLI = dentate line invasion, BMI = Body mass index, ASA = American Society of Anesthesiologists, CRM = Circumferential resection margin, LAPR = Laparoscopic abdominoperineal resection, OAPR = Open abdominoperineal resection

lymphatic drainage below the dentate line primarily directs towards the inguinal lymph nodes (ILNs), and recent studies have shown that DLI patients are more susceptible to ILN involvement [13–15]. Additionally, the superior rectal vein drains the rectum and anal canal above the dentate line into the portal venous system via the inferior mesenteric vein. Conversely, the external haemorrhoidal plexus, located below the dentate line, drains via the inferior rectal vein into the internal pudendal vein, then to the internal iliac vein, and ultimately into the systemic circulation [16]. Consequently, rectal tumours in this region might be predisposed to early metastasis to distant sites such as the lungs, due to the direct access provided by the venous pathway, bypassing the portal system [7]. This distinction in metastatic patterns based on tumour location has been supported by additional clinical studies [7, 17, 18]. In terms of local recurrence, a higher incidence was observed at central, anterior, and lateral sites in the DLI group. Anatomically, the area below the dentate line drains through the inferior rectal into the internal pudendal vein, subsequently flowing into the internal iliac vein, potentially facilitating a greater propensity for recurrence in the perineal and internal iliac regions. Additionally, the proximity of the dentate line to organs such as the urinary bladder, vagina, uterus, seminal vesicles, and prostate increases the likelihood of invasion and subsequent local recurrence [16]. Furthermore, the location of the rectal tumour below the dentate line within the confined distal pelvis presents surgical challenges. This study found a higher CRM positivity rate in the DLI group, which correlates with an increased rate of local recurrence [19].

Our findings highlight distinct patterns of locoregional recurrence and distant metastasis in patients with DLI, which may inform tailored surveillance strategies. Given the significantly higher incidence of lung and bone metastases in the DLI group (13.4% and 2.3% overall, with further enrichment in DLI patients), intensified imaging modalities targeting these sites—such as routine low-dose chest CT scans and bone scintigraphy—could

Table 6 Univariate and multivariate analysis of risk factors for OS

Variable	Univariate analysis		multivariate analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Sex(female/male)	0.716(0.533–0.962)	0.026	0.826(0.595–1.084)	0.211
Age	1.031(1.018–1.044)	<0.001*	1.023(1.009–1.037)	<0.001*
Comorbidity(yes/no)	1.360(1.028–1.798)	0.031*	1.117(0.827–1.508)	0.471
BMI	0.998(0.960–1.039)	0.937		
Previous abdominal operation(yes/no)	1.020(0.730–1.426)	0.907		
Tumor size	1.120(1.043–1.203)	0.002*	1.090(1.004–1.184)	0.040*
Neoadjuvant chemoradiotherapy(yes/no)	1.093(0.781–1.531)	0.602		
ASA score(1 ~ 2/3 ~ 6)	2.481(1.847–3.334)	<0.001*	1.982(1.492–2.749)	<0.001*
Histology		0.294		
Adenocarcinoma	Reference	Reference		
Mucinous adenocarcinoma	1.401(0.916–2.143)	0.120		
Signet-ring cell carcinoma	0.869(0.122–6.206)	0.889		
Differentiation degree		<0.001*		0.007*
Low	Reference	Reference	Reference	Reference
Moderate	0.535(0.399–0.718)	<0.001*	0.600(0.437–0.824)	0.002*
High	0.557(0.294–1.054)	0.072	0.688(0.353–1.341)	0.272
Lower edge of tumors with the dentate line invasion(yes/no)	1.327(0.959–1.835)	0.087	1.204(0.858–1.691)	0.283
pT category		<0.001*		0.004*
pT0	Reference	Reference	Reference	Reference
pT1	1.246(0.322–4.821)	0.750	1.445(0.371–5.636)	0.596
pT2	1.382(0.429–4.450)	0.587	1.549(0.490–5.188)	0.439
pT3	2.372(0.754–7.464)	0.140	2.185(0.679–7.039)	0.190
pT4	5.104(1.574–16.552)	0.007*	3.712(1.113–12.384)	0.033*
pN category(pN+/pN0)	1.975(1.506–2.590)	<0.001*	1.521(1.128–2.051)	0.006*
Lymphovascular invasion(yes/no)	2.128(1.508–3.001)	<0.001*	1.521(1.010–2.289)	0.045
Perineural invasion(yes/no)	1.514(1.058–2.166)	0.023*	0.892(0.581–1.372)	0.604
CRM(yes/no)	2.649(1.505–4.662)	<0.001*	1.510(0.818–2.789)	0.188
Surgical approach(OAPR/LAPR)	1.227(0.925–1.628)	0.157		
Adjuvant chemotherapy(yes/no)	1.061(0.751–1.498)	0.737		

DLI = dentate line invasion, BMI = Body mass index, ASA = American Society of Anesthesiologists, CRM = Circumferential resection margin, LAPR = Laparoscopic abdominoperineal resection, OAPR = Open abdominoperineal resection

be prioritized during follow-up. Similarly, the elevated rates of lateral pelvic and central locoregional recurrences in DLI patients (3.9% and 3.0%, respectively) suggest that pelvic MRI or contrast-enhanced CT should be incorporated into surveillance protocols for early detection of regional relapse. Furthermore, the temporal distribution of distant relapse in DLI patients (30.2% within the first year and 19.7% in the second year) underscores the importance of closer monitoring during the initial postoperative period. We propose that DLI-positive patients may benefit from a more frequent follow-up schedule compared to non-DLI patients, with a focus on high-risk anatomical sites. These recommendations align with emerging evidence supporting risk-adapted surveillance in rectal cancer and warrant validation in prospective studies.

The absence of a significant OS difference despite poorer DRFS and LRFS in the DLI group aligns with emerging evidence that advancements in salvage therapies have mitigated the survival impact of recurrence in rectal cancer [20]. As highlighted by recent trials, modern multimodal approaches—including combination chemotherapy, targeted agents, immunotherapy, and stereotactic radiotherapy—have significantly improved post-recurrence survival over time. In our cohort, the high 5-year OS rate suggests that even patients with recurrence may have benefited from these evolving salvage strategies. These observations underscore the dissociation between recurrence risk and OS in the era of precision oncology, where disease-specific outcomes may better reflect tumor biology, while OS is confounded by the efficacy of salvage interventions.

The limitations of the present study must be acknowledged. First, the analysis was conducted retrospectively. Differential missing data across endpoints, particularly for recurrence assessments, may introduce selection bias. However, rigorous exclusion of cases with incomplete follow-up strengthens internal validity at the cost of reduced sample size. Secondly, there were disparities in the baseline characteristics between the DLI and

Table 7 The failure patterns

Variable	Total ($n=1854$)	DLI($n=336$)	Non-DLI($n=1518$)	p value
Local recurrence, %	182(9.8%)	57(16.8%)	125(8.3%)	<0.001*
central	56(3.0%)	17(5.0%)	39(2.6%)	0.018*
anterior	27(1.5%)	8(2.4%)	19(1.3%)	0.134
posterior	23(1.2%)	8(2.1%)	15(1.0%)	0.054*
lateral	72(3.9%)	24(7.1%)	48(3.2%)	0.001*
Distant recurrence, %	437(23.6%)	102(30.0%)	335(23.1%)	0.002*
External iliac lymph node	12(0.6%)	4(1.2%)	8(0.5%)	0.250
Inguinal lymph node	19(1.0%)	9(2.6%)	10(0.7%)	0.003*
Retroperitoneal lymph node	27(1.5%)	7(2.1%)	20(1.3%)	0.315
Common iliac lymph nodes	28(1.5%)	12(3.5%)	16(1.1%)	0.001*
Lungs	249(13.4%)	61(17.9%)	188(12.4%)	0.007*
Liver	126(6.8%)	27(7.9%)	99(6.5%)	0.353
Bone	43(2.3%)	14(3.3%)	29(2.1%)	0.015*
Brain	25(1.3%)	7(2.1%)	18(1.2%)	0.199
Peritoneum	15(0.8%)	5(1.5%)	10(0.7%)	0.171
Adrenal gland	6(0.3%)	1(0.3%)	5(0.3%)	1.000
Ovary	4(0.2%)	0(0.0%)	4(0.3%)	1.000
Pleura	2(0.1%)	0(0.0%)	2(0.1%)	1.000
Left supraclavicular lymph node	9(0.5%)	2(0.6%)	7(0.5%)	0.673
Mediastinal lymph nodes	8(0.4%)	1(0.3%)	7(0.5%)	1.000
Pancreas	2(0.1%)	1(0.3%)	1(0.1%)	0.333
Other sites	70(3.8%)	13(3.8%)	57(3.8%)	0.959
Unknow	8(0.4%)	2(0.6%)	6(0.4%)	0.644

DLI = dentate line invasion

non-DLI groups. To address these disparities, Cox multivariate regression was used to control for confounding variables. Third, while our study highlights DLI as a prognostic marker for recurrence, the cohort's temporal span reflects evolving neoadjuvant therapy standards. Notably, only 24.4% of patients received neoadjuvant CRT. This precludes definitive conclusions about whether DLI-associated recurrence risk persists in patients treated with contemporary multimodal strategies. Future prospective studies integrating TNT and molecular profiling are needed to validate DLI's prognostic role in the context of intensified neoadjuvant therapy. Additionally, changes in oncological treatment protocols for rectal cancer occurred throughout the study period. These changes included the application of various neoadjuvant and adjuvant regimens and the adoption of enhanced recovery pathways, which might have affected the surgical outcomes for a subset of patients.

Conclusion

In summary, the presence of DLI might serve as a prognostic indicator for adverse local recurrence and distant metastasis in patients who have undergone APR for rectal cancer. Recognising DLI could be an instrumental factor in guiding clinical decision-making for patient management. Validation of these findings through a multicentre prospective study evaluating a surveillance protocol is warranted.

Author contributions

Z.Z is the first author. He designed the study, drafted the article, and made statistical analysis. D.J., Y.J. collected the data, analyzed data and interpreted data. J.Q., M.R., W.P. revised the article and interpreted data. J.B., F.Q., H.Z. and Z.W. help collect the data, interpret the data and created digital artwork. Z.Zheng, Q.L. contributed cases. J.L. and Z.Zhao are the corresponding authors. J.L. designed the study, interpreted data and revised the article. Final approval of manuscript is done by all authors.

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Data availability

The datasets generated during this study are not publicly available due to patient privacy restrictions but are available from the corresponding author on reasonable request. Data access requires approval from the Institutional Review Board of Cancer Hospital of Chinese Academy of Medical Sciences and a signed data use agreement.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by The National Cancer Center's Institute Research Medical Ethics Committee (23/180–3922, 11 May 2023). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Competing interests

The authors declare that they have no competing interests. Research registration unique identifying number.

Guarantor
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