Prospective Cohort Study

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Standardize the surgical technique and clarify the oncologic significance of robotic D3-D4 lymphadenectomy for upper rectum and sigmoid colon cancer with clinically more than N2 lymph node metastasis

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Background: The territory of D3-D4 lymphadenectomy for upper rectal and sigmoid colon cancer varies, and its oncological efficacy is unclear. This prospective study aimed to standardize the surgical technique of robotic D3-D4 lymphadenectomy and clarify its oncologic significance.

Methods: Patients with upper rectal or sigmoid colon cancer with clinically suspected more than N2 lymph node metastasis were prospectively recruited to undergo standardized robotic D3-D4 lymphadenectomy. Immediately postsurgery, the retrieved lymph nodes were mapped to five N3-N4 nodal stations: the inferior mesenteric artery, para-aorta, inferior vena cava, infra-renal vein, and common iliac vessels. Patients were stratified according to their nodal metastasis status to compare their clinicopathological data and overall survival. Univariate and multivariate analyses were performed to determine the relative prognostic significance of the five specific nodal stations. Surgical outcomes and functional recovery of the patients were assessed using the appropriate variables.

Results: A total of 104 patients who successfully completed the treatment protocol were assessed. The standardized D3-D4 lymph node dissection harvested sufficient lymph nodes (34.4 ± 7.2) for a precise pathologic staging. Based on histopathological analysis, 28 patients were included in the N3-N4 nodal metastasis-negative group and 33, 34, and nine patients in the single-station, double-station, and triple-station nodal metastasis-positive groups, respectively. Survival analysis indicated no significant difference between the single-station nodal metastasis-positive and N3-N4 nodal metastasis-negative groups in the estimated 5-year survival rate [53.6% (95% CI: 0.3353–0.7000) vs. 71.18% (95% CI: 0.4863–0.8518), $P = 0.563$], whereas patients with double-station or triple-station nodal metastatic disease had poor 5-year survival rates (24.76 and 22.22%), which were comparable to those of AJCC/UICC stage IV disease than those with single-station metastasis-positive disease. Univariate analysis showed that the metastatic status of the five nodal stations was comparable in predicting the overall survival; in contrast, multivariate analysis indicated that common iliac vessels and infra-renal vein were the only two statistically significant predictors ($P < 0.05$) for overall survival.

Conclusions: Using a robotic approach, D3-D4 lymph node dissection could be safely performed in a standardized manner to remove the relevant N3-N4 lymphatic basin en bloc, thereby providing significant survival benefits and precise pathological staging for patients. This study encourages further international prospective clinical trials to provide more solid evidence that would facilitate the optimization of surgery and revision of the current treatment guidelines for such a clinical conundrum.

Keywords: colorectal cancer, D3-D4 lymph node dissection, robotic surgery

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Introduction

The extent of D3-D4 lymph node dissection for treating advanced upper rectal or sigmoid colon cancer is poorly defined and has been a contentious issue between Western and Asian colorectal surgeons. Western surgeons reckon that advanced upper rectum or sigmoid colon cancer with lymph node metastasis up to the N3-N4 level indicates a systemic disease, and extirpation of such cancer-involved lymph nodes cannot improve the overall survival for the patients. In contrast, some Asian pioneer surgeons, especially the Japanese, firmly believe that a subset of advanced rectal or sigmoid colon cancers with N3-N4 lymph node metastasis still belonged to a 'locoregional' disease and extended abdominal aorto-iliac lymph node dissection could provide survival benefit for patients[1–10]. However, excessive lymph node dissection can result in additional surgical complications, including profuse bleeding, prolonged ileus, intra-abdominal abscess formation, wound infection, anastomotic leakage, and permanent loss of sexual function. Given the lack of quality data to weigh the survival benefits against surgical morbidities, most researchers have suggested that D3-D4 lymph node dissection should be implemented with already established treatment regimens within a multidisciplinary approach for patients with advanced colorectal cancer[11,12]. Further prospective multicenter international studies with standardized definitions and surgical techniques are required to better evaluate the long-term oncological outcomes of D3-D4 lymph node dissection.

Currently, the surgical treatment of colorectal cancer has moved into the era of minimally invasive surgery[13–15]. Previous studies have shown that minimally invasive surgical techniques, either laparoscopic or robotic, can be successfully applied for D3-D4 lymph node dissection with satisfactory oncologic outcomes and functional recovery[16–18]. Compared with the laparoscopic approach, robotic surgery has better technical precision and a shorter learning curve for this challenging surgical procedure.

We conducted this single-center prospective cohort study to assess the nodal metastatic distribution and oncologic significance after clearance of the N3-N4 lymphatic basin in patients with advanced upper rectal or sigmoid colon cancer, taking advantage of the enhanced surgical precision provided by the da Vinci Surgical System. We hypothesized that robotic D3-D4 lymph node dissection could be standardized and become a routine surgical procedure for our patients through this surgical endeavor.

HIGHLIGHTS

- The present study better delineated the territory of the N3-N4 lymph node for upper rectal and sigmoid colon cancer.
- A standardized D3-D4 lymph node dissection could be safely performed using the robotic approach without increasing surgical complications and thus could provide significant oncologic benefits for patients.
- This study encourages further international prospective clinical trials to provide more solid evidence that would facilitate the optimization of surgery and revision of the current treatment guidelines for such a clinical conundrum.

Material and methods

Patient selection

We followed the strengthening the reporting of cohort, cross-sectional and case–control studies in surgery (STROCSS) 2021 guidelines for the present study[19] (Supplemental Digital Content 1, http://links.lww.com/JS9/B652). All consecutive patients with upper rectal or sigmoid cancer treated at the Colorectal Division of a tertiary referral medical center were recruited for this study based on the following inclusion criteria: (1) histopathologically proven adenocarcinoma located in the upper rectum (above the pelvic peritoneal reflection), rectosigmoid junction, or sigmoid colon (generally 10–35 cm above the anal verge). Only sigmoid colon and rectal cancers above the peritoneal reflection were investigated because the lymphatic drainage of the upper rectum and sigmoid colon was along the inferior mesenteric artery (IMA) to the para-aortic area; therefore, they were treated with the same extent of lymph node dissection; (2) cancers suspected to be more than N2 lymph node metastasis on preoperative imaging studies; (3) patients who underwent robotic surgery to perform D3-D4 lymph node dissection; and (4) patients with physical status of American Society of Anesthesiology class I–III. The exclusion criteria were: (1) cancers located at other anatomic positions (cecum, ascending, transverse, descending colon, and middle or upper rectum); (2) patients who cannot achieve R0 lymphadenectomy because the lymph node metastasis has extended outside the upper (left renal vein), lower [common iliac vessels (CIV)], and/or bilateral (psoas muscle) boundaries; (3) lymph node metastasis has invaded major blood vessels and/or the retroperitoneal tissues, which cannot be R0-resected; (4) evidence of distant organ metastasis; (5) morbidly obese patients (BMI $\geq$ 40 kg/m2); and (6) previous major surgery of lower abdomen.

Patients were informed of the advantages and disadvantages of robotic surgery before enrollment. This study was approved by the Institutional Review Board of our hospital (unique protocol ID: 202002011RINB). All methods were performed in accordance with the relevant guidelines and regulations.

Preoperative nodal staging

The lymph node stage was determined by multislice spiral computed tomography (CT) of the chest, abdomen, and pelvis, selective use of abdominal MRI, and/or PET. Patients were considered to have clinically disease-positive lymph nodes when imaging showed the presence of mesenteric lymph nodes $\geq$ 4 mm in size and/or lymph nodes with a spiculated or indistinct border or mottled, heterogeneous appearance. In PET, cancer metastasis was considered positive if the standard fluorodeoxyglucose uptake value of the lymph nodes was higher than that of the background retroperitoneal tissues or regional organs[20].

Regarding nodal staging for colorectal cancer, there were some differences between the Japanese classification[21] and the American Joint Committee on Cancer (AJCC)[22] / Union for International Cancer Control (UICC)[23]. The Japanese classification defines N2 lymph nodes as lymph nodes along the marginal artery within 5–10 cm of the primary tumor or lymph nodes within the intermediate mesocolon between the branching of the left colic artery and the pericolic marginal artery. In contrast, the AJCC/UICC defines N2 lymph nodes as the number of lymphadenopathies ranging from 4 to 7. In this context, patients whose preoperative imaging findings met the criteria of one or both Japanese and AJCC/UICC classification systems as having more

than N2 lymphadenopathy were eligible for inclusion in this study.

In contrast, N3-N4 lymph nodes were poorly defined in both the AJCC/UICC and Japanese staging systems. In the present study, the N3 lymph nodes for upper rectal and sigmoid colon cancer were redefined as lymph nodes along the IMA from the branching point of the left colic artery upward to a circular base (diameter, 0.5 cm) around the origin of the IMA over the abdominal aorta, which was designated as (1) the IMA group. Furthermore, the N4 lymph nodes were defined as lymph nodes over the lymphatic basin bounded by the duodenal third portion, left renal vein, bilateral psoas muscles, and the bilateral CIV, which were divided into the following four groups and designated as: (2) the para-aorta group, which include lymph nodes over the ventral surface of the abdominal aorta and left lateral para-aortic gutter medial to the left ureter; (3) the inferior vena cava (IVC) group, which include lymph nodes over the right lateral sulcus, ventral surface of IVC and aortocaval trench; (4) the infra-renal vein (IRV) group, which include lymph nodes over the ventral surface of left renal vein and the infra-renal area between the duodenal third portion medially and gonadal vein laterally; and (5) the CIV group, which include lymph nodes over the CIV and the area lined by the bilateral CIV beyond sacral promontory (Fig. 1A).

Study endpoints

The primary endpoints of this study were the overall survival of patients after D3-D4 lymph node dissection and the prognostic significance of positive lymph nodes on five specific stations of the N3-N4 lymphatic basin, including the IMA, para-aorta, IVC, IRV, and CIV. Secondary endpoints included surgical outcomes, operative morbidity/mortality, and patient disability related to the implementation of D3-D4 lymph node dissection via a robotic approach. All the study endpoints were evaluated based on the intention-to-treat principle.

Operative technique

Robotic resection of primary colorectal cancer with D3-D4 lymph node dissection was performed using the same principle as the laparoscopic approach, which has been described in previous publications[13–18].

All robotic D3-D4 lymphadenectomy procedures were performed using the da Vinci Surgical System (Intuitive Surgical System). In the single-docking completely robotic technique, the robotic cart was stationed beside the left lower quadrant of the patient's abdomen, and the robotic system was used throughout the procedure.

Traditionally, standard anterior resection or low anterior resection for the treatment of upper rectal or sigmoid colon cancer was classified as D2-D3 lymph node dissection, according to whether the lymph node-containing mesocolon was transected at the root of the IMA (high ligation) or the superior rectal artery after branching of the left colic artery. In contrast, D3-D4 lymph node dissection was considered an additional extra-mesenteric N3-N4 lymph node dissection in continuation of the preceding anterior resection or low anterior resection procedures. To begin the conduction, D3-D4 lymph node dissection, we opened the visceral peritoneum over the bifurcation of the CIV, and the

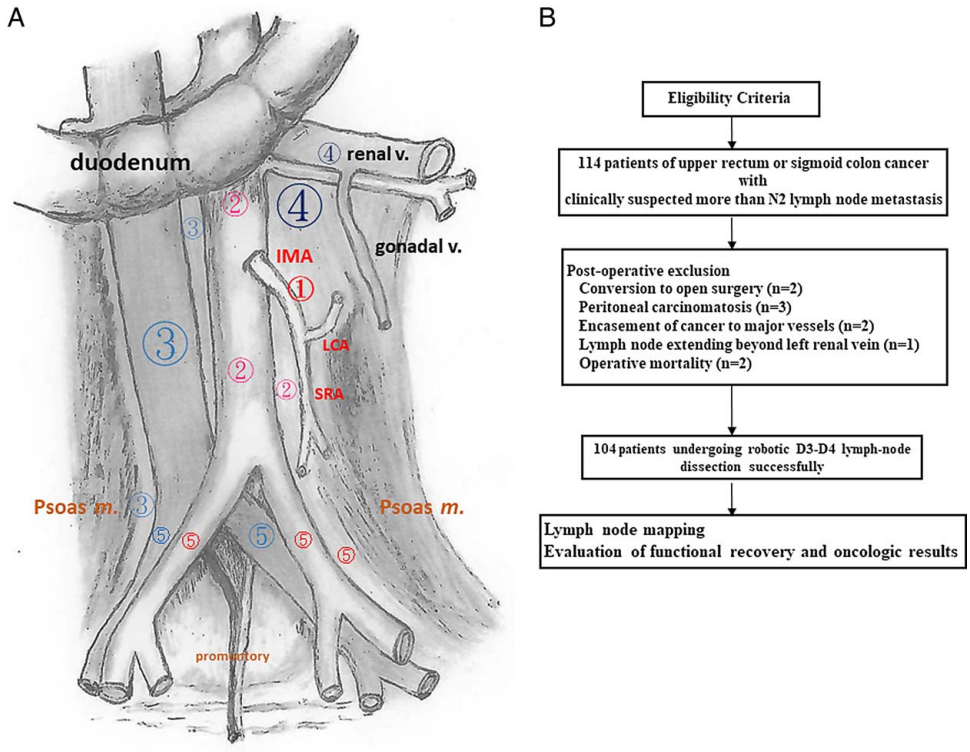

Figure 1. (A) Re-define the grouping of N3-N4 lymph nodes for the upper rectum and sigmoid colon cancer with reference to the Japanese classification. The territory of N3-N4 lymphatic basin was divided into five stations and the lymph node was grouped accordingly and designated as: (1) inferior mesenteric artery (IMA); (2) para-aorta; (3) inferior vena cava (IVC); (4) infra-renal vein (IRV); and (5) common iliac vessels (CIV), respectively. (B) The study profile.

mesentery of the sigmoid colon was then undermined from medial to lateral along Gerota's fascia and upward to the lower border of the pancreas. Thereafter, the inferior mesenteric vein was identified and transected, followed by the identification of the IMA and left ureter. The mesentery of the sigmoid and descending colon was swept over the left abdominal side to expose the territory of the extra-mesenteric N3-N4 lymphatic basin in preparation for additional D3-D4 lymph node dissection.

The surgical procedures of D3-D4 lymph node dissection were recorded in the five separate video clips, which showed removal of the lymphovascular tissues with the intent of en bloc resection over the five specific lymphatic stations: IMA (Video1_IMA, Supplemental Digital Content 2, http://links.lww.com/JS9/B653); para-aorta (Video2_Paraaortic, Supplemental Digital Content 3, http://links.lww.com/JS9/B654); IVC (Video3_IVC, Supplemental Digital Content 4, http://links.lww.com/JS9/B655); IRV (Video4_Infra-renal, Supplemental Digital Content 5, http://links.lww.com/JS9/B656); and CIV (Video5_CIV, Supplemental Digital Content 6, http://links.lww.com/JS9/B657).

Back-table lymph node retrieval and mapping

Immediately postsurgery, the lymph nodes were retrieved from the resected specimens. The harvested lymph nodes were mapped to the five lymphatic stations described above. Lymph nodes were examined in routine histopathological diagnostic practice using hematoxylin and eosin staining of a representative section of the lymph node. Tumor nodules with no histopathological evidence of lymph node structure were considered lymph node metastases, irrespective of their size and contour morphology.

Evaluation of surgical outcomes

Surgical quality metrics, including blood loss, operation time, surgical morbidity/mortality, hospitalization, and readmission, were reviewed. The length of hospital stay was calculated from the date of surgery to the day of discharge. The Clavien–Dindo classification system was used to assess the severity of surgical complications[24]. Postoperative morbidity and mortality were defined as those occurring within 30 days of the index procedure or in the hospital, if the hospital stay was ≥ 30 days. Patients with multiple interrelated surgical complications, such as anastomotic leakage, intra-abdominal abscess, and enterocutaneous fistula, were listed as having three surgical complications, even though the intra-abdominal abscess and/or enterocutaneous fistula were caused by anastomotic leakage. Similarly, if a patient developed both deep vein thrombosis and pulmonary embolism, these were counted as two surgical complications.

Assessment of postoperative disability and genitourinary function

A subjective-response standardized questionnaire was given to patients to assess the postoperative disability, which included the number of days until return to partial activity, full activity and work.

Before surgery, the genitourinary function of all male patients was assessed by a questionnaire-based interview. Patients with abnormal preoperative baseline functional data were excluded from further postoperative assessment of sexual or urinary function. Male sexual function was evaluated by potency and ejaculation. The evaluation of sexual function was performed 6 months after the operation, when the temporary colostomy, if present, has been closed and the patients were completely recovered from surgical disability. In evaluating the urinary function, the duration between initial voiding trial and spontaneous voiding was recorded. The questionnaire used for the assessment of urinary dysfunction was based on International Prostate Symptom Score[25,26], the parameters of which included incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia. Any voiding problems recovered within 3 months after operation were considered to be transient bladder voiding dysfunction; otherwise, such problems were deemed persistent. The genitourinary function was ranked as good, fair (decreased), and poor (impaired).

Postoperative treatment

Patients with histopathologically negative N3-N4 lymph node metastasis were treated as AJCC/UICC staged III disease and adjuvant therapy was given using chemotherapy with a fluoropyrimidine-based single-agent (capecitabine, Xeloda) or FOLFOX doublet therapy. However, patients with histopathologically positive N3-N4 lymph node metastasis were treated for metastatic stage IV disease, and a multidisciplinary therapeutic approach was adopted, which generally consists of the alternate use of combinational chemotherapy and targeted agents, based on the molecular biological markers, such as the mutation status of K-ras and mismatch repair genes.

Postoperative surveillance

Postoperatively, the patients completed a follow-up protocol that included periodic physical examinations and blood panels, including complete blood cell count, biochemistry, and carcinoembryonic antigen quantification every 3–6 months, and colonoscopy, abdominal ultrasonography, and chest/abdomen/pelvic CT scan or MRI every 6–12 months. Confirmation of local recurrence or distant metastasis was based on colonoscopy or imaging studies, such as CT scan, MRI, and/or PET. Overall survival was defined as the period between the date of surgery and the last visit or death. Patients who died without reported tumor recurrence were assumed to have had cancer-related deaths unless demonstrated otherwise.

Statistics

All patients were prospectively followed up (median: 52.5 months, range: 3–105 months). Kaplan–Meier survival curves were constructed for patients with or without histopathologically confirmed N3-N4 lymph node metastasis. The survival data of the patient groups were compared using a two-sided log-rank test. To evaluate the relative prognostic significance of the five specific nodal stations in the N3-N4 lymphatic basin, we first performed univariate analysis, followed by multivariate analysis using the stratified Cox proportional hazards regression model. To evaluate the secondary endpoints, the $\chi 2$ and two-tailed Fisher's exact tests with or without Yates' correction was used to analyze the categorical data, whereas continuous data were compared using Student's *t*-test. The significance level for all tests was set at $P < 0.05$.

Results

Between January 2014 and June 2023, 114 patients were recruited for the present study, and 10 were subjected to postoperative exclusion; therefore, 104 patients who successfully completed the treatment protocol were assessable (Fig. 1B).

Postoperative lymph node mapping showed that the D3-D4 lymphadenectomy facilitated the harvest of additional lymph nodes (34.4 ± 7.2) for a precise pathologic staging, with the mean number of 4.7 in IMA, 9.8 in para-aorta, 7.8 in IVC, 5.6 in IRV and 6.5 in CIV nodal station, respectively. Based on histopathological examination, 28 patients were included in the N3-N4 nodal disease-negative group. This means that despite the adoption of current imaging technology in the present case series, the preoperative diagnosis of patients with clinically disease-positive lymph nodes was still subject to a false-positive rate of 26.9%. In contrast, the other 76 patients were histopathologically proven to harbor metastatic cancer foci over the N3-N4 lymphatic basin; 33, 34, and nine patients had single-station, double-station, and triple-station lymphadenopathy (Table 1).

There were no statistically significant differences ($P > 0.05$) in various demographic and clinicopathological parameters between N3-N4 nodal disease-positive and disease-negative groups of patients (Table 2). However, survival analysis indicated that: (1) there was no significant difference between single-station nodal disease-positive and N3-N4 nodal disease-negative group of patients in the estimated survival rate [53.6% (95% CI: 0.3353–0.7000) vs. 71.18% (95% CI: 0.4863–0.8518), $P = 0.563$]; (2) the patient group with single-station lymph node metastasis were significantly higher in the estimated 5-year survival rate [53.56% (95% CI: 0.3353–0.7000) vs. 24.76% (95% CI: 0.1069–0.4183), $P = 0.016$] than the patient group with double-station lymph node metastasis; and (3) there was no significant difference between patient groups with double-station or triple-station lymph node metastasis in the estimated 5-year survival rate [24.76% (95% CI: 0.1069–0.4183) vs. 22.22% (95% CI: 0.0337–0.5131), $P = 0.603$] (Fig. 2). These findings imply that robotic D3-D4 lymph node dissection could achieve good locoregional control in patients with isolated single-station lymph node metastasis and in patients with negative N3-N4 nodal metastatic disease.

Through univariate analysis, we found that the status of the five lymph node stations over the N3-N4 lymphatic basin was comparable in predicting the overall survival of patients. Further multivariate analysis showed that the relative prognostic significance of the five nodal stations, in decreasing order, was CIV, IRV, IVC, IMA, and para-aorta (with hazard ratios of 2.336, 2.069, 1.589, 1.564, and 1.382, respectively). The only two statistically significant predictors ($P < 0.05$) of overall survival in these five nodal stations were CIV and IRV, which represent the lower and upper border of the N3-N4 lymphatic basin, respectively (Table 3).

Surgical outcome metrics are presented in Table 4. Briefly, robotic D3-D4 lymph node dissection was safely performed through five small wounds with an acceptable morbidity/mortality rate, a long operative time, and moderate blood loss. The patients had quick convalescence as assessed by the degree of postoperative pain, length of postoperative restoration of flatus passage, oral feeding, Foley catheter removal, hospitalization, and readmission rate.

The duration of postoperative disability was short and favorable (Table 5). The mean time of return to partial activity, full activity and work was 3, 5, and 7 weeks, respectively. However, the robotic D3-D4 lymph node dissection resulted in voiding dysfunction in 75.4% of patients, and in 13.0% of these, the bladder dysfunction was permanent. The incidence of sexual dysfunction was even greater, with 94.1% of patients experiencing complete loss of ejaculatory function or retrograde ejaculation and 47.1% of patients with a decrease in or loss of penile erection.

Table 1

N3-N4 lymph node mapping ($n = 104$).

Charateristics	Value
Total number of harvested lymph nodes (mean ± SD)	34.4 ± 7.2
Number of harvested lymph node in each specific station (mean, range)	
① Inferior Mesenteric Artery (IMA)	4.7 (1–9)
② Para-aorta	9.8 (3–42)
③ Inferior vena cava (IVC)	7.8 (2–24)
④ Infra-renal vein (IRV)	5.6 (2–12)
⑤ Common iliac vessels (CIV)	6.5 (2–14)
Level of lymph node involvement (*n*, %)	
N3-N4 (-)	28 (26.9)
Single-station	33 (31.7)
IMA only	8
Para-aorta only	10
IVC only	5
IRV only	6
CIV only	4
Double stations	34 (32.7)
IMA + Para-aorta	4
IMA + IVC	4
IMA + IRV	6
IMA + CIV	2
Para-aorta + IVC	3
Para-aorta + IRV	4
CIV + IRV	1
CIV + IVC	3
CIV + Para-aorta	7
Triple stations	9 (8.7)
IMA + Para-aorta + IVC	2
IMA + Para-aorta + IRV	5
CIV + Para-aorta + IRV	1
CIV + Para-aorta + IVC	1

Discussion

The optimal surgical treatment for left-sided colorectal cancer with clinically suspected N3-N4 nodal metastases remains an unmet need. Extended lymph node dissection in such lymphatic basins has not been established as a standard treatment because of insufficient evidence to support or refute the routine use of this practice. The American Society of Colon and Rectal Surgeon guidelines specify that a high tie at the origin of the IMA with lymphadenectomy is indicated only when lymphadenopathy is clinically suspected[27]. Similarly, the AJCC categorized N3-N4 lymph node metastasis as distant metastasis (M1) and, therefore, as stage IV disease[22]. The National Comprehensive Cancer Network guidelines do not recommend extended lymph node dissection as a routine practice, but state that clinically suspicious nodes beyond the field of resection should be biopsied and/or removed if possible[27].

Table 2

Comparison of demographic and clinicopathologic data stratified by pathologic nodal status in 104 patients undergoing a successful robotic D3-D4 lymph node dissection.

	Negative N3-N4 ($n=28$)	Positive N3-N4 ($n=76$)	P
Age (years, mean ± SD)	67.4 ± 7.6	68.2 ± 11.2	0.7278
Sex			0.7956
Female	11	32	
Male	17	44	
BMI(weight/height2, kg/m2)	26.8 ± 3.2	25.6 ± 4.4	0.1903
ASA class			0.9350
I	16	44	
II	10	28	
III	2	4	
Tumor location (cm above anal verge)	18.2 ± 4.2	17.8 ± 5.4	0.7240
Tumor morphology			0.8421
Polypoid	4	8	
Fungating	12	32	
Ulcerative	12	36	
Differentiation			0.9620
Well	2	5	
Moderate	25	69	
Poor	1	2	
Mucin production			0.4827
Absent	25	71	
Present	3	5	
T Stage (pathologic)			0.7339
T2	2	3	
T3	24	69	
T4	2	4	
CEA level			0.5212
< 5.0 ng/ml	8	31	
5.0 ng/ml–10.0 ng/ml	16	36	
> 10.0 ng/m	4	9	
K-ras mutation			0.6636
+	12	29	
–	16	47	
MMR mutation			0.7154
+	2	4	
–	26	72	

ASA, American Society of Anesthesiology; MMR, mismatch repair.

However, an increasing number of recent studies have reported that radical resection in combination with modern perioperative chemotherapy and/or targeted therapy extends the survival of colorectal cancer patients with para-aortic lymph node metastasis in recent years[2–4,7,28–32], as mentioned in the latest Japanese guidelines[21]. Kang *et al.*[28] reported that following curative resection, the 5-year disease-free rates were 31.9 and 69.4% in the IMA nodal metastasis-positive and metastasis-negative groups, respectively ($P < 0.001$). In studies on isolated para-aortic lymph node metastasis, the median survival time for radically resected patients was 34–64 months, which was significantly longer than that for patients who did not undergo radical resection[29,30]. Arimoto *et al.*[3] reported a 3-year survival rate of 41.2% in patients who underwent curative resection, and Bae *et al.*[31] indicated that the 5-year survival rate in rectal cancer patients with curatively resected simultaneous isolated para-aortic lymph node metastasis was 33.9%, which was comparable to that of curatively resected liver metastasis. Moreover, favorable outcomes such as a 5-year survival rate of 54.2%, a 5-year relapse-free survival rate of 42.1%, and a 5-year cancer-specific survival rate of 70.3% among R0 resection patients have also been reported recently[2,8,32]. However, these studies had some drawbacks. First, the extent of N3-N4 lymph nodes was not clearly defined, and thus, the surgical procedures were not standardized; second, nearly all the reports were retrospective and liable to many uncertain factors; third, the reports were mostly from veteran surgeons of high-volume centers and disregarded the steep learning curve and high surgical morbidity rate inherent in this technique. Therefore, despite all the aforementioned surgical endeavors, the barrier to the wider adoption of D3-D4 lymph node dissection is still not completely lifted.

To improve the methodology of previous reports, we conducted the present study in the following sequence: first, the N3-N4 lymphatic basin was defined as the area within the following boundaries: the aortic bifurcation (downward), the lower border of the left renal vein (upward), IVC (medially), and gonadal vessels (laterally)[2,9,11,32]; thereafter, the N3-N4 lymphatic basin was divided into five nodal stations; and then a standardized D3-D4 lymph node dissection was performed according to a preplanned protocol. Immediately postsurgery, the authors precisely mapped the harvested lymph nodes. In general, surgeons are better trained in handling fresh specimens than pathologists and, thus, are more capable of meticulously retrieving lymph nodes from unfixed surgical specimens. Although this was not common practice for Western surgeons, we demonstrated that it achieved a satisfactory number of retrieved lymph nodes, up to a mean number of 34.4 per patient, which was higher than that reported previously[1,9,11,12,20,28,32]. Therefore, we believe that the large number of lymph nodes evaluated, and the methodology used to assess their anatomical location ensured the quality of lymph node mapping and subsequent survival correlation.

In this study, univariate analysis showed that the five nodal stations had equal oncologic significance for patient survival after standardized D3-D4 lymph node dissection. In addition, a subset analysis of patients with single-station lymph node metastasis ($n=33$) showed that the five nodal stations were equally likely to develop nodal metastasis. Such findings imply that for patients with clinically suspected N2 lymph node metastasis requiring D3-D4 lymph node dissection, surgery should be performed with the intent of extirpating the five nodal stations en bloc and not just removing the involved lymph nodes individually (lymph node sampling). However, further multivariate analysis demonstrated that only the IRV and CIV nodal stations were significantly associated with patient survival. This finding suggests that the inferior mesenteric vein and CIV nodal stations represent the upper and lower border of the N3-N4 lymphatic basin. Thus, the overall survival of patients with nodal metastasis in these two frontier nodal posts may be skewed to that of patients with a systemic metastatic disease, which was beyond the scope of surgical treatment.

The surgery in the present study was implemented using the da Vinci Surgical System, which represents the largest case series of robotic D3-D4 lymph node dissection worldwide. It showed that D3-D4 lymph node dissection could be successfully performed using the robotic approach with acceptable oncologic efficacy and functional outcomes, as shown by the relevant metrics. However, the amount of blood loss and operation time were similar between robotic, laparoscopic, and traditional open surgeries[16–18]. To perform D3-D4 lymph node dissection is

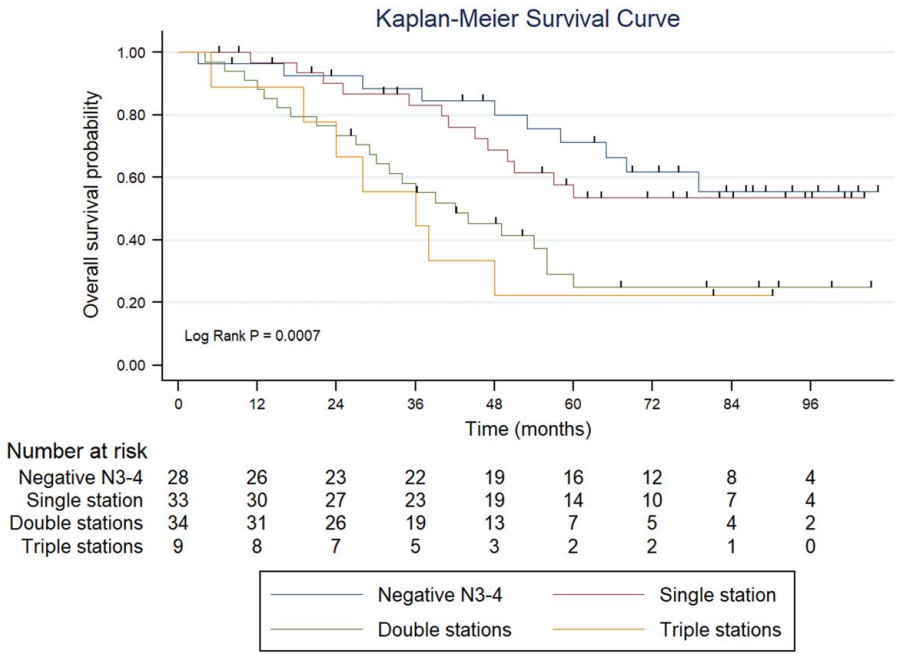

Figure 2. Comparison of the estimated 5-year overall survival rate among patient groups stratified by the number of metastasis-positive nodal station. After standardized robotic D3-D4 lymph node dissection, the estimated 5-year overall survival rate of patient groups with negative or single-station N3-N4 nodal metastasis was significantly higher ($P = 0.0007$, log rank test) than that of patients with double- or triple-station N3-N4 nodal metastasis.

labor-intensive work with 5–6 h of operation time and 350–400 ml of blood loss[3,32]. Based on the present study, we felt that robotic surgery was suitable for performing such complex, time-consuming surgeries because it could considerably lessen the physical stress for the operating surgeons; on the patient side, it could also obviously enhance the surgical precision and lead to quick convalescence after the operation.

Table 3

Cox proportional hazard model for overall survival of the five N3-N4 lymph node stations.

	Univariate analysis		Multivariate analysis	
Prognostic significance	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
①IMA, *n* = 31				
No	1.000		1.00	
Yes	2.523 (1.192—5.344)	0.016	1.564 (0.902—2.714)	0.111
②Para-aorta, *n* = 37				
No	1.000		1.00	
Yes	2.236 (1.035—4.833)	0.041	1.382 (0.753—2.537)	0.296
③IVC, *n* = 18				
No	1.000		1.00	
Yes	2.148 (0.908—5.081)	0.044	1.589 (0.781—3.231)	0.201
④IRV, *n* = 23				
No	1.000		1.000	
Yes	2.644 (1.179—5.929)	0.018	2.069 (1.050—4.075)	0.036[a]
⑤CIV, *n* = 19				
No	1.000		1.000	
Yes	3.169 (1.312—7.655)	0.010	2.336 (1.155—4.723)	0.018[a]

[a]Denotes the statistically significant parameter in multivariate analysis.

In this study, the 5-year survival rate of single-station N3-N4 nodal metastasis-positive patients was not significantly lower than that of N3-N4 nodal metastasis-negative patients. The 5-year survival rate of patients with two-station or three-station lymph node metastasis was similar to that of patients with AJC/UICC stage IV disease. These findings implied that it deserved to perform D3-D4 lymphadenectomy for patients with clinically more than N2 lymph node metastasis, because proactive D3-D4 lymph node dissection for single-station nodal metastatic disease has achieved a 5-year survival rate similar to that of AJC/UICC stage III disease. In this context, the single-station nodal metastasis should be treated as 'locoregional' in lieu of 'metastatic' disease. In contrast, for patients with two-station or three-station nodal metastatic disease, the implementation of D3-D4 lymph node dissection could facilitate the harvest of sufficient lymph nodes for a precise pathologic staging and prompt the patients to be adequately managed under the guidelines of the 'metastatic disease' in the framework of multidisciplinary treatment. Such clinical diagnosis and treatment scenarios can explain the remarkably higher 5-year overall survival rate (37.5%) in the present case series than that (around 20%) of other case series, in which the D3-D4 metastases were treated as the stage IV diseases using the modern chemotherapeutic and targeted agents.

On the other hand, although oncologic cure and overall survival are the main goals of treatments for such patient cohorts, self-reported quality of life (QoL) of individual cancer patients still represents a crucial factor for evaluating the overall impact of the surgical procedure on patients' lives[33,34]. The treatment of rectal cancer is often associated with the loss or severe

Table 4

Surgical outcomes of this case series treated by robotic D3-D4 lymphadenectomy.

Metrics	Value
Operation time (min)	344.4 ± 40.5
Blood loss	325.4 ± 50.6
Postoperative pain (visual analog scale)	3.5 ± 0.6
Flatus passage (h)	72.0 ± 12.5
Soft diet (d)	6.4 ± 2.5
Foley removal (d)	18.5 ± 2.0
Postoperative complications (*n**)	
Acute adhesive ileus	2
Anastomotic leakage	4
Cerebrovascular accident	1
Deep vein thrombosis	1
Duodenal paralysis	3
Enterocutaneous fistula	2
Internal herniation	1
Myocardial infarction	1
Pelvic abscess	1
Pneumonia	2
Protective ileostomy	2
Pulmonary embolism	1
Retroperitoneal abscess	2
Urinary tract infection	2
Urine retention	2
Wound infection	8
Clavin–Dindo classification (*n*, %)	
≥ II	31 (29.3)
≥ III	16 (15.1)
II	15 (14.6)
IIIa/IIIb	5/4 (8.5)
IVa	4 (3.8)
IVb	1 (0.9)
V(operative mortality)	2 (1.9)
Hospitalization (mean ± S.D, range, days)	14.0 ± 2.0
Readmission (*n*, %)	8 (7.7)

The continuous data were calculated by mean ± SD.
*One patient may have more than one kinds of surgical complications.

Table 5

Postoperative disability and genitourinary dysfunction of male patients after robotic D3-D4 lymph node dissection for the upper rectum and sigmoid colon cancer.

Disability	
Return to partial activity (mean ± SD, weeks)	3.0 ± 0.5 (94[a])
Return to full activity (weeks)	5.0 ± 0.8 (82[a])
Return to work (weeks)	7.0 ± 0.5 (54[a])
Bladder function (%, *n*)	
Voiding function after Foley removal	
Good	24.6 (15/61[a])
Fair	68.9 (42/61)
Poor	6.5 (4/61)
Status of voiding dysfunction	
Transient	87.0 (40/46[a])
Permanent	13.0 (6/46)
Sexual function (%, *n*)	
Ejaculation	
Good	0 (0/34[a])
Fair	5.9 (2/34)
Poor	94.1 (32/34)
Erection	
Good	52.9 (18/34)
Fair	32.4 (11/34)
Poor	14.7 (5/34)

[a]Denominator was the number of patients accepting the evaluation of postoperative disability or genitourinary dysfunction.

impairment of defecation function, alteration of body anatomy, urogenital problems and, sometimes, intractable pain, thus affecting the postoperative QoL[33–35]. Remarkably, Kim HJ *et al.*[25] performed a propensity score-matched analysis of patients undergoing total mesorectal excision with the robotic or laparoscopic approach and found that while global health status/QoL was similar between groups, the robotic approach was associated with less impairment of urinary and sexual function and social-emotional functioning, compared with the laparoscopic approach. In this study, we observed the baseline scores of QoL-evaluating items other than the genitourinary function can be satisfactorily maintained by using the robotic approach to perform the D3-D4 lymph node dissection. Anatomically, the impairment of genitourinary function is unavoidable during the D3-D4 lymph node dissection, irrespective of the surgical approach (traditional open, laparoscopic, or robotic) used. The present study showed that 94.1% male patients lost the ejaculation function permanently and 75.4% of male patients lost the urinary function temporally. Therefore, for male patients with advanced sigmoid colon or upper rectal cancer, to perform the D3-D4 lymph node dissection has been a trade-off between oncologic clearance and preservation of genitourinary function. However, since the robotic approach presented with quick convalescence and shorter postoperative disability, it still deserves recommendation for patients requiring the D3-D4 lymph node dissection in the context of a better postoperative QoL.

The present study had several limitations. First, this study was conducted in a tertiary referral center, the findings of which may not be representative of patients elsewhere. The surgical indications and interpretation of preoperative imaging findings may still be subject to case-selection bias, although this study was prospectively conducted by a well-trained surgical team according to a preplanned protocol. Second, the present study did not consider the influence of systemic chemotherapy or targeted therapy on patient survival because the regimens and administration of postoperative treatment were not standardized. Third, the present study failed to adequately control the molecular biological markers that may affect the effectiveness of chemotherapy or targeted therapy and, thus, the patient's prognosis.

In conclusion, the present study better delineated the territory of the N3-N4 lymph node for upper rectal and sigmoid colon cancer. A standardized D3-D4 lymph node dissection could be safely performed using the robotic approach without increasing surgical complications and thus could provide significant oncologic benefits for patients. Further multicenter prospective studies are warranted to provide more solid evidence to facilitate the optimization of surgery and even revise the current treatment guidelines for such a clinical conundrum.

Ethical approval

The study was approved by the Institutional Review Board of NTUH, which waived the requirement for informed consent (Unique Protocol ID: 202002011RINB).

Consent

The study was approved by the institutional review board at each participating hospital, and the need for informed consent was waived due to the retrospective nature of the study.

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Author contribution

T.-C.C.: conducted the study, analyzed the data, and wrote the manuscript; J.-T.L.: supervised study design, conduction, data analysis, and manuscript writing of the present study; J.H.: assisted the conduction of this study; Y.-T.L. and J.-S.H.: assisted the conduction and analysis data of the present study.

Conflicts of interest disclosure

The authors declare that they have no financial conflicts of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

The present study was registered in the name of 'Robotic versus Laparoscopic D3-D4 Lymphadenectomy for Colorectal Cancer' and designated as ClinicalTrials.gov ID: NCT05961423.

Guarantor

Jin-Tung Liang.

Data availability statement

All data are provided on request from the authors.

Provenance and peer review

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