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D3 Lymph Node Dissection Improves Survival Outcomes in Patients With cT2 Colorectal Non-well-differentiated Adenocarcinoma

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Abstract. *Background/Aim: The extent of lymphadenectomy appropriate for patients with cT2 colorectal cancer (CRC) remains controversial. This study was conducted to compare the survival outcomes of patients with cT2 CRC after D3 or D2 lymph node dissection (LND). Patients and Methods: Qualifying subjects (N=590) had undergone radical colorectal resections for cT2 CRC and were grouped according to tumor histological type as either well-differentiated (WDA) or non-well-differentiated (nWDA) adenocarcinoma. Each group was further stratified into D3 or D2 LND according to the extent of lymph node dissection. Propensity score matching (PSM) was applied to balance potential confounding factors, and identify independent prognostic risk factors using Cox regression analysis. Primary outcome measures were overall survival (OS), cancer-specific survival, (CSS) and relapse-free survival rate (RFS). Results: Prior to PSM, OS and CSS differed significantly (p=0.001 and p=0.021, respectively) for D3 and D2 LND subsets in the nWDA group. Estimated hazard ratios (HRs) for OS and CSS were 3 [95% confidence interval (CI)=1.3-6.8; p=0.0084] and 3.2 (95%CI=1-10; p=0.047), respectively, in the D3 LND subset. After matching, significant differences in OS (p=0.007) and CSS (p=0.012) were also observed, with corresponding estimated HRs of 4 (95%CI=1.2-14; p=0.028) and 16 (95%CI=1.2-220; p=0.034). In the WDA group, D2 and D3 LND procedures displayed similar favorable prognoses before and after matching. Postoperative complications emerged as independent risk factors for prognosis in the WDA group of patients with cT2 CRC. Conclusion: D3 LND improved survival outcomes in patients with non-well-differentiated cT2 CRC. In patients with well-differentiated cT2 adenocarcinoma, D3 LND was preferred to reduce perioperative complications.*

At present, radical resection remains the preferred treatment for locally advanced colorectal cancer (CRC). The Japanese Society for Cancer of the Colon and Rectum (JSCCR) maintains that the appropriate extent of lymph node dissection depends on nodal metastasis and depth of tumor invasion determined before or during surgery (1). JSCCR guidelines for treating CRC clearly advocate D2 lymph node dissection (D2 LND) for cT1 CRC, and D3 LND should be performed when lymph node metastasis is suspected or in cases of T3 or T4 tumor depth. However, a clear recommendation for the optimal LND level for cT2 CRC is lacking (1, 2).

Propensity score matching (PSM) has been widely used in recent clinical studies to minimize effects of confounding variables across study groups (3). In our previous study, we observed better long-term survival after D3 LND than after D2 LND in patients with pT2 tumors with PSM (4), although in practice, surgeons cannot gauge the exact depth of invasion before surgery. It is therefore critical to determine whether patients with cT2 CRC should undergo D3 or D2 LND. Consequently, the aim of this study was to investigate the optimal extent of LND in patients with cT2 CRC.

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Key Words: cT2 colorectal cancer, D3 lymph node dissection, propensity score matching.

Patients and Methods

Data collection. This was a retrospective cohort study conducted at the International Medical Center of the Saitama Medical University, a large cancer center in Japan. Data retrieval encompassed a 13-year period, from April 2007 to December 2020, and was approved by the hospital's ethics committee.

T categorization and nodal dissection definitions. Tumor staging, and lymph node dissection adhered to the Japanese Colorectal Cancer Protocol, 7th edition. D1 LND entailed pericolic lymph node dissection; D2 LND called for dissection of both pericolic and intermediate lymph nodes; and D3 LND required dissection of pericolic, intermediate, and apical lymph nodes.

Depending on the depth of tumor invasion, removal of the bowel 10 cm proximal and distal to the tumors is standard for colon cancers. For rectal cancers, proximal resection margins were stipulated as 10 cm, with distal margins of 2-3 cm (5).

Statistical analysis. In the given time frame, 6,273 patients with CRC underwent surgical resections, all granting written informed consent prior to surgery. Among these, 629 (10.03%) were clinically diagnosed with T2 (cT2) CRC preoperatively. Grounds for exclusion were benign tumors, multiple cancers, recurrent CRC, inflammatory colitis with malignant tumors, unresectable CRC, and D0 or D1 LND (Figure 1).

Preliminary analysis of the overall cohort was based on the level of LND (D2 *vs*. D3). We used PSM to balance potential confounding factors, assessing LND subsets before and after PSM. Propensity score weights were used to balance the basic variable logistic regression models for comparative analysis. Sex, age, body mass index, tumor location, abdominal surgery history, neoadjuvant chemotherapy, comorbidity, operation method, operative time (min), tumor size, proximal and distal resection margins, gross tumor type, lymphatic invasion, perineural infiltration, vascular invasion, lymph node metastasis, and pathological stage were incorporated into a multivariate model for PSM. Subjects were then grouped according to tumor histological types as well-differentiated (WDA) or non-well-differentiated (nWDA) adenocarcinoma. The latter included moderately or poorly differentiated adenocarcinoma, signet-ring cell carcinoma, mucinous adenocarcinoma, and undifferentiated adenocarcinoma. These two groups were further stratified according to LND level as D2 or D3 subsets to compare clinical characteristics, postoperative pathologic findings, and survival outcomes. Prognostic analyses were similarly conducted before and after PSM. Cox logistic regression analysis was applied to determine differences in overall survival (OS), cancer-specific survival (CSS), and relapse-free survival (RFS) for D2 and D3 LND procedures.

All computations were driven by standard software (SPSS v22; IBM Corp, Armonk, NY, USA), setting significance at $p<0.05$. To compare categorical variables, chi-square or Fisher's exact test was invoked. The Kaplan–Meier method was used to estimate OS, CSS, and RFS.

Results

Overall cohort (cT2 CRC). A total of 590 patients with cT2 CRC were selected for study (D2 LND: 107/590, 18.1%; D3 LND: 483/590, 81.9%). Members of the D3 LND subset were younger [mean±standard deviation (SD)=66.3±10.0 *vs*. 73.2±11.0 years; $p<0.001$], showed greater proclivity for rectal cancer (52.0% *vs*. 35.5%; $p=0.003$), and laparoscopic surgery was more likely (95.2% *vs*. 79.4%; $p<0.001$). However, family history of cancer was less (12.8% *vs*. 25.2%; $p=0.002$) in this subset, as were postoperative complications (15.7% *vs*. 28.0%; $p=0.004$), and instances of substantial (≥100 ml) operative blood loss (9.5% *vs*. 20.6%; $p=0.002$). No significant group-wise differences (all $p\geq0.05$) were determined for sex, BMI (mean±SD, 22.9±3.55 *vs*. 22.8±3.26 kg/m^2; $p\geq0.05$), CEA level ≥5 ng/ml (21.5% *vs*. 14.1%), neoadjuvant chemotherapy (2.8% *vs*. 3.3%), and operative time (mean±SD, 211±94.6 *vs*. 210±73.9 min) (Supplementary Table I).

Upon further analysis of the cT2 CRC cohort, 42 subjects (39.3%) were eventually categorized as pathologic T0-1 (pT0-1), whereas 160 (27%) were pT3-4. In only 236 cases (40%) the clinical diagnoses were consistent with pathologic outcomes (Supplementary Table I).

In terms of postoperative pathologic findings, lymph node metastasis was confirmed in 172 (29.2%) of all cT2 CRC cohort members. In the D3 LND subset, proximal resection margin was 1.1 cm longer (mean±SD, 13.0±4.51 *vs*. 11.9±4.55 cm; $p=0.0199$), and postoperative hospital stay was 2.32 days shorter (9.28±8.22 *vs*. 11.6±8.71; $p=0.012$). There were also comparatively more infiltrating or ulcerative tumor types (60.2% *vs*. 48.6%; $p=0.0356$) and more harvested lymph nodes (mean±SD, 23.1±10.9 *vs*. 19.7±9.71; $p=0.0013$) in the D3 LND subset, although positive lymph node counts (D2 *vs*. D3) did not differ significantly (29.8% *vs*. 26.2%; $p\geq0.05$). No significant differences were otherwise observed with respect to tumor size, distal resection margin, time to first food intake, tumor histological type, infiltrative pattern, lymphatic invasion, venous invasion, or postoperative pathologic status (Supplementary Table II).

We also analyzed long-term prognosis of the LND subsets and discovered that the 5-year OS for D3 (*vs*. D2) LND was significantly better (93.8% *vs*. 83.2%; $p=0.001$) (Supplementary Figure 1A), although CSS (96.5% *vs*. 94.4%; $p=0.321$), and RFS (91.9% *vs*. 92.5%; $p=0.869$) did not differ significantly (Supplementary Figure 1C, E).

To accurately assess the effects of various parameters on patient prognosis, Cox regression analysis was performed prior to PSM. D3 LND subsequently emerged as a significant independent predictor of OS [hazard ratio (HR)=2.3, 95% confidence interval (CI)=1.2-4.3; $p=0.012$], as did age (HR=1, 95%CI=1-1.1; $p=0.034$), tumor size (HR=1.3, 95%CI=1-1.6; $p=0.025$) and venous invasion (HR=2.2, 95%CI=1.1-4.3; $p=0.024$) (Supplementary Table III). CEA level (HR=2.6, 95%CI=1.1-6.4; $p=0.031$), family cancer history (HR=3, 95%CI=1-8.6; $p=0.047$), tumor size (HR=1.5, 95%CI=1.1-2; $p=0.0035$), and lymphatic invasion (HR=3.1, 95%CI=1.2-7.7; $p=0.015$) were identified as independent prognostic factors for CSS (Supplementary Table IV).

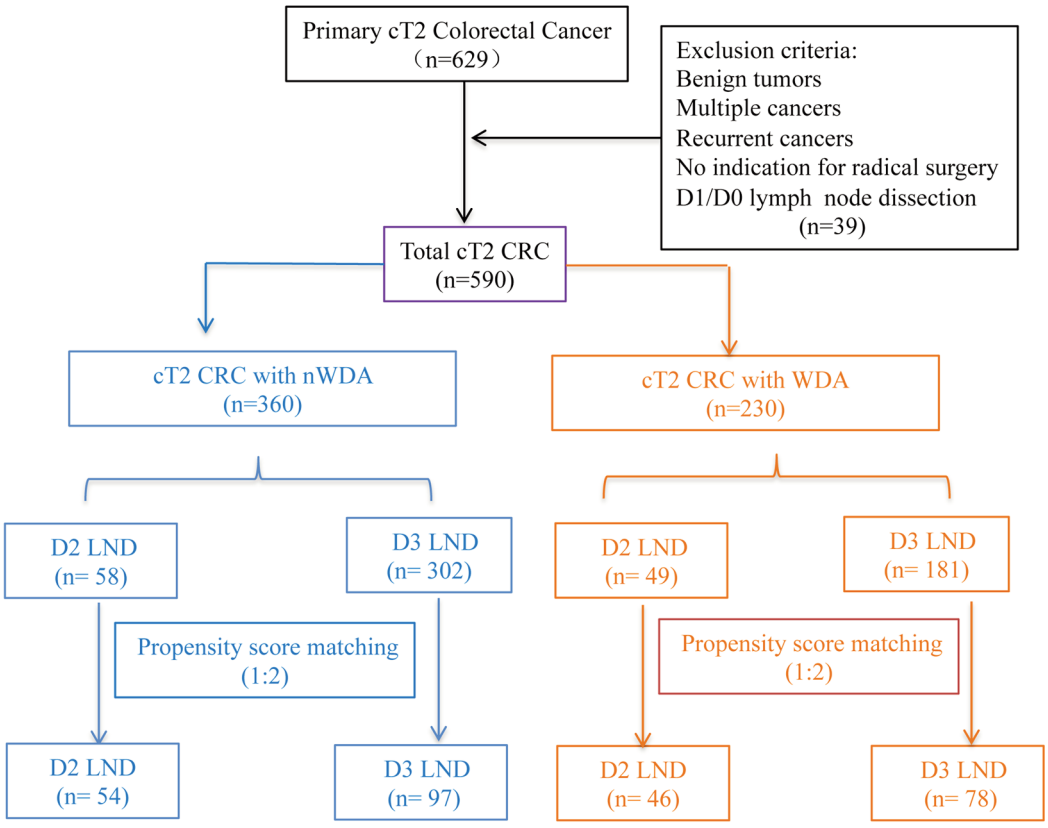

Figure 1. *Schematic of patient allocation/study design. CRC: Colorectal cancer; LND: lymph node dissection; PSM: propensity score matching; WDA: well-differentiated adenocarcinoma; nWDA: non-well-differentiated adenocarcinoma (moderately and poorly differentiated adenocarcinoma, signet-ring cell carcinoma, mucinous adenocarcinoma, and undifferentiated adenocarcinoma).*

D2 and D3 LND subsets were finally subjected to PSM at a 1:1 ratio (n=98 each) and compared again. Other than harvested lymph node counts, pathologic features of the two groups were similar by univariate analysis (Supplementary Table I and Supplementary Table II). In Cox regression analysis, only age (HR=1.1, 95%CI=1-1.1; p=0.004) was independently predictive of OS. Independent prognostic factors for CSS included D3 LND (HR=0.041, 95%CI=0.0086-0.19; p<0.001), as well as age, family cancer history, tumor size, and venous invasion (Supplementary Table III and Supplementary Table IV).

In comparing survival outcomes of D2 and D3 LND after PSM, 5-year OS (p=0.187), CSS (p=0.626), and RFS (p=0.676) rates were not significantly different (Supplementary Figure 1B, D, E). There were no significant differences in recurrence rates recorded for D2 and D3 LND subsets before (7.5% *vs*. 8.1%) or after (7.1% *vs*. 9.2%) matching (both p≥0.05 (Supplementary Table V).

Group with nWDA CRC. Next, we conducted a controlled study of the nWDA group before (D2 LND: 58/360, 16.1%; D3 LND: 302/360, 83.9%) and after 1:2 matching (D2 LND, 54; D3 LND, 97). Clinical characteristics and pathologic findings in members of the nWDA group were like those of the overall cohort (Table I and Table II). The D3 (*vs*. D2) LND subset fared significantly better before and after PSM in terms of OS (before: 93.7% *vs*. 79.3, p=0.001; after: 94.8% *vs*. 81.5, p=0.007) and CSS (before: 96.7% *vs*. 89.7%, p=0.021; after: 99.0% *vs*. 90.7%, p=0.012) (Figure 2).

In Cox multivariate analysis, D3 LND was also identified as an independent risk factor for OS before (HR=3, 95%CI=1.3-6.8; p=0.0084) and after (HR=4, 95%CI=1.2-14; p=0.028) matching (Table III). The same was true for D3 LND in CSS, before PSM (HR=3.2, 95%CI=1-10; p=0.047) and after (HR=16, 95%CI=1.2-220; p=0.034) (Table IV). Another independent prognosticator for CSS, both before (HR=1.8, 95%CI=1.2-2.6; p=0.0039) and after (HR=2.5, 95%CI=1.2-5.3; p=0.018) matching, was tumor size. RFS did not differ significantly by LND subset before (p=0.217) or after (p=0.383) PSM (Figure 2A). Recurrences in the D2 (*vs*. D3) LND subset appeared 3-5% higher, but there were no real statistical differences pre- and post-PSM (before:

Table I. *Clinical and surgical characteristics of patients with non-well-differentiated adenocarcinoma (cT2 CRC) before and after propensity score matching (PSM).*

Parameters	Before PSM			After PSM (1:2)		
	D2 LND (N=58)	D3 LND (N=302)	*p*-Value	D2 LND (N=54)	D3 LND (N=97)	*p*-Value
Sex						
Male	37 (63.8%)	177 (58.6%)	N.S.	36 (66.7%)	66 (68.0%)	N.S.
Female	21 (36.2%)	125 (41.4%)		18 (33.3%)	31 (32.0%)	
Age (years)						
Mean (SD)	72.7±12.5	66.6±9.53	<0.001	72.9±11.9	69.3±9.59	N.S.
BMI						
Mean (SD)	22.3±3.06	22.7±3.28	N.S.	22.4±3.13	22.6±3.13	N.S.
CEA (ng/ml)						
<5	45 (77.6%)	252 (83.4%)	N.S.	43 (79.6%)	83 (85.6%)	N.S.
≥5	13 (22.4%)	50 (16.6%)		11 (20.4%)	14 (14.4%)	
Tumor location						
Colon	34 (58.6%)	144 (47.7%)	N.S.	30 (55.6%)	50 (51.5%)	N.S.
Rectum	24 (41.4%)	158 (52.3%)		24 (44.4%)	47 (48.5%)	
Abdominal surgery history						
No	30 (51.7%)	196 (64.9%)	N.S.	28 (51.9%)	56 (57.7%)	N.S.
Yes	28 (48.3%)	106 (35.1%)		26 (48.1%)	41 (42.3%)	
Neoadjuvant chemotherapy						
No	55 (94.8%)	293 (97.0%)	N.S.	51 (94.4%)	95 (97.9%)	N.S.
Yes	3 (5.2%)	9 (3.0%)		3 (5.6%)	2 (2.1%)	
Comorbidity						
No	16 (27.6%)	111 (36.8%)	N.S.	15 (27.8%)	36 (37.1%)	N.S.
Yes	42 (72.4%)	191 (63.2%)		39 (72.2%)	61 (62.9%)	
Operation method						
Laparoscopic surgery	46 (79.3%)	289 (95.7%)	<0.001	46 (85.2%)	89 (91.8%)	N.S.
Open surgery	12 (20.7%)	13 (4.3%)		8 (14.8%)	8 (8.2%)	
Operative time(min)						
Mean (SD)	204±87.1	208±72.0	N.S.	207±88.2	209±75.1	N.S.
Postoperative complications						
No	45 (77.6%)	262 (86.8%)	N.S.	42 (77.8%)	85 (87.6%)	N.S.
Yes	13 (22.4%)	40 (13.2%)		12 (22.2%)	12 (12.4%)	
Operative blood loss(ml)						
<100	45 (77.6%)	275 (91.1%)	0.00574	44 (81.5%)	90 (92.8%)	N.S.
≥100	13 (22.4%)	27 (8.9%)		10 (18.5%)	7 (7.2%)	

BMI: Body mass index; CEA: carcinoembryonic antigen; D2 LND: D2 lymph node dissection; D3 LND: D3 lymph node dissection.

13.8% *vs*. 8.9%; after: 13.0% *vs*. 9.3%) (both $p \geq 0.05$) (Supplementary Table VI).

Group with WDA CRC. We similarly stratified the WDA group according to LND level (D2: 49/230, 21.3%; D3: 181/230, 78.7%) for comparisons before and after 1:2 matching (D2 LND, 46; D3 LND, 78). Before and after PSM, postoperative complications alone were shown to be significantly more frequent in the D2 (*vs*. D3) LND subset [before: 34.7% *vs*. 19.9% ($p=0.0464$); after: 32.6% *vs*. 15.4% ($p=0.0434$)], with total harvested lymph node counts higher in the D3 (*vs*. D2) LND subset (before PSM: 23.3±11.3 *vs*. 18.7±11.1; $p=0.012$; after PSM: 23.2±10.1 *vs*. 17.4±8.08; $p<0.001$). Other parameters were not significantly different (Table V and Table VI). Based on LND level, there were no significant differences in OS, CSS, or RFS before ($p=0.191$, $p=0.169$, and $p=0.066$, respectively) or after ($p=0.891$, $p=0.283$, and $p=0.179$, respectively) PSM (Figure 3).

In the multivariate analysis, postoperative complications proved to be independent risk factors for OS before (HR=5.1, 95%CI=1.6-16; $p=0.0067$) and after (HR=6, 95%CI=1.4-26; $p=0.017$) matching (Table VII) and for CSS before (HR=11, 95%CI=1.5-80; $p=0.019$) and after ($p<0.001$) matching. D3 LND was not independently associated with OS, before ($p=0.7$) or after ($p=0.520$) matching, or with CSS, before ($p=1$) or after ($p=1$) matching (Table VIII). There were no significant differences in recurrence rates for D2 and D3 LND in the WDA group (with cT2 CRC) (Supplementary Table VII).

Table II. *Pathologic findings in patients with non-well-differentiated adenocarcinoma (cT2 CRC) before and after propensity score matching (PSM).*

Parameters	Before PSM			After PSM (1:2)		
	D2 LND (N=58)	D3 LND (N=302)	*p*-Value	D2 LND (N=54)	D3 LND (N=97)	*p*-Value
Tumor size (cm)						
Mean (SD)	2.59±1.12	2.57±1.04	N.S.	2.59±1.08	2.74±1.15	N.S.
Proximal resection margin (cm)						
Mean (SD)	11.8±5.08	13.1±4.32	N.S.	12.1±5.07	12.9±4.53	N.S.
Distal resection margin (cm)						
Mean (SD)	6.33±3.88	6.06±4.09	N.S.	6.42±3.98	6.05±4.02	N.S.
Postoperative hospital stay (days)						
Mean (SD)	11.4±7.81	8.66±4.88	0.0124	11.1±7.24	9.21±5.19	N.S.
Time to first food intake (days)						
Mean (SD)	3.33±1.80	3.55±2.88	N.S.	3.37±1.86	3.47±2.15	N.S.
Gross type						
Protruding	28 (48.3%)	94 (31.1%)	0.0175	26 (48.1%)	43 (44.3%)	N.S.
Infiltrate or ulcerative	30 (51.7%)	208 (68.9%)		28 (51.9%)	54 (55.7%)	
Histology type						
Mod	53 (91.4%)	276 (91.4%)	N.S.	49 (90.7%)	84 (86.6%)	N.S.
Poor, Sig, Muc	5 (8.6%)	26 (8.6%)		5 (9.3%)	13 (13.4%)	
Infiltration form						
a	7 (12.1%)	28 (9.3%)	N.S.	7 (13.0%)	11 (11.3%)	N.S.
b and c	51 (87.9%)	274 (90.7%)		47 (87.0%)	86 (88.7%)	
Lymphatic invasion						
No	38 (65.5%)	199 (65.9%)	N.S.	35 (64.8%)	69 (71.1%)	N.S.
Yes	20 (34.5%)	103 (34.1%)		19 (35.2%)	28 (28.9%)	
Venous invasion						
No	24 (41.4%)	116 (38.4%)	N.S.	24 (44.4%)	40 (41.2%)	N.S.
Yes	34 (58.6%)	186 (61.6%)		30 (55.6%)	57 (58.8%)	
Harvested lymph nodes						
Mean (SD)	20.5±8.33	23.0±10.7	0.0455	20.3±8.22	23.0±9.73	N.S.
pT						
0	0 (0%)	2 (0.7%)	N.S.	0 (0%)	1 (1.0%)	N.S.
1	19 (32.8%)	67 (22.2%)		17 (31.5%)	25 (25.8%)	
2	20 (34.5%)	139 (46.0%)		20 (37.0%)	43 (44.3%)	
3	16 (27.6%)	89 (29.5%)		14 (25.9%)	28 (28.9%)	
4	3 (5.2%)	5 (1.7%)		3 (5.6%)	0 (0%)	
Nodal metastasis						
No	39 (67.2%)	194 (64.2%)	N.S.	36 (66.7%)	68 (70.1%)	N.S.
Yes	19 (32.8%)	108 (35.8%)		18 (33.3%)	29 (29.9%)	
Pathological stage						
0	0 (0%)	2 (0.7%)	N.S.	0 (0%)	1 (1.0%)	N.S.
I	29 (50.0%)	147 (48.7%)		29 (53.7%)	49 (50.5%)	
II	9 (15.5%)	44 (14.6%)		7 (13.0%)	18 (18.6%)	
III	16 (27.6%)	100 (33.1%)		15 (27.8%)	28 (28.9%)	
IV	4 (6.9%)	9 (3.0%)		3 (5.6%)	1 (1.0%)	

Protruding: Type 0, superficial; Type 1, protuberant, infiltrative, or ulcerative; Type 2, expansive ulceration; Type 3, infiltrative ulcerating; Type 4: diffusely ulcerating; Mod: moderately differentiated adenocarcinoma; Poor: poorly differentiated adenocarcinoma; Muc: mucinous carcinoma; Sig, signet-ring carcinoma; D2 LND: D2 lymph node dissection, D3 LND: D3 lymph node dissection.

Discussion

In the present study, we found that OS and CSS in patients of the nWDA group (with cT2 CRC) fared significantly better after D3 (*vs*. D2) LND procedures. Multivariate analysis also identified D3 LND as an independent predictor of OS and CSS. However, long-term prognosis in patients with WDA was no worse after D2 LND than after D3 LND. The nature of malignant cells plays a decisive role in selecting clinical treatment for CRC (1). After timely endoscopic resection of T1b tumors, additional radical

Table III. *Multivariate logistic regression analysis of overall survival (OS) in patients with non-well-differentiated adenocarcinoma (cT2 CRC) before and after propensity score matching (PSM).*

Variable	OS before PSM			OS after PSM		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
D3 LND *vs*. D2 LND	3	1.3-6.8	0.0084	4	1.2-14	0.028
Age (years)	1	1-1.1	0.077	1.1	1-1.2	0.011
CEA (ng/ml), <5 vs ≥5	1.6	0.71-3.5	0.27	1.1	0.29-4.5	0.860
Tumor location, Colon *vs*. Rectum	1.2	0.57-2.7	0.6	2.7	0.77-9.2	0.120
Operation method, laparoscopic *vs*. open	1	0.31-3.2	1	1.4	0.2-9.2	0.760
Tumor size (cm)	1.3	0.97-1.8	0.078	1.2	0.73-1.9	0.510
pT 0-1 *vs*. pT 2-4	4.2	0.95-19	0.058	7.50×10^{8}	0-Inf	1.000
Histology type, Mod *vs*. Poor, Sig, Muc	0.37	0.08-1.7	0.21	0.6	0.12-3	0.540
Lymphatic invasion, No *vs*. Yes	1.2	0.54-2.6	0.67	0.81	0.25-2.7	0.740
Venous invasion, No *vs*. Yes	2.1	0.84-5.3	0.11	0.81	0.23-2.8	0.740

LND: Lymph node dissection; HR: hazard ratio; CI: confidence interval.

Table IV. *Multivariate logistic regression analysis of cancer-specific survival (CSS) in patients with non-well-differentiated adenocarcinoma (cT2 CRC) before and after propensity score matching (PSM).*

Variable	CSS before PSM			CSS after PSM		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
D3 LND *vs*. D2 LND	3.2	1-10	0.047	16	1.2-220	0.034
Age (years)	1	0.97-1.1	0.46	1	0.93-1.2	0.460
CEA (ng/ml), <5 *vs*. ≥5	3	1.1-8.4	0.037	0.76	0.072-8.1	0.820
Operation method, laparoscopic *vs*. open	0.28	0.04-2	0.2	0.2	0.0071-5.9	0.350
Tumor size (cm)	1.8	1.2-2.6	0.0039	2.5	1.2-5.3	0.018
pT 0-1 *vs*. pT 2-4	8.60×10^{7}	0-Inf	1	4.90×10^{8}	0-Inf	1.000
Histology type, Mod *vs*. Poor, Sig, Muc	0.24	0.024-2.4	0.22	0.59	0.05-7	0.680
Lymphatic invasion, No *vs*. Yes	2.5	0.82-7.6	0.11	1.9	0.29-12	0.500

surgical resection is advised if differentiation is poor, owing to the potential for later recurrence or lymph node metastasis (6). In Europe, the United States, and China, adjuvant chemotherapy is also recommended for stage II CRC that is poorly differentiated (7-9). According to our data, CSS after D2 LND was significantly better (by 10-11%) in patients with WDA (*vs*. nWDA), and postoperative recurrence rate was significantly higher (by 13%) in those with nWDA (*vs*. WDA). Thus, D2 LND does not seem therapeutically sufficient in the setting of nWDA.

As is generally known, radical resection of CRC in Japan is tentatively based on D3 LND, whereas complete mesenterectomy (CME), with central vascular ligation (CVL) (10) and total mesorectal excision (TME) (11), is the rule in Europe and the United States. The aim of CME/CVL is to mobilize the colon along embryonic and anatomic planes so that circumferential margins of excision are tumor-free, ligate the root of the primary arterial feeder (to tumor), and excise an adequate portion of mesentery, all of which represent the same basic concept as D3 LND (12, 13). Moreover, it has been reported that the incidence of mesenteric lymph node metastasis >10 cm from tumors is extremely low (5), perhaps explaining the rather good prognosis achieved by either approach.

In 2015, Kotake's team noted that D3 LND did not improve the prognosis of patients with pT2 colon cancer, using data collected from 1974 to 2005. Of course, open surgery did predominate during that era, and the Japanese nodal staging system was based on locations of lymph nodes relative to tumors (14). An earlier study of ours, dating from 2007 to 2020, focused on laparoscopic resection of both colon and rectal cancers. According to the latest TNM criteria, lymph node staging is determined by positive lymph node counts. All these factors may have contributed to the differing results between the two studies.

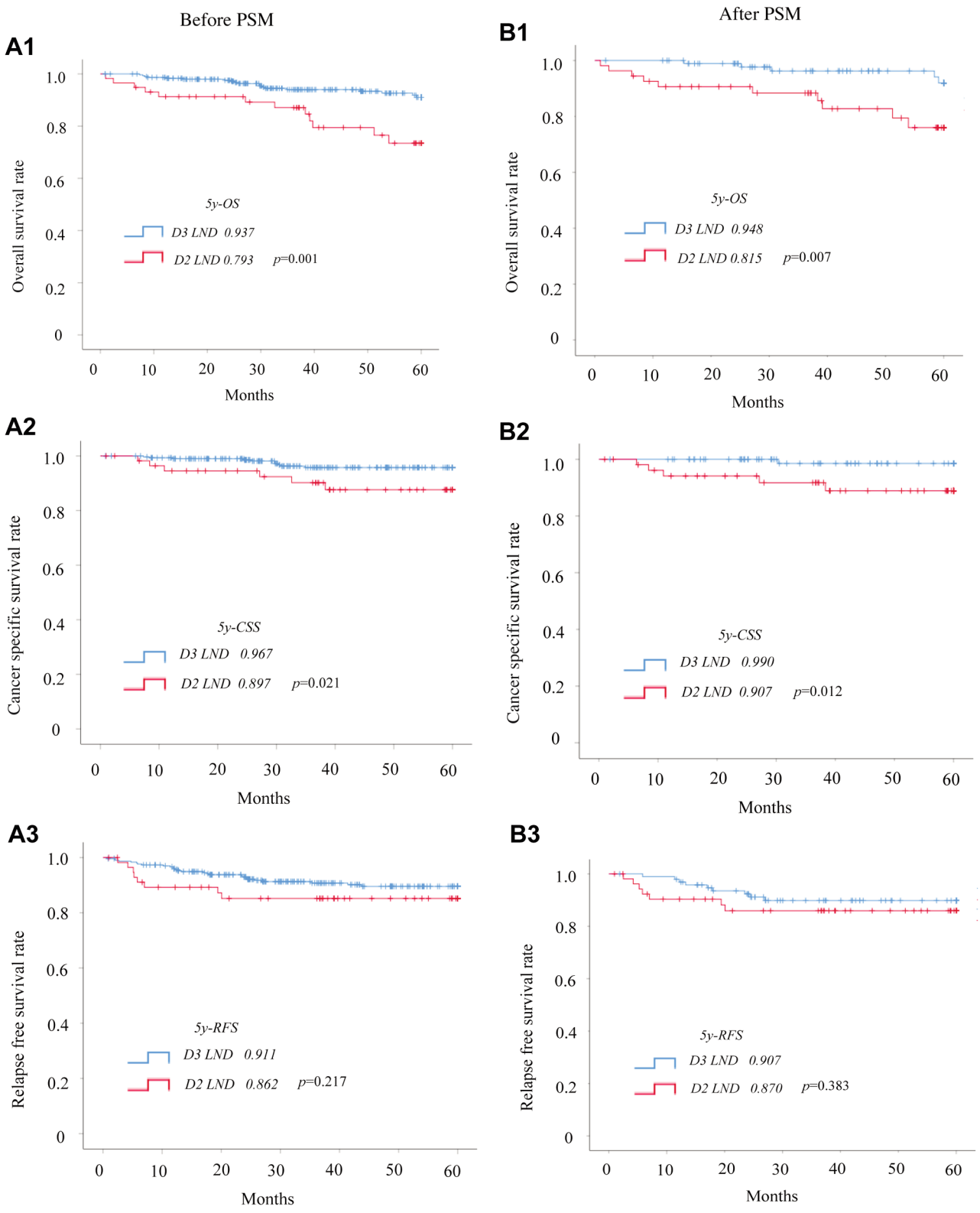

Figure 2. *Survival outcomes of patients with non-well-differentiated adenocarcinoma stratified by lymph node dissection (D2 vs. D3) before and after propensity score matching (PSM) [A1: overall survival (OS) before PSM, A2: cancer specific survival (CSS) before PSM, A3: relapse-free survival (RFS) before PSM; B1: OS after PSM, B2: CSS after PSM, B3: RFS after PSM].*

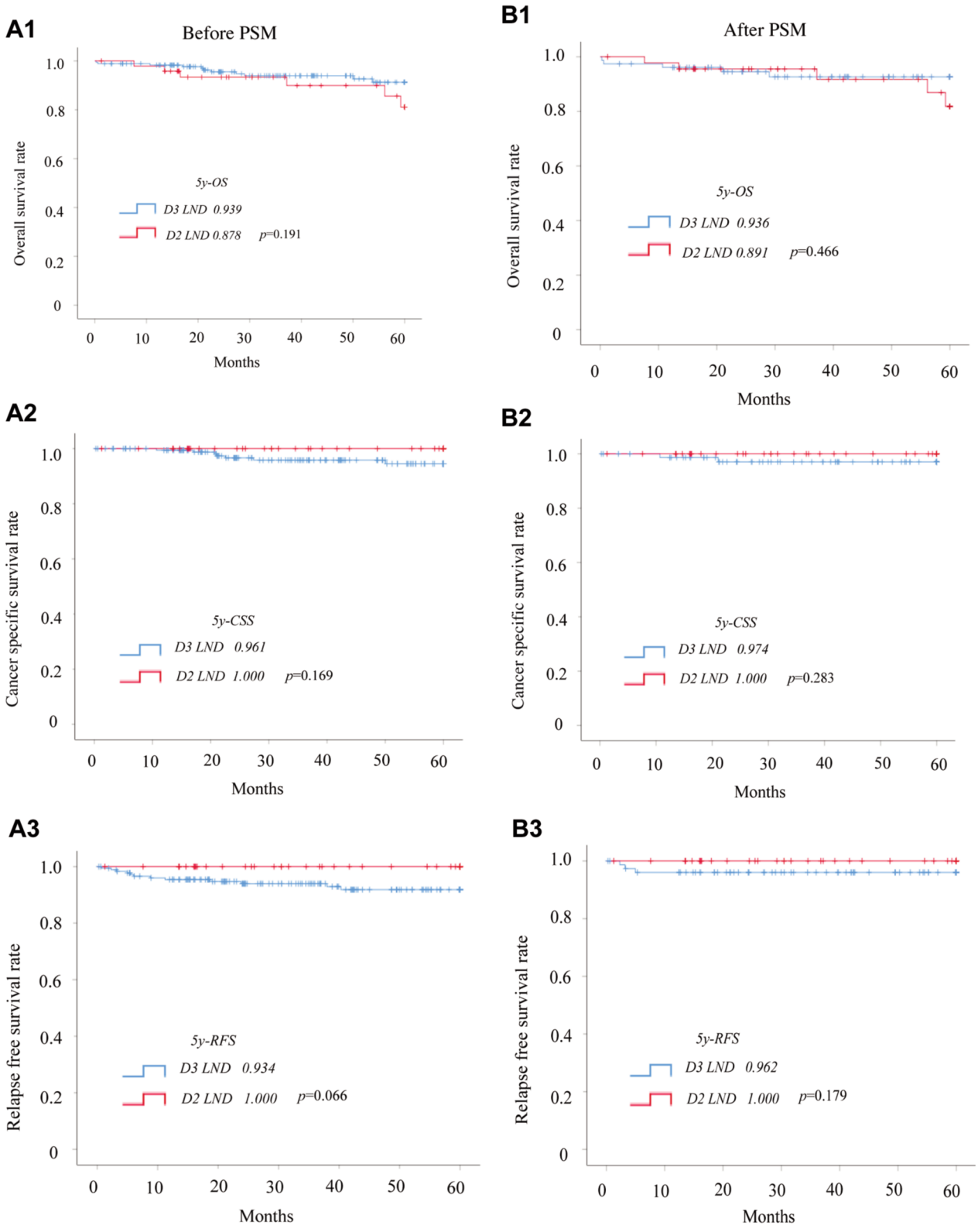

Figure 3. *Survival outcomes of patients with well-differentiated adenocarcinoma, stratified by lymph node dissection (D2 vs. D3) before and after propensity score matching (PSM) [A1: overall survival (OS) before PSM, A2: cancer specific survival (CSS) before PSM, A3: relapse-free survival (RFS) before PSM; B1: OS after PSM, B2: CSS after PSM, B3: RFS after PSM].*

Table V. *Clinical and surgical characteristics of patients with well-differentiated adenocarcinoma (cT2 CRC) before and after propensity score matching (PSM).*

Parameters	Before PSM			After PSM (1:2)		
	D2 LND (N=49)	D3 LND (N=181)	*p*-Value	D2 LND (N=46)	D3 LND (N=78)	*p*-Value
Sex						
Male	34 (69.4%)	105 (58.0%)	N.S.	31 (67.4%)	54 (69.2%)	N.S.
Female	15 (30.6%)	76 (42.0%)		15 (32.6%)	24 (30.8%)	
Age (years)						
<70	15 (30.6%)	103 (56.9%)	0.0019	14 (30.4%)	28 (35.9%)	N.S.
≥70	34 (69.4%)	78 (43.1%)		32 (69.6%)	50 (64.1%)	
BMI						
Mean (SD)	23.6 (3.95)	22.8 (3.22)	N.S.	23.7 (3.93)	22.6 (3.31)	N.S.
CEA (ng/ml)						
<5	39 (79.6%)	163 (90.1%)	N.S.	32 (69.6%)	59 (75.6%)	N.S.
≥5	10 (20.4%)	18 (9.9%)		14 (30.4%)	19 (24.4%)	
Tumor location						
Colon	35 (71.4%)	88 (48.6%)	0.0074	32 (69.6%)	59 (75.6%)	N.S.
Rectum	14 (28.6%)	93 (51.4%)		14 (30.4%)	19 (24.4%)	
Abdominal surgery history						
No	22 (44.9%)	109 (60.2%)	N.S.	22 (47.8%)	40 (51.3%)	N.S.
Yes	27 (55.1%)	72 (39.8%)		24 (52.2%)	38 (48.7%)	
Neoadjuvant chemotherapy						
No	49 (100%)	174 (96.1%)	N.S.	46 (100%)	76 (97.4%)	N.S.
Yes	0 (0%)	7 (3.9%)		0 (0%)	2 (2.6%)	
Comorbidity						
No	10 (20.4%)	59 (32.6%)	N.S.	9 (19.6%)	17 (21.8%)	N.S.
Yes	39 (79.6%)	122 (67.4%)		37 (80.4%)	61 (78.2%)	
Operation method						
Laparoscopic surgery	39 (79.6%)	171 (94.5%)	0.00275	39 (84.8%)	73 (93.6%)	N.S.
Open surgery	10 (20.4%)	10 (5.5%)		7 (15.2%)	5 (6.4%)	
Operative time(min)						
Mean (SD)	218 (103)	212 (77.0)	N.S.	211 (91.9)	195 (74.3)	N.S.
Postoperative complications						
No	32 (65.3%)	145 (80.1%)	0.0464	31 (67.4%)	66 (84.6%)	0.0434
Yes	17 (34.7%)	36 (19.9%)		15 (32.6%)	12 (15.4%)	
Operative blood loss (ml)						
<100	40 (81.6%)	162 (89.5%)	N.S.	40 (87.0%)	74 (94.9%)	N.S.
≥100	9 (18.4%)	19 (10.5%)		6 (13.0%)	4 (5.1%)	

LND: Lymph node dissection; BMI: body mass index.

Prognostication in cancer treatment is a multifactorial effort. Perioperative complications also directly affect long-term survival rates (15). D3 LND entails complete removal of all mesenteric and ligated root vessels, which D2 LND does not; therefore, fewer harvested lymph nodes (range=3.4-5.9) result through D2 LND. Furthermore, D2 LND leaves many free mesenteric vascular branches as potential sources of bleeding. Postoperative complications in our WDA group were in fact more frequent after D2 (*vs*. D3) LND. Such complications may ultimately undermine patient immunity and directly interfere with postoperative adjuvant chemotherapy, impacting prognosis if not performed as scheduled. In patients with WDA, D3 LND is therefore preferential as a means of reducing perioperative complications.

Study limitations. The accuracy of clinically assessed preoperative T status and the presence/absence of lymph node metastasis are key elements in determining the need for D3 *vs*. D2 LND. Only 40% of our patients with cT2 CRC were confirmed as pT2 postoperatively, thus, it is still difficult for surgeons to reliably assess degrees of tumor penetration before surgery. Although endoscopic ultrasonography may help in this regard (16, 17), the necessity of endoscopic ultrasonography for every patient and its broad clinical acceptance remains to be seen. Another

Table VI. *Pathologic findings in patients with well-differentiated adenocarcinoma (cT2 CRC) before and after propensity score matching (PSM).*

Parameters	Before PSM			After PSM (1:2)		
	D2 LND (N=49)	D3 LND (N=181)	*p*-Value	D2 LND (N=46)	D3 LND (N=78)	*p*-Value
Tumor size (cm)						
Mean (SD)	2.48±1.08	2.85±1.34	N.S.	2.47±1.09	2.62±1.11	N.S.
Proximal resection margin (cm)						
Mean (SD)	11.9±3.90	13.0±4.82	N.S.	12.0±3.93	12.4±5.54	N.S.
Distal resection margin (cm)						
Mean (SD)	8.48±5.32	6.35±4.62	0.0157	8.30±5.34	8.52±4.58	N.S.
Postoperative hospital stay (days)						
Mean (SD)	11.9±9.75	10.3±11.8	N.S.	11.5±9.82	9.74±15.4	N.S.
Time to first food intake (days)						
Mean (SD)	4.45±4.06	3.56±2.67	N.S.	4.28±4.06	3.41±2.09	N.S.
Gross type						
Protruding	27 (55.1%)	98 (54.1%)	N.S.	24 (52.2%)	42 (53.8%)	N.S.
Infiltrate or ulcerative	22 (44.9%)	83 (45.9%)		22 (47.8%)	36 (46.2%)	
Infiltration form						
a	10 (20.4%)	44 (24.3%)	N.S.	9 (19.6%)	16 (20.5%)	N.S.
b and c	39 (79.6%)	137 (75.7%)		37 (80.4%)	62 (79.5%)	
Lymphatic invasion						
No	44 (89.8%)	153 (84.5%)	N.S.	41 (89.1%)	67 (85.9%)	N.S.
Yes	5 (10.2%)	28 (15.5%)		5 (10.9%)	11 (14.1%)	
Venous invasion						
No	25 (51.0%)	109 (60.2%)	N.S.	24 (52.2%)	52 (66.7%)	N.S.
Yes	24 (49.0%)	72 (39.8%)		22 (47.8%)	26 (33.3%)	
Harvested lymph nodes						
Mean (SD)	18.7±11.1	23.3±11.3	0.012	17.4±8.08	23.2±10.1	<0.001
pT						
0	5 (10.2%)	20 (11.0%)	N.S.	4 (8.7%)	6 (7.7%)	N.S.
1	18 (36.7%)	63 (34.8%)		16 (34.8%)	30 (38.5%)	
2	13 (26.5%)	64 (35.4%)		13 (28.3%)	31 (39.7%)	
3	13 (26.5%)	30 (16.6%)		13 (28.3%)	11 (14.1%)	
4	0 (0%)	4 (2.2%)		0 (0%)	0 (0%)	
Nodal metastasis						
No	40 (81.6%)	145 (80.1%)	N.S.	37 (80.4%)	57 (73.1%)	N.S.
Yes	9 (18.4%)	36 (19.9%)		9 (19.6%)	21 (26.9%)	
Pathological stage						
0	5 (10.2%)	19 (10.5%)	N.S.	4 (8.7%)	6 (7.7%)	N.S.
I	27 (55.1%)	107 (59.1%)		25 (54.3%)	47 (60.3%)	
II	8 (16.3%)	15 (8.3%)		8 (17.4%)	3 (3.8%)	
III	9 (18.4%)	34 (18.8%)		9 (19.6%)	20 (25.6%)	
IV	0 (0%)	6 (3.3%)		0 (0%)	2 (2.6%)	

LND: Lymph node dissection.

issue is the single-center, retrospective nature of our investigation. Although PSM minimizes background differences, some biases in patient selection and treatment are inherent. Randomized and controlled prospective clinical studies are needed to evaluate the therapeutic benefits derived from D3 LND in patients with cT2 CRC.

Conclusion

D3 LND improved survival outcomes in patients with non-well-differentiated cT2 CRC. In patients with well-differentiated cT2 adenocarcinoma, D3 LND was preferential to reduce perioperative complications.

Supplementary Material

The supplementary tables and figures can be found here: https://kdocs.cn/l/cqFsFLT3iABA

Conflicts of Interest

The Authors declare no competing interests in relation to this study.

Table VII. *Multivariate logistic regression analysis of overall survival (OS) in patients with well-differentiated adenocarcinoma (cT2 CRC) before and after propensity score matching (PSM).*

Variable	OS before PSM			OS after PSM		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
D3 LND *vs*. D2 LND	0.79	0.23-2.6	0.7	0.63	0.16-2.6	0.520
Age (years)	1.1	1-1.2	0.026	1.1	0.99-1.2	0.073
CEA (ng/ml), <5 *vs*. ≥5	0.98	0.26-3.7	0.98	0.69	0.13-3.7	0.660
Operation method, laparoscopic *vs*. open	1.8	0.43-7.6	0.42	3.7	0.58-24	0.170
Tumor location, Colon *vs*. Rectum	0.45	0.14-1.5	0.19	1.2	0.28-5.1	0.810
Postoperative complications, Yes *vs*. No	5.1	1.6-16	0.0067	6	1.4-26	0.017
pT 0-1 *vs*. pT 2-4	3.3	0.86-13	0.081	2.8	0.56-14	0.210
Lymphatic invasion, No *vs*. Yes	1.4	0.28-6.9	0.69	1.7	0.17-16	0.670
Venous invasion, No *vs*. Yes	3.1	0.99-9.8	0.053	4.5	0.92-22	0.064

HR: Hazard ratio; CI: confidence interval; LND: lymph node dissection.

Table VIII. *Multivariate logistic regression analysis of cancer-specific survival (CSS) in patients with well-differentiated adenocarcinoma (cT2 CRC) before and after propensity score matching (PSM).*

Variable	CSS before PSM			CSS after PSM		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
D3 LND *vs*. D2 LND	1.10×10^{-9}	0-Inf	1	7.20×10^{-53}	0-Inf	1
Age (years)	0.98	0.89-1.1	0.59	0.00039	0.00033-0.00046	<0.001
CEA (ng/ml), <5 *vs*. ≥5	0.77	0.067-8.9	0.84	4.00×10^{-23}	0-Inf	1
Operation method, laparoscopic *vs*. open	2.20×10^{-9}	0-Inf	1	8.90×10^{47}	0-Inf	1
Tumor location, Colon *vs*. Rectum	0.38	0.053-2.8	0.34	4.00×10^{13}	2.4×1012-6.6×1014	<0.001
Postoperative complications, Yes *vs*. No	11	1.5-80	0.019	6.10×10^{110}	3.7×10109-1×10112	<0.001
pT 0-1 *vs*. pT 2-4	1.10×10^{9}	0-Inf	1	2.40×10^{-6}	0-Inf	1
Lymphatic invasion, No *vs*. Yes	2.4	0.33-18	0.38	1.60×10^{66}	9.6×1064-2.7×1067	<0.001
Venous invasion, No *vs*. Yes	1.7	0.27-11	0.57	7.40×10^{72}	0-Inf	0.99

HR: Hazard ratio; CI: confidence interval; LND: lymph node dissection.

Authors' Contributions

Liming Wang and Bolun Song provided original pictures and drafted the manuscript, which was reviewed by Yinggang Chen and Yasumitsu Hirano. All Authors have approved the final submission.

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