International Journal of Colorectal Disease (2019) 34:1121–1129
https://doi.org/10.1007/s00384-019-03294-2

ORIGINAL ARTICLE

Long-term outcome and prognostic factors for patients with para-aortic lymph node dissection in left-sided colorectal cancer

Kota Sahara[1] · Jun Watanabe[2] · Atsushi Ishibe[1] · Yusuke Suwa[2] · Hirokazu Suwa[3] · Mitsuyoshi Ota[1] · Chikara Kunisaki[2] · Itaru Endo[1]

Accepted: 5 April 2019 / Published online: 1 May 2019

Abstract

Background Para-aortic lymph node (PALN) metastasis of colorectal cancer is rare, and the treatment strategy for PALN metastasis (PALNM) is not established in contrast to liver or lung metastases. We sought to evaluate the survival outcomes and prognostic factors among patients undergoing surgery combined with extended lymphadenectomy for PALNM from left-sided colorectal cancer.

Methods From 1992 to 2012, 322 patients who underwent PALN dissection (PALND) synchronously with primary resection, among 1819 left-sided colorectal surgical cases, were retrospectively examined. We investigated the overall survival (OS) and prognostic factors for patients with PALNM.

Results Of the 322 patients, 62 (19.3%) were histologically confirmed to have PALNM. The 5-year OS in patients with and without PALNM was 19.5% and 67.0% ($p < 0.001$), respectively. Among patients with PALNM, on the multivariable analysis, the positive resection margin (hazard ratio (HR) 3.61; 95% confidence interval (CI) 1.85–7.06), undifferentiated histological type ((por/muc/sig), HR 4.51; 95% CI, 2.22–9.19), ≥ 4 PALNMs (HR 3.34; 95% CI 1.53–7.31), and preoperative CEA ≥ 10 ng/mL (HR 2.1; 95% CI 1.11–4.27) were significant prognostic factors. Among R0 resected cases, the 5-year OS of the 17 cases with ≤ 3 PALNM and well/moderately differentiated adenocarcinoma was 54.2%, which was comparable to that of patients undergoing PALND and diagnosed with stage IIIC (49.6%).

Conclusion Patients with PALNM of colorectal cancer had a poor prognosis. However, curative resection, ≤ 3 PALNM, and well/moderately differentiated histology type were associated with the long-term survival.

Keywords Para-aortic lymph node · Metastasis · Colorectal cancer · Prognosis · Lymph node dissection

Introduction

Approximately 10–20% of newly diagnosed colorectal cancer (CRC) patients have simultaneous distant metastasis [1, 2]. At present, aggressive resection is the standard strategy for managing liver or lung metastasis when negative margin resection can be achieved [3, 4]. In contrast, due the low frequency of para-aortic lymph node (PALN) metastasis (PALNM) compared with liver or lung metastasis, the efficacy of PALNM resection has not yet been proven.

According to the 8th American Joint Committee on Cancer (AJCC) staging, when the sigmoid colon or rectal cancer metastases to the inferior mesenteric lymph nodes, they are considered regional lymph nodes belonging to the N category, whereas, when the cancer metastasis to the PALN, they are categorized as systemic lymph nodes and are considered to belong to M category [5]. Although PALNM is defined as M1 in the AJCC guideline, a subset of patients may be able to achieve similar benefits from PALNM removal as at other metastatic sites. Several studies have reported the oncologic impact of PALNM resection, but data demonstrating the efficacy of PALNM removal remain scarce [6–10].

A concise and informative title: Prognostic factors for para-aortic lymph node dissection

✉ Jun Watanabe
nabe-jun@comet.ocn.ne.jp

[1] Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, Yokohama, Japan

[2] Department of Surgery, Gastroenterological Center, Yokohama City University Medical Center, 4-57, Urafune-cho, Minami-ku, Yokohama 232-0024, Japan

[3] Department of Surgery, Yokosuka Kyosai Hospital, Yokosuka, Japan

The aim of this study was to evaluate the survival outcomes of patients with left-sided colorectal cancer surgery combined with extended lymphadenectomy of PALNM and the prognostic factors for patients with PALNM.

Patients and method

Patients and study design

From December 1992 to October 2012, 1819 patients underwent surgery at two institutions, Yokohama City University Hospital and Yokohama City University Medical Center, for left-sided CRC. Left-sided CRC was defined as a tumor with its major part located in the descending colon (D), sigmoid colon (S), recto-sigmoid colon (Rs), or rectum. Among such cases, the 322 patients (17.7%) who underwent PALN dissection (PALND) synchronously with primary resection were analyzed. During the study period, the indication of PALND was determined by a radiologic evaluation based on enhanced computed tomography (CT). PALND was attempted for patients with PALN ≥ 10 mm in diameter (long axis). Institutional approval for this retrospective study was obtained from the Ethical Advisory Committee of Yokohama City University School of Medicine before initiating the study.

Following surgery, all patients underwent general follow-up examinations and measurements of serum CEA levels every three months, as well as chest and abdominal CT every six months and a colonoscopy every year until five years after their surgery. Recurrence was confirmed in the tumor that had been diagnosed histologically and/or radiologically. The overall survival (OS) was defined as the time from the date of surgery to the date of death, and the disease-free survival (DFS) was calculated as the time from the date of surgery to the date of diagnosed local recurrence, distant metastasis, or death.

Patient characteristics were compared among patients with and without PALNM. Prognostic factors were investigated separately in patients with PALNM, and in those with only R0 resection. The definitions of curability of surgical resection were as follows: R0 resection, no macroscopic or microscopic residual tumor; R1 resection, no macroscopic residual tumor but with microscopic tumor at the resection margin; R2 resection, regional macroscopic residual tumor and/or unresected distant metastasis.

Surgical procedure

After primary tumor resection with central vascular ligation, PALN dissection was performed via an open approach. The Japanese Society for Cancer of the Colon and Rectum (JSCCR) defines PALN as #216b2 from inferior mesenteric artery (IMA) to bifurcation of the common iliac artery, and as #216b1 from left renal vein to IMA [2]. Our routine extent of PALN dissection is #216b1 and #216b2 (Fig. 1).

Statistical analyses

Quantitative data are expressed as the median and interquartile range (IQR). Categorical variables were compared using chi-square tests and Fisher's exact tests where appropriate. Continuous variables were compared using the Mann-Whitney *U* test. The OS and DFS cases were evaluated using the Kaplan-Meier method, and the significance was determined using the log-rank test. The log-rank test was used for the univariable analysis, and independent prognostic factors were identified by a multivariable analysis using the Cox proportional hazards model to calculate hazard ratios (HRs). Age (≤ 65 or > 65 years), sex (female or male), histological type of primary tumor, T category (T2 or T3, T4), N category (N0–N1, N2), M category (M1a, M1b), tumor size (< 60 or ≥ 60 mm), preoperative CEA (< 10 or ≥ 10 ng/mL), number of positive PALNs (≤ 3 or > 4), and curability (R0, R1–2) were included as covariates. N0 and N1 were combined into a single group because there were only two N0 patients among the 62 with PALNM. The results of the Cox model analysis are reported using HRs and 95% confidence intervals (CIs). The probability (*p*) values were statistically significant at a level < 0.05. Statistical analyses were performed using the IBM SSPS Statistics software program, ver. 23.0 (IBM Corporation, Somers, NY, USA).

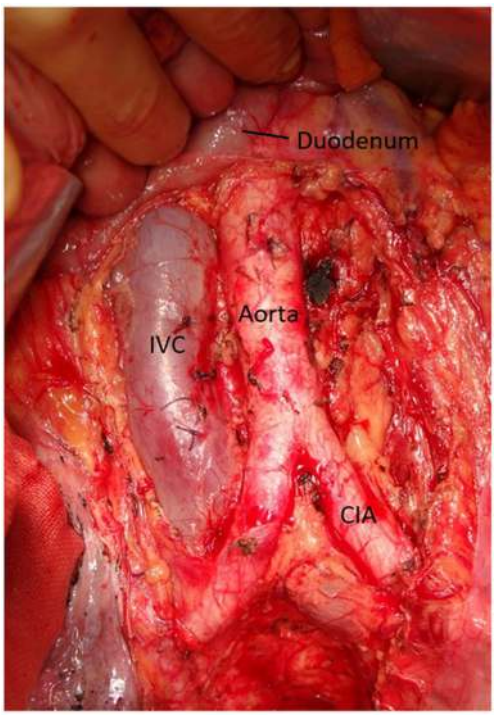

Fig. 1 Photograph taken after para-aortic lymph node dissection. IVC, inferior Vena Cava; CIA, common iliac artery

Results

Characteristics of the patients in the entire cohort

Of the 322 patients, 62 (19.3%) were histologically confirmed to have PALNM, whereas 260 (80.7%) did not have PALNM (Table 1). The median age was 61 years old (IQR 53–67), and 204 (63.5%) were male. In 158 cases (49.1%), the tumor was in the rectum. The preoperative median CEA level was 6.5 ng/mL (IQR 3.2–17.2).

Forty-six cases (14.3%) underwent distant metastasis resection other than PALN, including hepatectomy (N = 31, 9.6%), peritonectomy (N = 14, 4.3%), and both (N = 1, 0.3%). The median numbers of total harvested and metastatic PALNs were 10 (IQR 5–16) and 2 (IQR 1–5), respectively. The tumor was either well/moderately differentiated adenocarcinoma (N = 281, 87.3%) or poorly differentiated/mucinous/signet ring cell carcinoma (N = 41, 12.7%). The median tumor size was 5.2 cm (IQR 4.0–6.5). Ninety-nine cases (30.8%) were T4, and 113

Table 1 Demographic and patient characteristics in the entire cohort

	Total	PALNM (+)	PALNM (−)	
Variable	N = 322	N = 62	N = 260	p
Age[a]	61 (53–67)	63 (55–69)	60 (53–66)	0.159
Male	204 (63.5%)	39 (62.9%)	165 (63.5%)	0.935
Location				0.905
D/S/Rs	164 (50.9%)	32 (51.6%)	132 (50.8%)	
Rectum	158 (49.1%)	30 (48.4%)	128 (49.2%)	
CEA[a] (ng/mL)	6.5 (3.2–17.2)	10.1 (4.1–29.2)	6.2 (2.8–15.8)	0.123
Distant metastasis resection other than PALNM				0.013
No	276 (85.7%)	47 (75.8%)	229 (88.1%)	
Yes	46 (14.3%)	15 (24.2%)	31 (11.9%)	
Procedure of distant metastasis resection				0.024
Hepatectomy (Hx)	31 (9.6%)	9 (14.5%)	22 (8.5%)	
Peritonectomy	14 (4.3%)	5 (8.1%)	9 (3.5%)	
Hx + peritonectomy	1 (0.3%)	1 (1.6%)	0	
Number of PALN dissected [a]	10 (5–16)	10 (5–14)	11 (3–51)	0.346
Number of PALNM [a]	–	2 (1–5)	–	–
Histological type				0.003
tub1/tub2	281 (87.3%)	47 (75.8%)	234 (90.0%)	
por/muc/sig	41 (12.7%)	15 (24.2%)	26 (10.0%)	
Tumor size[a] (cm)	5.2 (4.0–6.5)	5.5 (4.0–6.6)	5.0 (4.0–6.5)	0.476
T category				< 0.001
T1/T2/T3	222 (69.2%)	29 (46.8%)	193 (74.5%)	
T4	99 (30.8%)	33 (53.2%)	66 (25.5%)	
N category				< 0.001
N0/N1	209 (64.9%)	14 (22.6%)	195 (75.0%)	
N2	113 (35.1%)	48 (77.4%)	65 (25.0%)	
M category				< 0.001
M0	209 (64.9%)	0	209 (80.4%)	
M1a	83 (25.8%)	40 (64.5%)	43 (16.5%)	
M1b	30 (9.3%)	22 (35.5%)	8 (3.1%)	
Margin status				<0.001
R0	246 (76.6%)	35 (56.5%)	211 (81.5%)	
R1/2	75 (23.4%)	27 (43.5%)	48 (18.5%)	

D, descending colon; *S*, sigmoid colon; *Rs*, rectosigmoid colon; *CEA*, carcinoembryonic antigen; *PALN*, para-aortic lymph node; *PALNM*, para-aortic lymph node metastasis; *tub1*, well differentiated tubular adenocarcinoma; *tub2*, moderately differentiated tubular adenocarcinoma; *por*, poorly differentiated tubular adenocarcinoma; *muc*, mucinous adenocarcinoma; *sig*, signet ring cell carcinoma; −, not available

[a] Median (IQR)

(35.1%) were N2. There were 83 cases (25.8%) of M1a with PALNM only and 30 cases (9.3%) of M1b with metastasis other than PALNM. Regarding the final pathological curability, R0 resection was performed in 246 cases (76.6%), while 75 cases (23.4%) received R1 or R2 resection.

Patients with PALNM significantly tended to have distant metastasis resection (24.2% vs. 11.9%, $p = 0.013$), tumor with a histological type of por/muc/sig (24.2% vs. 10.0%, $p = 0.003$), T4 (53.2% vs. 25.5%, $p < 0.001$), N2 (77.7% vs. 25.0%, $p < 0.001$), and R1/2 resection (43.5% vs. 18.5%, $p < 0.001$). There were no marked differences between patients with and without PALNM in the age, gender, tumor location, CEA level, number of PALNs dissected, or tumor size. Among the 22 patients with PALNM and other distant metastasis, the distant metastatic site was the liver ($N = 18$, 81.8%), peritoneal dissemination ($N = 7$, 31.8%), lung ($N = 2$, 9.1%), and spleen ($N = 1$, 4.5%), including overlap cases.

The OS stratified by PALNM

After a median follow-up period of 71.8 months (IQR 25.5–124.7), the 5-year OS in the patients with and without PALNM was 19.5% and 67.0% ($p < 0.001$), respectively (Fig. 2a). Regarding patients without PALNM, those with stage IIIC disease showed a significantly poorer prognosis than those with stage I to IIIB disease (all $p < 0.05$), and the prognosis in patients with stage IV disease was significantly worse than that in those with stage IIIC disease (5-year OS 49.6% vs. 19.0%, $p = 0.001$).

Prognostic factors in patients with PALNM

Univariable and multivariable survival analyses of prognostic factors were performed for patients with PALNM (Table 2). In the univariable analysis, preoperative CEA ≥ 10 ng/mL ($p = 0.031$), N2 ($p = 0.021$), undifferentiated type (por/muc/sig, $p < 0.001$), number of PALNMs ≥ 4 ($p = 0.007$), and R1/2 ($p < 0.001$) were identified as factors. In the multivariable analysis including factors with a p value of < 0.05 in the univariable analysis, preoperative CEA ≥ 10 ng/mL (HR 2.18; 95% CI 1.11–4.27, $p = 0.023$), undifferentiated type (por/muc/sig, HR 4.51; 95% CI 2.22–9.19, $p < 0.001$), number of PALNMs ≥ 4 (HR 3.34; 95 %CI 1.53–7.31, $p = 0.002$), and R1/2 (HR 3.61; 95% CI 1.85–7.06, $p < 0.001$) were shown to be significantly correlated with the OS. The Kaplan-Meier curves described the 5-year OS according to the curability of surgical resection, showing that the 5-year OS in patients with an R0 margin was higher than in those with an R1/2 margin (29.7% vs. 5.1%, $p < 0.001$) (Fig. 2c). Among the 35 patients with PALNM and R0 resection achieved, the 5-year DFS was 17.1%, and the median disease-free duration was 18.0 months (95% CI 12.8–23.1 months) (Fig. 3). The proportion of patients undergoing postoperative adjuvant chemotherapy mainly with a 5-FU agent was 85.7% ($N = 30$), and only two patients received chemotherapy with oxaliplatin. Five patients did not receive postoperative adjuvant therapy due to postoperative complications or patient refusal. Univariable and multivariable survival analyses of the prognostic factors for patients with R0 resection were evaluated (Table 3). In the univariable analysis, undifferentiated type (por/muc/sig, $p = 0.001$) and number of

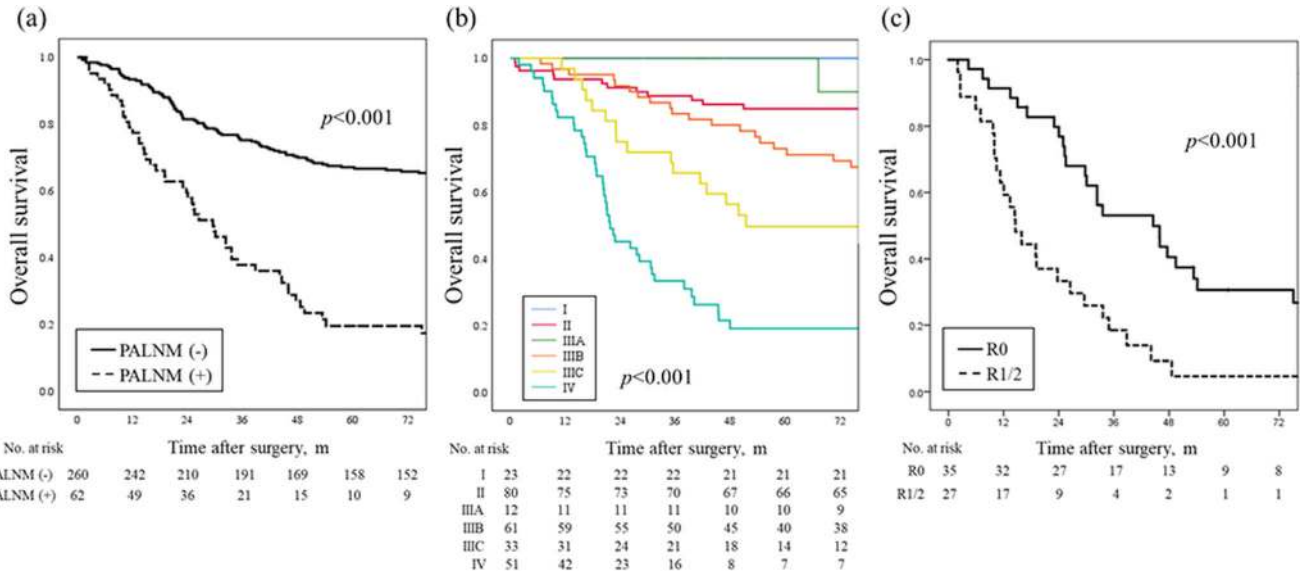

Fig. 2 The overall survival after para-aortic lymph node dissection (**a**) in patients with and without PALNM, (**b**) in patients without PALNM stratified by stage, and (**c**) in patients with PALNM stratified by margin status

Table 2 Cox regression analysis of clinicopathological factors associated with overall survival among patients with PALNM

Variable	No.	Univariable analysis		Multivariable analysis	
		5-y OS (%)	*p*	HR (95% CI)	*p*
Age					
< 65	35	17.5			
≥ 65	27	22.2	0.837		
Gender					
Male	39	14.6			
Female	23	28.3	0.797		
CEA (ng/mL)					
≤ 10	28	26.9		Ref	
> 10	29	13.7	0.031	2.18 (1.11–4.27)	0.023
Tumor size (cm)					
<6.0	33	18.9			
≥6.0	27	22.3	0.587		
T category					
T2/3	29	27.9			
T4	33	12.7	0.257		
N category					
N0/1	14	38.1		Ref	
N2	48	17.2	0.021	1.48 (0.69–3.16)	0.313
M category					
M1a	40	20.1			
M1b	22	18.7	0.413		
Histological type					
tub1/tub2	47	24.0		Ref	
por/muc/sig	15	6.7	< 0.001	4.51 (2.22–9.19)	< 0.001
Number of PALNM					
1–3	42	27.0		*Ref*	
≥ 4	20	5.0	0.007	3.34 (1.53–7.31)	0.002
Margin status					
R0	35	30.6		*Ref*	
R1/2	27	4.6	< 0.001	3.61 (1.85–7.06)	< 0.001

CEA, carcinoembryonic antigen; *PALNM*, para-aortic lymph node metastasis; *tub*, well differentiated tubular adenocarcinoma; *tub2* moderately differentiated tubular adenocarcinoma; *por*, poorly differentiated tubular adenocarcinoma; *muc*, mucinous adenocarcinoma; *sig*, signet ring cell carcinoma

PALNMs ≥ 4 ($p = 0.025$) were identified as factors. In the multivariable analysis including factors with a p value of < 0.05 in the univariable analysis, undifferentiated type (por/muc/sig, HR 6.05; 95% CI 2.24–16.32, $p < 0.001$), and number of PALNMs ≥ 4 (HR 3.81; 95%CI 1.53–9.47, $p = 0.004$) were shown to be correlated with the OS.

When patients with R0 resection were stratified by the histological type and number of PALNMs, the 5-year OS and MST of the 17 patients with 0 factors (well/mod and PALNMs ≤ 3), 15 patients with 1 factor (well/mod and PALNMs ≥ 4 or por/muc/sig and PALNMs ≤ 3), and 3 patients with both factors (por/muc/sig and PALNMs ≥ 4) were 54.2% (75 months), 10.0% (32.3 months), and 0% (7.5 months), respectively (Fig. 4).

Discussion

Unlike liver and lung metastases, PALNM is a relatively rare pattern of synchronous distant metastases, with an incidence of < 1.3% [11]. In a separate study, only 0.7–1.7% of patients with primary colorectal cancer who underwent surgery had isolated extra-regional lymph node metastasis [10, 12]. Regarding its prognosis, synchronous PALNM from CRC is categorized as stage IV disease. Indeed, the current study demonstrated that patients with PALNM were associated with poorer prognostic factors, despite the results of the unadjusted analysis, such as a histological type of por/muc/sig, T4 and N2, than patients without PALNM (Table 1). Furthermore, the 5-year OS in patients with PALNM was comparable to that in

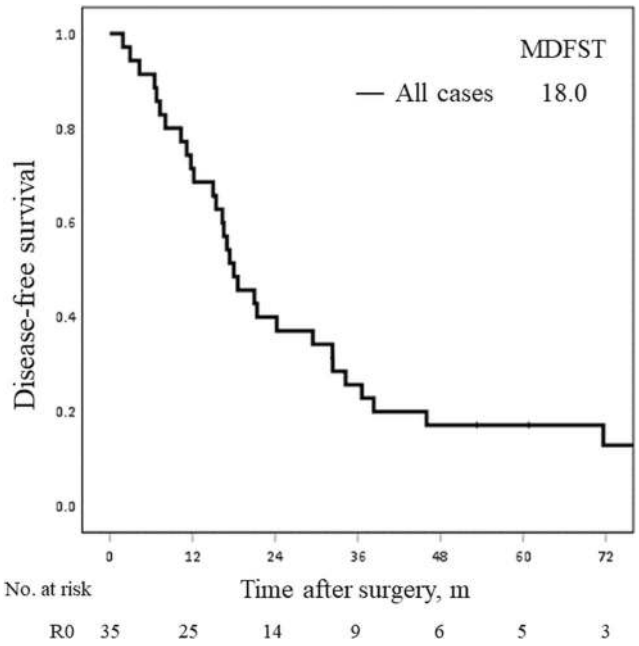

Fig. 3 The disease-free survival after para-aortic lymph node dissection among patients with R0 resection

patients without PALNM but with stage IV disease (19.5% vs. 19.0%). Since PALNM can be considered a systemic disease, there is no argument that chemotherapy is useful, but literature regarding the efficacy of PALNM resection remains scarce.

Several articles have described the role of extended lymph node dissection in CRC patients by comparing the long-term survival between patients with and without PALNM. Bae et al. reported that the 5-year OS and DFS in patients with PALNM were comparable to those values in patients with resectable liver metastasis in cases that achieved R0 resection [8]. In addition, Choi et al. noted that the 5-year OS rate in patients undergoing PALNM dissection ($N = 24$) was significantly higher than that in control patients without PALNM dissection ($N = 53$) (53.4% vs. 12.0%, $p = 0.045$) [6]. Furthermore, the importance of R0 resection was mentioned by Nakai et al.; among 30 patients with synchronous PALNM including distant metastases other than PALNM, the 5-year OS rates for 18 patients who underwent R0 resection and 12 who did not were 29.1% and 10.4%, respectively ($p = 0.017$) [9]. Ogura et al. noted that the 5-year cancer-specific survival differed significantly between the R0 and control groups (70.3% vs. 12.5%; $p = 0.0003$) in 28 patients with synchronous isolated PALNM

Table 3 Cox regression analysis of clinicopathological factors associated with overall survival among patients with PALNM and R0 margin

		Univariable analysis		Multivariable analysis	
Variable	No.	5-y OS (%)	*p*	HR (95% CI)	*p*
Age					
< 65	19	31.1			
≥ 65	16	31.3	0.994		
Gender					
Male	23	23.6			
Female	12	46.3	0.336		
CEA (ng/mL)					
≤ 10	21	36.1			
> 10	13	22.4	0.154		
Tumor size (cm)					
< 6.0	21	24.8			
≥ 6.0	13	42.7	0.731		
T category					
T2/3	14	47.1			
T4	21	20.2	0.177		
N category					
N0/1	10	46.7			
N2	25	24.5	0.073		
M category					
M1a	28	25.2			
M1b	7	57.1	0.583		
Histological type					
tub1/tub2	26	38.3		Ref	
por/muc/sig	9	11.1	0.001	6.05 (2.24–16.32)	< 0.001
Number of PALNM					
1–3	23	43.6		Ref	
≥ 4	12	8.3	0.025	3.81 (1.53–9.47)	0.004
Adjuvant chemotherapy					
No	5	0			
Yes	30	36.0	0.066		

CEA, carcinoembryonic antigen; *PALNM*, para-aortic lymph node metastasis; *tub1*, well differentiated tubular adenocarcinoma; *tub2*, moderately differentiated tubular adenocarcinoma; *por*, poorly differentiated tubular adenocarcinoma; *muc*, mucinous adenocarcinoma; *sig*, signet ring cell carcinoma

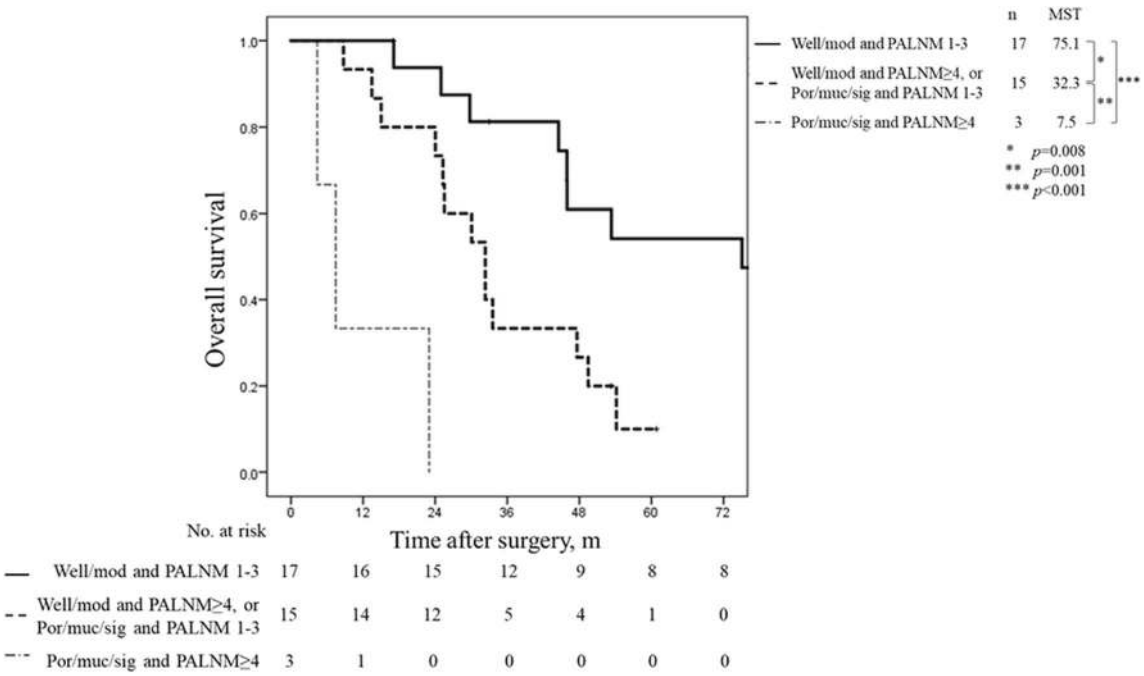

Fig. 4 The overall survival after para-aortic lymph node dissection among patients with R0 resection stratified by histological type and number of para-aortic lymph node metastasis

[10]. The current study built on previous work and suggested that the 5-year OS rates among patients with R0 or R1/2 resection were 29.7% and 5.1%, respectively ($p < 0.001$) (Fig. 2b). Of interest, the rates of achieving R0 resection for PALNM are relatively low, ranging from 56–60% [9, 10], including in the present study. Therefore, it is necessary to thoroughly evaluate the possibility of R0 resection in preoperative imaging diagnosis.

The lack of clear guidelines makes it difficult to determine the indications for PALNM dissection. As mentioned, information on specific prognostic factors for patients with PALNM can help physicians avoid performing unnecessary surgery in patients. In the present study, four prognostic factors—the preoperative CEA level, histological type, number of PALNMs, and completeness of resection—were identified in the whole population; these factors were all stronger than the M category (Table 2). Furthermore, among patients who achieved R0 resection, the histological type and number of PALNMs remained weighty prognostic factors. Stratifying by these factors showed that the subset of patients with well/mod differentiation and 1–3 PALNMs had a relatively good prognosis of 54.2% for the 5-year OS, which was comparable to that of patients undergoing PALND and diagnosed with stage IIIC (5-year OS 49.6%), despite the small sample size (Fig. 2b and 4). Bae et al. noted that ≥ 7 positive PALNs was an independent poor prognostic factor for the OS [13]. In a different study by Nakai et al., the factors associated with a poor postoperative survival among patients who achieved R0 resection were the presence of conversion therapy, lack of adjuvant chemotherapy, carcinoembryonic antigen > 20 ng/mL, and lateral lymph node metastasis [9]. No factors have yet been established, so prospective studies with a larger population are desired.

Regarding recurrence after PALNM dissection, the 5-year DFS rate was 17.1% in the present study, which was comparable with that of other studies (14–22%) [9, 14]. Only the study by Ogura et al. reported a good DFS of 60%, but that study excluded M1b cases and was performed relatively recently compared with other studies [10]. In terms of adjuvant chemotherapy, a multidisciplinary treatment may be required rather than surgery alone owing to the high recurrence rate of 82% in the current study. Specifically, the addition of oxaliplatin to 5-FU-based adjuvant chemotherapy that has been shown to improve DFS and OS will be noteworthy for patients with PALNM dissection [15–17]. As such, the extension of disease control benefit from PALNM dissection is expected with the development of multimodality treatments, including chemotherapy, in the current era. In addition, the benefits associated with removing PALNM should be weighed against the risk of complications. Although our group has not analyzed the risk of complications, several articles have mentioned the risk of postoperative complications, with reported rates of overall complications ranging from 7.8–50.0% [7, 8, 14, 18]. In addition, excessive lymph node dissection, which includes dissection of the neural plexus, results in serious morbidities, including diarrhea and sexual

dysfunction [19, 20]. Therefore, adopting PALNM for patients suspected of R1 resection, PALNM > 3 or an undifferentiated histological type may not be warranted.

This study has several limitations. This was a retrospective study with a small sample size and selection bias. The study period was long, lasting over 20 years; during this time, the surgical staff, chemotherapy regimen, and surgical quality/methods likely changed. Optimal indication for PALNM dissection cannot be predicted with total accuracy based on the present results. A larger-scale prospective, multi-institutional study is therefore needed to confirm our findings.

In conclusion, R0 resection with PALNM dissection was achieved in roughly half of patients, regardless of the presence of distant metastasis other than PALNM. Among patients who achieved R0 resection, well/mod differentiation and ≤ 3 PALNMs were strongly associated with the OS. PALNM resection might be beneficial in carefully selected patients with highly differentiated tumors and less-extensive PALNM.

Compliance with ethical standards

Institutional approval for this retrospective study was obtained from the Ethical Advisory Committee of Yokohama City University School of Medicine before initiating the study

Conflict of interest The authors declare that they have no conflicts of interest..

References

1. Siegel RL, Miller KD, Jemal A (2015) Cancer statistics, 2015. CA Cancer J Clin 65(1):5–29. https://doi.org/10.3322/caac.21254
2. Watanabe T, Muro K, Ajioka Y, Hashiguchi Y, Ito Y, Saito Y, Hamaguchi T, Ishida H, Ishiguro M, Ishihara S, Kanemitsu Y, Kawano H, Kinugasa Y, Kokudo N, Murofushi K, Nakajima T, Oka S, Sakai Y, Tsuji A, Uehara K, Ueno H, Yamazaki K, Yoshida M, Yoshino T, Boku N, Fujimori T, Itabashi M, Koinuma N, Morita T, Nishimura G, Sakata Y, Shimada Y, Takahashi K, Tanaka S, Tsuruta O, Yamaguchi T, Yamaguchi N, Tanaka T, Kotake K, Sugihara K (2018) Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. Int J Clin Oncol 23(1):1–34. https://doi.org/10.1007/s10147-017-1101-6
3. Ike H, Shimada H, Ohki S, Togo S, Yamaguchi S, Ichikawa Y (2002) Results of aggressive resection of lung metastases from colorectal carcinoma detected by intensive follow-up. Dis Colon Rectum 45(4):468–473 **discussion 473-465**
4. Saiura A, Yamamoto J, Hasegawa K, Koga R, Sakamoto Y, Hata S, Makuuchi M, Kokudo N (2012) Liver resection for multiple colorectal liver metastases with surgery up-front approach: bi-institutional analysis of 736 consecutive cases. World J Surg 36(9):2171–2178. https://doi.org/10.1007/s00268-012-1616-y
5. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP (2017) The eighth edition AJCC Cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 67(2):93–99. https://doi.org/10.3322/caac.21388
6. Choi PW, Kim HC, Kim AY, Jung SH, Yu CS, Kim JC (2010) Extensive lymphadenectomy in colorectal cancer with isolated para-aortic lymph node metastasis below the level of renal vessels. J Surg Oncol 101(1):66–71. https://doi.org/10.1002/jso.21421
7. Arimoto A, Uehara K, Kato T, Nakamura H, Kamiya T, Nagino M (2015) Clinical significance of para-aortic lymph node dissection for advanced or metastatic colorectal cancer in the current era of modern chemotherapy. Dig Surg 32(6):439–444. https://doi.org/10.1159/000439547
8. Bae SU, Han YD, Cho MS, Hur H, Min BS, Baik SH, Lee KY, Kim NK (2016) Oncologic outcomes of colon cancer patients with extraregional lymph node metastasis: comparison of isolated paraaortic lymph node metastasis with resectable liver metastasis. Ann Surg Oncol 23(5):1562–1568. https://doi.org/10.1245/s10434-015-5027-9
9. Nakai N, Yamaguchi T, Kinugasa Y, Shiomi A, Kagawa H, Yamakawa Y, Numata M, Furutani A (2017) Long-term outcomes after resection of para-aortic lymph node metastasis from left-sided colon and rectal cancer. Int J Color Dis 32(7):999–1007. https://doi.org/10.1007/s00384-017-2806-8
10. Ogura A, Akiyoshi T, Takatsu Y, Nagata J, Nagasaki T, Konishi T, Fujimoto Y, Nagayama S, Fukunaga Y, Ueno M (2017) The significance of extended lymphadenectomy for colorectal cancer with isolated synchronous extraregional lymph node metastasis. Asian J Surg 40(4):254–261. https://doi.org/10.1016/j.asjsur.2015.10.003
11. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, Hamaguchi T, Hyodo I, Igarashi M, Ishida H, Ishiguro M, Kanemitsu Y, Kokudo N, Muro K, Ochiai A, Oguchi M, Ohkura Y, Saito Y, Sakai Y, Ueno H, Yoshino T, Fujimori T, Koinuma N, Morita T, Nishimura G, Sakata Y, Takahashi K, Takiuchi H, Tsuruta O, Yamaguchi T, Yoshida M, Yamaguchi N, Kotake K, Sugihara K (2012) Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. Int J Clin Oncol 17(1):1–29. https://doi.org/10.1007/s10147-011-0315-2
12. Wong JS, Tan GH, Teo MC (2016) Management of para-aortic lymph node metastasis in colorectal patients: a systemic review. Surg Oncol 25(4):411–418. https://doi.org/10.1016/j.suronc.2016.09.008
13. Bae SU, Hur H, Min BS, Baik SH, Lee KY, Kim NK (2017) Which patients with isolated para-aortic lymph node metastasis will truly benefit from extended lymph node dissection for colon cancer? Cancer Res Treat. https://doi.org/10.4143/crt.2017.100
14. Yamada K, Tsukamoto S, Ochiai H, Shida D, Kanemitsu Y (2018) Improving selection for resection of synchronous para-aortic lymph node metastases in colorectal cancer. Dig Surg:1–7. https://doi.org/10.1159/000491100
15. Rodel C, Graeven U, Fietkau R, Hohenberger W, Hothorn T, Arnold D, Hofheinz RD, Ghadimi M, Wolff HA, Lang-Welzenbach M, Raab HR, Wittekind C, Strobel P, Staib L, Wilhelm M, Grabenbauer GG, Hoffmanns H, Lindemann F, Schlenska-Lange A, Folprecht G, Sauer R, Liersch T (2015) Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 16(8):979–989. https://doi.org/10.1016/s1470-2045(15)00159-x
16. Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, Bonetti A, Clingan P, Bridgewater J, Rivera F, de Gramont A (2009) Improved overall survival with oxaliplatin, fluorouracil,

and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol Off J Am Soc Clin Oncol 27(19): 3109–3116. https://doi.org/10.1200/jco.2008.20.6771

17. Yothers G, O'Connell MJ, Allegra CJ, Kuebler JP, Colangelo LH, Petrelli NJ, Wolmark N (2011) Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. J Clin Oncol Off J Am Soc Clin Oncol 29(28):3768–3774. https://doi.org/10.1200/jco.2011.36.4539
18. Song SH, Park SY, Park JS, Kim HJ, Yang CS, Choi GS (2016) Laparoscopic para-aortic lymph node dissection for patients with primary colorectal cancer and clinically suspected para-aortic lymph nodes. Ann Surg Treat Res 90(1):29–35. https://doi.org/10.4174/astr.2016.90.1.29
19. Nomura M, Kunisaki C, Akiyama H, Matsuda G, Otsuka Y, Ono H, Takahashi M, Shimada H (2005) Surgical outcome of para-aortic lymph node dissection preserving neural tissue based on anatomical evaluations. J Gastrointest Surg 9(6):781–788. https://doi.org/10.1016/j.gassur.2005.03.004
20. Kunisaki C, Shimada H, Takahashi M, Nomura M, Matsuda G, Otsuka Y, Ono H, Akiyama H (2003) Implication of extended lymph node dissection stratified for advanced gastric cancer. Anticancer Res 23(5b):4181–4186