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Does Pathological T-Factor Affect Long-term Prognosis of Locally Advanced Colorectal Cancer Treated With Laparoscopic Multivisceral Resection?

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Abstract. *Background/Aim: Locally advanced colorectal cancer (LACC) has poor long-term outcomes. Our hypothesis was that the pathological tumor depth would affect postoperative outcomes in patients who underwent multivisceral resection with clear margins (R0). The aim of this study was to analyze short- and long-term outcomes in patients who underwent multivisceral resection for LACC, comparing between T3 and T4 stages. Patients and Methods: This was a propensity score-matched, retrospective study. All 8,764 consecutive patients who underwent surgery for colorectal cancer between April 2007 and January 2021 at the Saitama Medical University International Medical Center were screened; 572 underwent multivisceral resection for LACC. We compared the T3 and T4 groups to evaluate outcomes. Results: The 5-year disease-free survival (DFS) rates did not significantly differ between the two groups (hazard ratio=1.344, 95% confidence interval=0.638-2.907, p=0.33). The 5-year overall survival (OS) rates were significantly worse for the T4 group than for the T3 group (hazard ratio=3.162, 95% confidence interval=1.077-11.44), p=0.037). To determine the association between American Society of Anesthesiologists (ASA) score, transfusion, pathological T and OS, we performed univariate and multivariate analyses. ASA, transfusion, and pathological T-stage were associated with worse OS in univariate analysis (T4 vs. T3, respectively). Conclusion: Our study showed that postoperative complications and DFS of the T4 group were similar to those of the T3 group of locally advanced colorectal cancer treated with laparoscopic multivisceral resection. However, OS was worse in the T4 group compared with the T3 group. Multivariate risk factors for poor OS were ASA>2, transfusion, and T4 stage.*

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Key Words: Locally advanced colorectal cancer, multivisceral resection, long-term outcomes, T4, laparoscopic multivisceral resection.

Colorectal cancer is the third most diagnosed malignancy in the world. Recently, computer-aided diagnosis for colonoscopy has been shown to be useful in the detection of colonic cancer and colon polyps (1, 2). However, approximately 10-20% of patients diagnosed with colonic cancer will present with locally advanced disease (3). Locally advanced colorectal cancer (LACC) has worse long-term outcomes.

Operations include extended radical resections when the primary organ and at least one of the surrounding organs is removed en bloc (4). However, previous studies reported that multivisceral resection (MVR) was a feasible treatment for LACC (5, 6). On the other hand, because blind division of suspect adhesions risks compromising oncological resection, more than 20% of MVRs in this review were 'negative' meaning that the invasion was inflammatory rather than malignant on pathological analysis (7).

A meta-analysis reported that some factors were predictive for poor survival, such as age <65 years, depth of tumor invasion >pT3 (8), carcinoembryonic antigen (CEA) >10 U/ml, R1/R2 resection (9), and preoperative pain (10). There were no independent risk factors for poor survival. However, there are few studies on the prognostic risk factors for recurrence in patients who underwent MVR with R0 resection

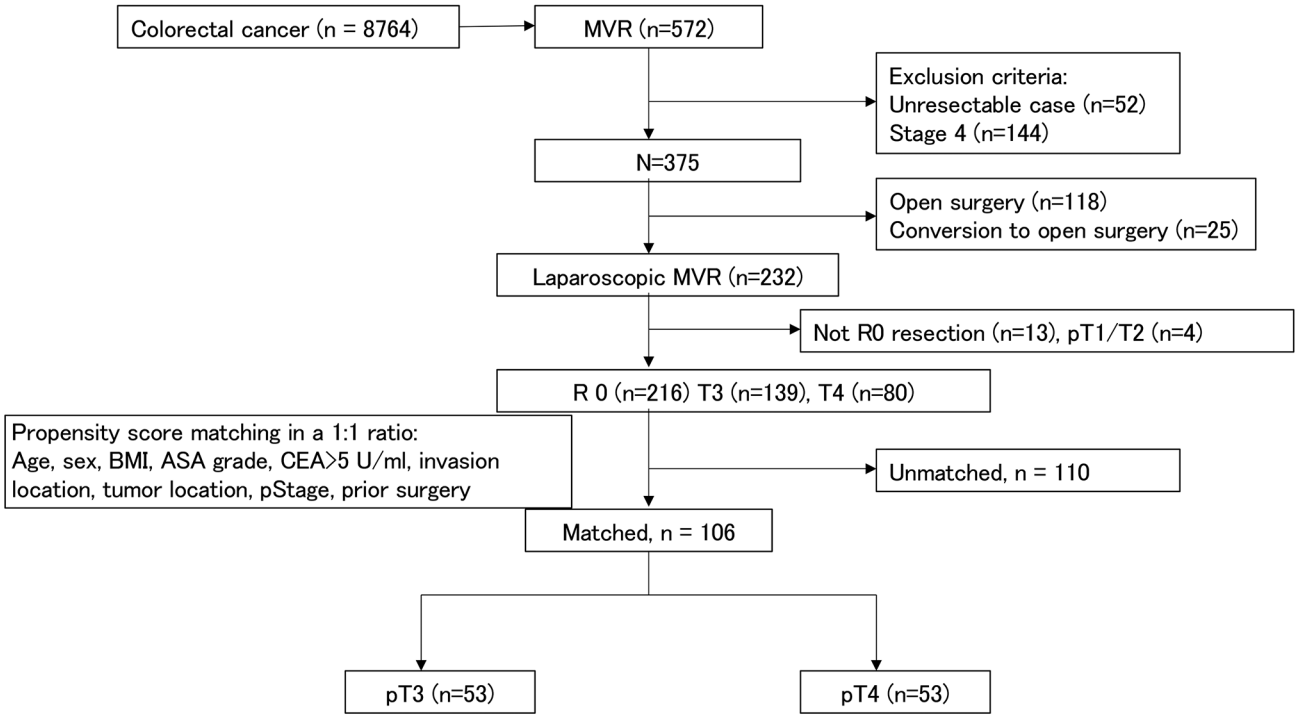

Figure 1. *Study flow chart. ASA: American Society of Anesthesiologists; BMI: body mass index; CEA: carcinoembryonic antigen; MVR: multivisceral resection.*

for LACC. Our hypothesis was that the pathological tumor depth affects the postoperative outcome in patients who undergo R0 MVR. The aim of this study was to analyze and compare short-term and long-term outcomes between patients who underwent MVR for LACC pT3 and pT4 stages.

Patients and Methods

This was a propensity score-matched (PSM) retrospective study. All 8,764 consecutive patients who underwent surgery for colorectal cancer between April 2007 and January 2021 at Saitama Medical University International Medical Center, Japan were included. Among these patients, 572 underwent MVR for LACC. The study was approved by the Institutional Review Board of Saitama Medical University International Medical Center (IRB number 2022-034).

Eligible patients were medically cleared for LACC and aged ≥18 years. The diagnosis of colonic cancer was confirmed by colon biopsy. For evaluation of distant metastasis, abdominopelvic and chest computed tomography (CT) were performed. Clinical stage 4 [tumor-nodes-metastasis (TNM) classification, eighth edition (11)], unresectable cases, and, pathological T1-T2 cases were excluded. Cases of conversion from laparoscopy to open surgeries were excluded. Finally, 375 cases were selected for analysis in our study. All patients underwent preoperative evaluation of tumor depth by colonoscopy, CT, and magnetic resonance imaging (when pelvic organ invasion was suspected).

The main outcome measures were postoperative complications, disease-free survival (DFS), recurrence location, and overall survival (OS). Additionally, data on patient age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score, previous abdominal surgery, medical comorbidities, and TNM stage were retrospectively collected from the electronic medical records. Postoperative morbidity and mortality were defined as complications or death occurring within 30 days of surgery or during hospitalization, respectively. Postoperative complications were defined as those classified as grade 2 or above in accordance with the Clavien-Dindo system (12). The length of OS was defined as the time from surgery to the date of death from any cause; DFS was defined as the time from surgery to the date of recurrence or death from any cause.

Patient follow-up. All patients were followed up for survival. Recurrence and distant metastasis were diagnosed on the basis of blood tests, including tumor marker, CT, endoscopy, magnetic resonance imaging, and positron-emission tomography-CT. Blood testing was performed every 3 months for 3 years postoperatively. CT was performed every 6 months for 5 years postoperatively. Endoscopy was performed annually for 5 years postoperatively. Patients with pathological stage III disease consulted oncologists for chemotherapy.

Propensity-score matching. Laparoscopic MVR for LACC. To minimize the effect of differences, PSM was applied. Propensity scores were calculated for each patient with bivariate logistic regression based on the following covariates: sex, age, BMI, ASA score, CEA, location of tumor invasion, TNM stage, tumor location, and previous abdominal surgery. These propensity scores were used

Table I. *Patient characteristics*.

Characteristic		Pathological T factor			Pathological T factor		
		T3 (n=136)	T4 (n=80)	*p*-Value	T3 (n=53)	T4 (n=53)	*p*-Value
Age, years	Median (range)	69 (33-93)	70.5 (41-92)	0.433[a]	72 (35-93)	70 (49-87)	0.899[a]
Sex, n (%)	Male	69 (50.74%)	48 (60%)	0.186[b]	29 (54.7%)	28 (52.83%)	0.845[b]
	Female	67 (49.26%)	32 (40%)		24 (45.28%)	25 (47.17%)	
BMI, kg/m^2	Median (range)	50 (14-31)	21.7 (14.5-33)	0.966[a]	21.3 (14.4-204.3)	21.8(16.7-33.9)	0.51[a]
ASA, n (%)	3, 4	125 (91.9%)	72 (90%)	0.63[b]	3 (5.66%)	4 (7.55%)	0.69[b]
	1, 2	11 (8.09%)	8 (10%)		50 (94.34%)	49 (92.45%)	
CEA, U/ml	Median (range)	4.85 (0.7-541.4)	6.7 (1-162)	0.72[a]	6.1 (0.7-541.4)	7.4 (1-162.6)	0.51[a]
Prior surgery	Median (range)	47 (34.56%)	29 (36.25%)	0.8[b]	52 (28.73%)	54 (29.83%)	0.817[b]
Tumor location, n (%)	Rectal	48 (35.29%)	27 (33.75%)	0.82[b]	21 (39.62%)	19 (35.85)	0.68[b]
	Colon	88 (64.71%)	53 (66.25%)		32 (60.38%)	34 (64.15)	
Location of tumor	Abdominal wall	44 (32.35%)	27 (33.75%)	0.83[b]	37 (69.81%)	37 (69.81%)	>0.99[b]
invasion, n (%)	Other organ	92 (67.65%)	53 (66.25%)		16 (30.2%)	16 (30.2%)	
pStage, n (%)	2	68 (50%)	31 (38.75%)	0.108[b]	23 (43.4%)	23 (43.4%)	>0.99[b]
	3	68 (50%)	49 (61.25%)		30 (56.6%)	30 (56.6%)	

ASA: American Society of Anesthesiologists; BMI: body mass index; CEA: carcinoembryonic antigen. [a]Fisher's exact test; [b]chi-squared test.

Table II. *Surgical outcomes of matched groups*.

Characteristic		Pathological T factor		
		T3 (n=53)	T4 (n=53)	*p*-Value*
Operative time, min	Median (range)	232 (88-381)	204 (111-519)	0.87[a]
Bleeding volume, ml	Median (range)	5 (0-200)	10 (5-255)	0.12[a]
Complications, n (%)	Intraoperative	0	0	>0.99
	Postoperative	26 (19.12%)	16 (20%)	0.87
Anastomotic leakage, n (%)	Yes	1 (1.89%)	4 (7.55%)	0.155
Ileus, n (%)	Yes	4 (7.55%)	2 (3.77%)	0.39
Urinary tract infection, n (%)	Yes	2 (3.77%)	1 (1.89%)	0.55
SSI, n (%)	Yes	1 (1.89%)	1 (1.89%)	>0.99
Transfusion, n (%)	Yes	1 (1.89%)	0	0.23
Mortality, n	Yes	0	0	>0.99
Comorbidity	Cardiovascular	4 (7.55%)	2 (3.77%)	0.39
	Renal failure	2 (3.77%)	1 (1.89%)	0.55
	Diabetes	7 (13.21%)	8 (15.09%)	0.78
	Respiratory system	0	1 (1.89%)	0.23
	Cerebral infarction	1 (1.89%)	5 (9.43%)	0.797
	Hypertension	18 (33.96%)	15 (28.30%)	0.52
CRT	Yes	1 (1.89%)	7 (13.21%)	0.019
NAC	Yes	2 (3.77%)	0	0.093
Adjuvant chemotherapy	Yes	12 (22.64%)	7 (13.21%)	0.2

CRT: Chemoradiotherapy; NAC: neoadjuvant chemotherapy; SSI: surgical site infection. *By Fisher's exact test, except [a]Mann-Whitney *U*-test.

to match patients at a 1:1 ratio between groups with pathological stage T3 and T4. We used the nearest-available Mahalanobis metric-matching distance with calipers, defined by the propensity score (caliper=0.02).

Statistical analysis. Statistical analyses were performed using JMP Pro 10 software (SAS Institute, Cary, NC, USA). The results are summarized as the means and standard deviations, or the medians and ranges for continuous variables; categorical variables are summarized as numbers and frequencies. Median and mean values were compared between groups by means of the Mann-Whitney test or the chi-square test in univariate analyses. All postoperative complications were analyzed using binary logistic regression. OS and DFS rates were analyzed using the Kaplan-Meier method and Cox's proportional hazards model. Comparisons between survival curves were performed using the

Table III. *Pathological findings*.

Characteristic		Pathological T factor		
		T3 (n=53)	T4 (n=53)	*p*-Value*
Tumor size, mm	Median (range)	60 (12-150)	55 (15-130)	0.392[a]
Harvested lymph nodes, n	Median (range)	27 (7-57)	26 (5-55)	0.6[a]
Positive lymph nodes, n (%)	No	23 (43.4%)	23 (43.4%)	>0.99
	Yes	30 (56.6%)	30 (56.6%)	
Histological type, n (%)	tub1	18 (33.96%)	14 (26.42%)	0.177
	tub2	30 (56.6%)	32 (60.38%)	
	Muc	3 (5.66%)	4 (7.55%)	
	por1	0	1 (1.89%)	
	por2	0	2 (3.77%)	
	Pap	2 (3.77%)	0	
Pathological stage, n (%)	2	23 (43.4%)	23 (43.4%)	
	3	30 (56.6%)	30 (56.6%)	
Recurrence, n (%)	Lung	2 (3.77%)	7 (13.21%)	0.22
	Liver	4 (7.55%)	2 (3.77%)	
	Lymph	3 (5.66%)	1 (1.89%)	
	Dissemination	1 (1.89%)	2 (3.77%)	
	Local	2 (3.77%)	2 (3.77%)	
	Bone	1 (1.895)	0	
	Distant	11 (20.75%)	2 (3.77%)	0.36
	Local	12 (22.64%)	5 (9.45%)	

Muc: Mucinous adenocarcinoma; Pap: papillary; por: poorly differentiated adenocarcinoma; tub: tubular adenocarcinoma. *By Fisher's exact test, except [a]Mann-Whitney *U*-test.

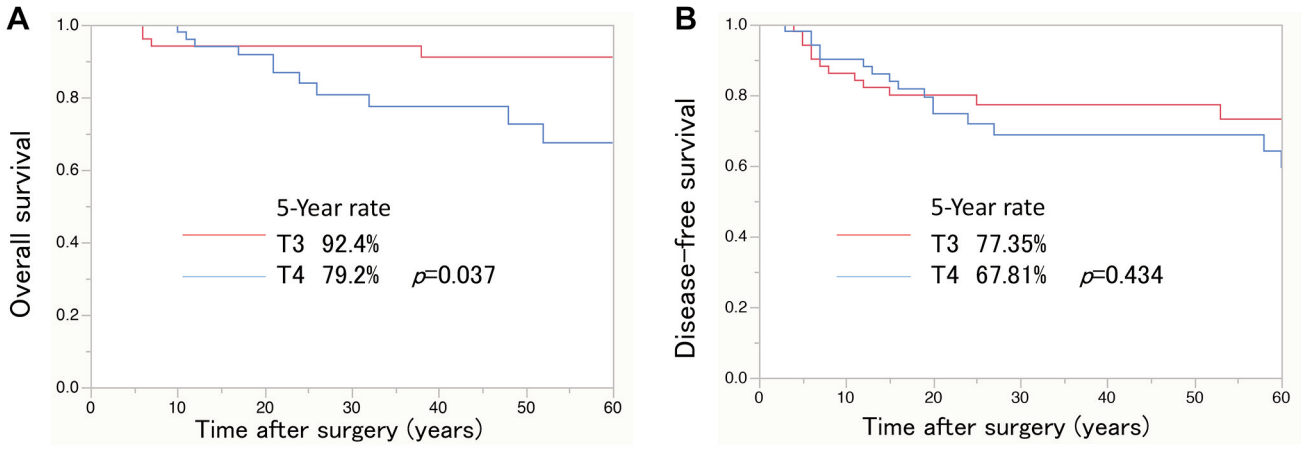

Figure 2. *Oncological long-term outcomes. Kaplan-Meier curves for overall (A) and disease-free (B) survival.*

log-rank test. The results are reported as hazard ratios (HR) with 95% confidence interval (CIs). Values of $p<0.05$ were considered to indicate significant differences.

Results

Characteristics before and after PSM. Before PSM, there were no significant differences between the two groups. After matching, the two groups each included 106 patients, and did not significantly differ in any patient characteristic (Figure 1 and Table I).

Perioperative outcomes. Perioperative outcomes are summarized in Table II. The rate of preoperative chemoradiotherapy was significantly higher in the T3 group than in the T4 group. The two groups did not significantly differ regarding the incidences of intra- and postoperative complications, comorbidities, and mortality. The median

bleeding volume, operative time, adjuvant chemotherapy rate, and transfusion rate did not significantly differ between the two groups.

Pathological and oncological outcomes. The pathological and oncological outcomes are summarized in Table III. There were no significant differences between groups regarding the median tumor size, median number of harvested lymph nodes, histological type, pathological TNM stage, or N classification. The recurrence pattern was not significantly different between the two groups.

Survival outcomes. After PSM, the median follow-up for the T3 group was 44 (range=1-100) months and in the T4 group, it was 25 (range=2-66) months (not significantly different). The 5-year DFS rates did not differ significantly between the two groups [T3 *vs*. T4: 77.35% *vs*. 67.81%; hazard ratio (HR)=1.344, 95% CI=0.638-2.907, p=0.33 Figure 2]. The 5-year OS rates were significantly worse for the T4 group than the T3 group at 79.2% *vs*. 92.4%, respectively (HR=3.162, 95% CI=1.077-11.44, p=0.037) (Figure 2).

Univariate analyses of 15 factors (age, sex, ASA, BMI, tumor location, CEA, transfusion, adjuvant chemotherapy, neoadjuvant chemotherapy, chemoradiotherapy, number of lymph nodes >12, tumor size, tumor of invasion location, T4/3, N1/0) possible prognostic factors found no significant associated with DFS after laparoscopic MVR (Table IV).

In addition, to determine the association between ASA, transfusion, T-stage, and OS, we performed univariate and multivariate analyses. ASA, transfusion, and T-stage were associated with worse OS in univariate analysis, and this was confirmed in multivariate analysis: ASA>2: HR=6.80, 95% CI=1.37-27.1, p=0.0218; transfusion: HR=774, 95% CI=22.98-28135, p=0.00016; and T4 *vs*. T3: HR=4.44, 95% CI=1.326-20.154, p=0.0143 (Table V).

Table IV. *Univariate analyses of factors prognostic for disease-free survival after laparoscopic multivisceral resection.*

Parameter	Subgroup	HR (95% Cl)	p-Value
Age	<65 Years	1	
	≥65 Years	0.91 (0.38-2.43)	0.84
Sex	Female	1	
	Male	0.88 (0.38-1.99)	0.76
ASA	≥2	2.84 (0.72-9.23)	0.123
	<2		
BMI	≥25 kg/m^2	0.58 (0.18-1.56)	0.298
	<25 kg/m^2	1	
Tumor location	Rectum	0.745 (0.27-1.79)	0.524
	Colon	1	
CEA	≥5 U/ml	1.72 (0.71-4.37)	0.123
	<5 U/ml	1	
Transfusion	Yes	1.27 (0.85.-1.87)	0.229
	No	1	
Adjuvant chemotherapy	Yes	1.14 (0.38-3.05)	0.799
	No	1	
Neoadjuvant chemotherapy	Yes	0.46 (0.014-4.88)	0.57
	No	1	
Chemoradiotherapy	Yes	1.52 (0.34-4.86)	0.53
	No	1	
Number of lymph nodes	≥12	0.51 (0.085-9.98)	0.57
	<12	1	
Tumor size	≥50 mm	1.094 (0.359-3.90)	0.87
	<50 mm	1	
Location of tumor invasion	Abdominal wall	2.48 (0.89-8.55)	0.084
	Other organ	1	
Tumor stage	T4	1.22 (0.54-2.81)	0.61
	T3	1	
N-Stage	N1	1.77 (0.72-4.622)	0.214
	N0	1	

ASA: American Society of Anesthesiologists; BMI: body mass index; CEA: carcinoembryonic antigen; CI: confidence interval; OR: odds ratio.

Discussion

Our hypothesis was that the pathological tumor depth affects the postoperative outcome in patients who undergo MVR with R0 resection. This retrospective PMS study reported that the postoperative complications and DFS of the T4 group were similar to those of the T3 group. However, OS was worse in the T4 group compared to that in the T3 group. Multivariate risk factors for poor OS were ASA>2, transfusion, and pT4. Some studies reported that ASA scores affected postoperative complications such as surgical site infection and anastomotic leakage after laparoscopic cancer surgery (13, 14). However, in the case of urothelial bladder cancer, a high ASA score was independently associated with reduced OS (15). Our results were consistent with that study.

McSorley *et al*. reported that blood transfusion was associated with postoperative inflammation, complications, and poorer survival in patients undergoing colorectal cancer surgery (16). Similar results have been reported elsewhere (17, 18). Postoperative blood transfusion was also a risk factor in our study.

Recently, Smith *et al*. reported in a retrospective study that robotic multivisceral resection for malignant disease of the pelvis is safe and feasible. All patients had R0 resection, and no patients had recurrence at the 12-month follow-up (18). Zhang *et al*. reported that in multivariate analysis, laparoscopic MVR for LACC was a protective factor for OS, but the laparoscopic surgery group had less invasion of abdominal organs than pelvic organs (19). Abdominal organs might be easier to resect than pelvic organs. More difficult abdominal organs include the liver, pancreas, and spleen.

However, our findings showed that T4 cases had worse OS than T3 cases in LACC for MVR. In our study, we used PMS to minimize any bias in patient characteristics because it has been reported in the literature that high T classification was significantly associated with the lymph node count (20).

Table V. *Univariate and multivariate analyses of factors prognostic for overall survival after laparoscopic multivisceral resection.*

		Univariate		Multivariate	
Parameter	Subgroup	HR (95% Cl)	*p*-Value	HR (95% Cl)	*p*-Value
Age	<65 Years	1.24 (0.33-5.51)	0.75		
	≥65 Years	1			
Sex	Female	1			
	Male	2.29(0.62-9.21)	0.21		
ASA	≥2	9.95 (1.54-65.0)	0.017	6.80 (1.37-27.1)	0.0218
	<2	1			
BMI	≥25 kg/m^2	0.188 (0.009-1.08)	0.63		
	<25 kg/m^2	1			
Tumor location	Rectum	1			
	Colon	0.80 (0.16-3.13)	0.76		
CEA	≥5 U/ml	3.99 (0.99-21.1)	0.051		
	<5 U/ml	1			
Transfusion	Yes	5,623 (78.3-702,865)	0.0005	774 (22.98-28,135)	0.0016
	No	1			
Adjuvant chemotherapy	Yes	0.18 (0.0082-1.302)	0.09		
	No	1			
Neoadjuvant chemotherapy	Yes	2.71 (0-108)	0.75		
	No	1			
Chemoradiotherapy	Yes	3.81 (0.50-20.0)	0.16		
	No	1			
Number of lymph nodes	≥12	0.11 (0.008-2.84)	0.153		
	<12	1			
Tumor size	≥50 mm	1.26 (0.21-11.9)	0.81		
	<50 mm	1			
Location of tumor invasion	Abdominal wall	2.70 (0.55-18.4)	0.232		
	Other organ	1			
Tumor stage	T4	4.5 (1.2-23.8)	0.0242	4.44 (1.326-20.154)	0.0143
	T3	1			
N-Stage	N1	5.56 (1.41-26.7)	0.0132		
	N0	1			

ASA: American Society of Anesthesiologists; BMI: body mass index; CEA: carcinoembryonic antigen; CI: confidence interval; OR: odds ratio.

Peacock *et al*. reported that among the patients included in their study of extended radical resection, 16.4% experienced major complications. Their univariate analysis showed that certain medical comorbidities, types of organs resected, formation of an ileal conduit and requirement for a blood transfusion were all associated with major morbidities (21). In particular, resection of the uterus, ovaries, prostate, bladder, and sacrum were independent risk factors for major complications. Resection of the colon, rectum, anus, small bowel, and vagina were not significant risk factors for major complications (22). We did not find any significant differences in complications experienced by the two groups.

The deterministic approach of the TNM system has been called into question by evidence that patients with deeply invading but node-negative colorectal cancer have a worse prognosis than patients with less invasive but node-positive cancer (23-25). To our knowledge, there are no studies comparing patients after colorectal surgery for T3 and T4 disease. Our study showed that short-term outcomes and DFS were similar for the two groups, but OS was worse in the T4 group. Thus, if R0 resection can been achieved in T4 cases, and these are observed carefully after surgery, OS might be improved.

This study has several limitations. Firstly, this study was a retrospective study, at a single institution. Secondly, our study did not consider the learning curve for surgical techniques. Finally, all surgeons were colorectal cancer surgeons, but the level of experience varied. Thus, the surgical expertise might not have been consistent.

In conclusion, our study showed that postoperative complications and DFS of the T4 group were similar to those of the T3 group. However, OS was worse in the T4 group compared with T3 group. Multivariate risk factors for poor OS were ASA>2, transfusion, and pT4 stage. Therefore, patients with pT4 disease who undergo MVR with R0 need to undergo careful follow-up.

Conflicts of Interest

The Authors declare no competing interests.

Authors' Contributions

YI, KD and YH designed the study; HY, TF, MS, and YI analyzed the data, and wrote the article.

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