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ORIGINAL ARTICLE

Apical Lymph Nodes in the Distant Metastases and Prognosis of Patients with Stage III Colorectal Cancer with Adequate Lymph Node Retrieval Following FOLFOX Adjuvant Chemotherapy

Hsiang-Lin Tsai[1,2] · Yi-Ting Chen[3,4] · Yung-Sung Yeh[1,5,6] · Ching-Wen Huang[1,2,7] · Cheng-Jen Ma[1,8] · Jaw-Yuan Wang[1,2,5,7,9,10]

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Abstract

The aim of the study was to assess apical lymph nodes (APNs) for predicting distant metastases in patients with stage III colorectal cancer (CRC) curatively treated with FOLFOX adjuvant chemotherapy and adequate lymph node retrieval. We investigated the correlation between APN metastasis and clinical outcomes. This retrospective study examined 97 patients. All patients were followed until death, loss to follow-up, or May 2017. Clinicopathological variables, including the APN status, were assessed. Multivariate logistic regression model was used to identify the independent risk factors for APN and distant metastases, and Cox proportional regression model was used to evaluate the association between APN metastasis and oncologic outcomes. Multivariate analyses revealed the N2 stage as an independent predictor of APN metastasis [$P = 0.036$; odds ratio (OR): 3.016; 95% confidence interval (CI): 1.076–8.499], while APN metastasis was an independent risk factor for distant metastases ($P < 0.001$; OR: 13.876; 95% CI: 3.815–50.475). Furthermore, APN metastasis was an independent risk factor for poorer disease-free survival (DFS) and overall survival (OS) ($P < 0.001$ and $P = 0.005$, respectively). The liver (31.6%) was the most common site of distant metastases in patients with APN metastases. APN metastasis is an important prognostic factor for node-positive CRC; it enhanced the distant metastases in patients with stage III CRC curatively treated with adequate lymph node retrieval following FOLFOX adjuvant chemotherapy. Therefore, for patients with stage III CRC involving APN metastasis, prospectively randomized trials are mandatory to investigate different therapeutic strategies in addition to conventional FOLFOX adjuvant chemotherapy.

Keywords Apical lymph nodes · Distant metastases · Prognosis · Stage III colorectal cancer

✉ Jaw-Yuan Wang
cy614112@ms14.hinet.net; jayuwa@cc.kmu.edu.tw

[1] Division of Colorectal Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, No. 100, Tzyou 1st Road, Kaohsiung 807, Taiwan

[2] Department of Surgery, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

[3] Department of Pathology, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

[4] Department of Pathology, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

[5] Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

[6] Division of Trauma and Surgical Critical Care, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

[7] Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

[8] Division of General and Digestive Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

[9] Center for Biomarkers and Biotech Drugs, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

[10] Research Center for Environmental Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

Introduction

The tumor, node, metastasis (TNM) classification is typically used for making treatment decisions and determining the prognosis of colorectal cancer; it is the most commonly used staging system worldwide [1]. Following distant metastasis, lymph node metastasis is the second most important factor for poor prognosis in CRC [2, 3]. A minimum of 12 lymph nodes is presently accepted as an indicator of adequate resection considering the associations among node yield, staging, and outcomes [4, 5].

The anatomical distribution of nodes is important, and apical lymph nodes (APNs), in particular, were reported to provide prognostic information [6]. The APN can be defined as any node within 1 cm of the main vascular pedicle ligation [6]. In the United Kingdom, the Royal College of Pathologists recommends routine APN examination as well as detailed examination of all lymph nodes in the tumor specimen [7].

Many studies have supported that the location of the metastatic lymph node has a prognostic value [8–10]. For example, the inferior mesenteric artery lymph node metastasis in patients with sigmoid colon or rectal cancer was used to predict para-aortic nodal recurrence [8]. Furthermore, the distribution of lymph node metastasis has been reported to be an independent predictor of overall survival (OS) in sigmoid colon or rectal cancer [9, 10].

The number of positive lymph nodes is widely recognized to be important for the prognosis of stage III CRC [11]. APN metastasis has high potential as a prognostic factor for further systematic metastasis and subsequent death. However, it remains unclear whether APN metastasis has a prognostic value in patients with curatively resected stage III CRC with adequate lymph node retrieval after FOLFOX adjuvant chemotherapy. Therefore, the present study investigated the factors that might influence APN metastasis and the role of APN metastasis in distant metastases and prognostic significance in the aforementioned patients.

Material and Methods

Patient Selection

This retrospective, single-institution study included a total of 106 patients with stage III CRC in whom at least 12 lymph nodes were retrieved between June 2013 and May 2016; patients who died because of surgery (2 patients) and who were lost to follow-up postoperatively (7 patients) were excluded. Finally, we enrolled 97 patients with stage III CRC. Patients were included in this study if they had (1) pathologically proven stage III CRC, (2) undergone curative resection and retrieval of at least 12 lymph nodes, (3) not received preoperative therapy, (4) undergone operation by a single surgeon, and (5) received FOLFOX adjuvant chemotherapy. The study patients underwent comprehensive examinations, namely laboratory and chemical data analyses, colonoscopy, and imaging studies (i.e., abdominal computed tomography [CT], chest X-ray, and magnetic resonance imaging) preoperatively. All patients were followed until death, loss to follow up, or May 2017. All clinical data were obtained with informed consent from each patient, and the study protocol was approved by the institutional review committee [KMUHIRB-2012-03-02(II)].

Surgery Types

The patients selected either of the following treatments: open, laparoscopy-assisted, or robotic (rectal cancer only) surgery. Any gross residual tumor that did not remain in the surgical bed is called radical (R0) resection, and the surgical resection margin is pathologically negative for tumor invasion. All patients with middle and lower rectal tumors underwent total mesorectal excision, and a distal clearance of at least 2 cm from the tumor edge was performed. Adjuvant FOLFOX chemotherapy was administered according to the cancer center guidelines of our institution. Each FOLFOX cycle comprised oxaliplatin (85 mg/m^2) as a 2-h infusion on day 1, folinic acid (400 mg/m^2) as a 2-h infusion concurrently with oxaliplatin on day 1, and a 46-h infusion of fluorouracil (2800 mg/m^2) repeated every 2 weeks.

Definitions of APNs and APN Metastases

During CRC resection, the lymphovascular pedicle was ligated at its origin. The ligation and division of the inferior mesenteric artery were flush with the aorta and above the left colic artery for the patients with left colon, sigmoid, or rectal cancer. For right-sided colon cancer surgery, the ligation and division of the proximal colonic vessels were flush with the superior mesenteric artery at the border of the duodenum and pancreas. APNs are the lymph nodes within 1 cm from the origin of the feeding vessels to the tumor [11]. APN metastasis was defined as metastasis in the highest nodes, which was identified by slicing the mesentery serially and distally from the main vascular tie [12].

Detection of Preoperative and Postoperative Carcinoembryonic Antigen

Peripheral blood sample (3 mL) was obtained from the patients at less than 1 week preoperatively (preoperative carcinoembryonic antigen [CEA]) and 4 weeks postoperatively (postoperative CEA) [13]. An enzyme immunoassay test kit (Beckman Coulter, Inc., Fullerton, CA, USA) was used for determining serum CEA levels; an upper limit of 5 ng/mL was defined as normal, according to the manufacturer's instructions.

Clinicopathological Features, Postoperative Surveillance, and Distant Metastases

The following clinicopathological features of patients were analyzed in this study: sex; age; tumor location, size (largest diameter), histology, grade, and stage; operative methods; invasion depth (T stage); N stage; lymphovascular and perineural invasion; APN metastases status; and preoperative and postoperative CEA levels. By lymphovascular invasion, we mean spread of cancer cells through blood vessels including venous or small vessels and/or lymphatics.

Right-sided cancers were defined as tumors located from the cecum to the splenic flexure, and those located from the splenic flexure to the sigmoid colon were defined as left-sided cancers. Rectal cancers included tumors originating from the rectosigmoid junction or rectum. The seven edition of the TNM classification was used to determine the tumor stage [14]. The guidelines of the World Health Organization was followed for the tumor grading [15].

Postoperative surveillance involved medical history taking, physical examination, and laboratory studies. Moreover, serum CEA levels were determined every 3 months, abdominal ultrasonography was performed every 6 months, and chest radiography and abdominal or chest CT were performed once annually or as indicated by each patient's clinical condition. All patients were followed at 3-month intervals for the initial 2 years and thereafter at 6-month intervals until 5 years. Distant metastases were defined as hematogenous or lymphatic metastases to the distant organs, diffuse peritoneal seeding or metastases in all other nonregional lymph nodes (e.g., interaortocaval and external iliac lymph nodes).

Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD), and dichotomous variables as numbers and percentages. All statistical analyses were performed using the Statistical Package for Sciences, Version 19.0 (SPSS, Inc., Chicago, IL, USA). The clinicopathological characteristics of the two groups, including four subgroups (APN metastasis and no metastasis subgroups and distant and no distant metastasis subgroups), were compared using Pearson's chi-squared test. Logistic regression coefficients were used to estimate the odds ratios (OR) for each independent variable in the model. Disease-free survival (DFS) was defined as the time from the date of primary treatment to that of diagnosis for recurrence or metastatic disease or the last follow-up. OS was defined as the time from the date of primary treatment to that of death from any cause or the last follow-up. DFS and OS were evaluated using the Kaplan–Meier method, and the log-rank test was used to compare time-to-event distributions. $P < 0.05$ was considered statistically significant.

Results

Demographics of the Enrolled Patients

Table 1 summarizes the clinicopathological data of the study patients (45 men, 46.4% and 52 women, 53.6%). The median age of the patients was 64 years (11–86 years),

Table 1 The clinicopathologic characteristics of 97 stage III colorectal cancer patients following radical resection and adequate lymph node retrieval

Variables	Number (%)
Gender	
Male/Female	45 (46.4) / 52 (53.6)
Age (y/o)	
≧65/<65	44 (45.4) / 53 (54.6)
Tumor location	
R't colon/L't colon/Rectum[a]	24 (24.7) / 51 (52.6) / 22 (22.7)
Maximum size (cm)	
≧5/<5	31 (32.0) / 66 (68.0)
T stage	
T1/T2/T3/T4	5 (5.2) / 12 (12.4) / 69 (71.1) / 11 (11.3)
N stage	
N1/N2	66 (68.0) / 31 (32.0)
Lymphovascular invasion	
Yes/No	73 (75.3) / 24 (24.7)
Perineural invasion	
Yes/No	40 (41.2) / 57 (58.8)
Histology	
A/M[b]	91 (93.8) / 6 (6.2)
Tumor grade	
WD/MD/PD[c]	3 (3.1) / 80 (82.5) / 14 (14.4)
Tumor stage	
IIIA/IIIB/IIIC	16 (16.5) / 57 (58.8) / 24 (24.7)
Apical L.N[d] metastases	
Yes/No	19 (19.6) / 78 (80.4)
Preoperative CEA[e] (ng/ml)	
≧5/<5	32 (33.0) / 65 (67.0)
Postoperative CEA[e] (ng/ml)	
≧5/<5	8 (8.2) / 89 (91.8)
Distant metastases	
Yes/No	23 (23.7%) / 74 (76.3%)

[a] R't colon: Right-sided colon was defined as cecum to splenic flexure; L't colon: Left-sided colon was defined as splenic flexure to sigmoid colon

[b] A: Adenocarcinoma; M: Mucinous carcinoma

[c] WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated

[d] L.N: Lymph node

[e] CEA: Carcinoembryonic antigen

and the median number of retrieved lymph nodes was 17 (12–61 lymph nodes). Moreover, 24 patients had right-sided colon cancer (24.7%), 51 had left-sided colon cancer (52.6%), and 22 had rectal cancer (22.7%); 73 (75.3%) and 40 (41.2%) patients had lymphovascular and perineural invasion, respectively. Regarding tumor differentiation grades, 3 were well-differentiated carcinomas (3.1%), 80 were moderately differentiated carcinomas (82.5%), and 14 were poorly differentiated carcinomas (14.4%). Furthermore, 19 (19.6%) and 23 (23.7%) patients were found to have APN metastases and postoperative distant metastases, respectively. We followed all patients until May 2017, with a median follow-up period of 22 months (12–46 months).

Correlations Between Clinicopathological Features and APN Metastases and Postoperative Distant Metastases

Univariate analysis performed for determining the correlations between the APN metastasis status and clinicopathological features of the patients revealed that only the N2 stage was significant ($P = 0.031$). Multivariate logistic regression analysis showed that APN metastasis was

Table 2 Univariate analysis and multivariate logistic regression analysis correlations between the APN[1] metastasis group and APN[a] non-metastasis group among 97 stage III colorectal cancer patients with radical resection and adequate lymph node retrieval

Variables	APN[a] metastasis (n=19) (%)	APN[a] non-metastasis (n=78) (%)	Univariate analysis *P*-value	Logistic analysis OR[b] (95% CI[c])	*P*-value
Gender					
Male/Female	9(47.4)/10(52.6)	36(46.2)/42(53.8)	0.924	—	—
Age (y/o)					
≧65/<65	8(42.1)/11(57.9)	36(46.2)/42(53.8)	0.751	—	—
Tumor location					
R't colon/L't colon/Rectum[d]	4(21.1)/12(63.2)/3(15.7)	20(25.6)/39(50.0)/19(24.4)	0.569	—	—
Tumor size (cm)					
≧5/<5	4(21.1)/15(78.9)	27(34.6)/51(65.4)	0.256	—	—
Depth of invasion					
T3+T4/T1+T2	16(84.2)/3(15.8)	64(82.1)/14(17.9)	0.824	—	—
N stage					
N2/N1	10(52.6)/9(47.4)	21(26.9)/57(73.1)	0.031	3.016(1.076-8.499)	0.036
Lymphovascular invasion					
Yes/No	16(84.2)/3(15.8)	57(73.1)/21(26.9)	0.313	—	—
Perineural invasion					
Yes/No	9(47.4)/10(52.6)	31(39.7)/47(60.3)	0.545	—	—
Histology					
M/A[e]	1(5.3)/18(94.7)	5(6.4)/73(93.6)	0.852	—	—
Tumor grade					
PD/WD+MD[f]	2(10.5)/17(89.5)	12(15.4)/66(84.6)	0.589	—	—
Tumor stage					
IIIA/IIIB/IIIC	2(8.7)/13(56.5)/8(34.8)	14(18.9)/44(59.5)/16(21.6)	0.141	—	—
Preoperative CEA[g] (ng/ml)					
≧5/<5	5(26.3)/14(73.7)	27(34.6)/51(65.4)	0.490	—	—
Postoperative CEA[g] (ng/ml)					
≧5/<5	1(5.3)/18(94.7)	7(9.0)/71(91.0)	0.598	—	—

[a] APN: Apical lymph node

[b] OR: odds ratio

[c] 95% CI: 95% Confidence interval

[d] R't colon: Right-sided colon was defined as cecum to splenic flexure; L't colon: Left-sided colon was defined as splenic flexure to sigmoid colon

[e] A: Adenocarcinoma, M: Mucinous carcinoma

[f] WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated

[g] CEA: Carcinoembryonic antigen

statistically predominant in patients with N2 stage ($P = 0.036$, odds ratio [OR]: 3.016, 95% confidence interval [CI]: 1.076–8.499; Table 2). As shown in Table 3, APN metastasis ($P < 0.001$) was correlated to the distant metastases, as observed through univariate analysis, and was also an independent factor for distant metastases, as observed through multivariate analysis (OR: 13.876, 95% CI: 3.815–50.475, $P < 0.001$). Table 4 shows the combined effect of APN and regional lymph node metastases as predictors of distant metastases; APN metastasis was significantly more important for distant metastases than for regional lymph node metastasis ($P < 0.001$).

Correlations Between APN Metastasis Status and Stage III CRC and Metastatic Sites

As shown in Table 5, APN metastasis was not significantly related with tumor stages in patients with stage III CRC with adequate lymph node retrieval ($P = 0.141$). The liver was the most common site of distant

Table 3 Univariate analysis and multivariate logistic regression analysis correlations between the distant metastases group and non-distant metastases group among 97 stage III colorectal cancer patients with radical resection and adequate lymph node retrieval

Variables	Distant metastases (n=23) (%)	Non-distant metastases (n=74) (%)	Univariate analysis *P*-value	Logistic analysis OR[a] (95% CI[b])	*P*-value
Gender					
Male/Female	14(60.9)/9(39.1)	31(41.9)/43(58.1)	0.111	—	—
Age (y/o)					
≧65/<65	10(43.5)/13(56.5)	34(45.9)/40(54.1)	0.836	—	—
Tumor location					
R't colon/L't colon/Rectum[c]	6(26.1)/12(52.2)/5(21.7)	18(24.3)/39(52.7)/17(23.0)	0.983	—	—
Tumor size (cm)					
≧5/<5	7(30.4)/16(69.6)	24(32.4)/50(67.6)	0.858	—	—
Depth of invasion					
T3+T4/T1+T2	19(82.6)/4(17.4)	61(82.4)/13(17.6)	0.985	—	—
N stage					
N2/N1	9(39.1)/14(60.9)	22(29.7)/52(70.3)	0.398	—	—
Lymphovascular invasion					
Yes/No	19(82.6)/4(17.4)	54(72.9)/20(27.1)	0.350	—	—
Perineural invasion					
Yes/No	11(47.8)/12(52.2)	29(39.2)/45(60.8)	0.462	—	—
Histology					
M/A[d]	1(4.3)/22(95.7)	5(6.8)/69(93.2)	0.675	—	—
Tumor grade					
PD/WD+MD[e]	2(8.7)/21(91.3)	12(16.2)/62(83.8)	0.370	—	—
Tumor stage					
IIIA/IIIB/IIIC	2(8.7)/13(56.5)/8(34.8)	14(18.9)/44(59.5)/16(21.6)	0.306	—	—
Apical L.N[f] metastases					
Yes/No	12(52.2)/11(47.8)	7(9.5)/67(90.5)	< 0.001	13.876(3.815-50.475)	< 0.001
Preoperative CEA[g] (ng/ml)					
≧5/<5	7(30.4)/16(69.6)	25(33.8)/49(66.2)	0.765	—	—
Postoperative CEA[g] (ng/ml)					
≧5/<5	4(17.4)/19(82.6)	4(5.4)/70(94.6)	0.068	—	—

[a] OR: odds ratio

[b] 95% CI: 95% Confidence interval

[c] R't colon: Right-sided colon was defined as cecum to splenic flexure; L't colon: Left-sided colon was defined as splenic flexure to sigmoid colon

[d] A: Adenocarcinoma, M: Mucinous carcinoma

[e] WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated

[f] LN: Lymph node

[g] CEA: Carcinoembryonic antigen

Table 4 correlations between the apical lymph nodes, regional lymph nodes and distant metastases among the 97 stage III colorectal cancer patients with radical resection and adequate lymph node retrieval

Event	Apical LN(+) / Regional LN(+)[a] (n=16) (%)	Apical LN(+) / Regional LN(-)[b] (n=3) (%)	Apical LN(-) / Regional LN(+)[c] (n=78) (%)	*P*-value
Distant metastases				< 0.001
Yes / No	10 (62.5) / 6 (37.5)	2 (66.7) / 1 (33.3)	11 (14.1) / 67 (85.9)	

[a] Apical LN(+) + Regional LN(+): Apical lymph node metastases and regional lymph node metastases

[b] Apical LN(+) + Regional LN(-): Apical lymph node metastases and regional lymph node no-metastases

[c] Apical LN(-) + Regional LN(+): Apical lymph node no-metastases and regional lymph node metastases

metastases in patients with APN metastasis receiving FOLFOX adjuvant treatment (31.6%).

DFS and OS of APN Metastases

We further validated the clinical significance of APN metastasis in DFS and OS in patients with stage III CRC. DFS (Fig. 1) and OS (Fig. 2) were shorter in the APN metastasis group than in the APN no metastasis group (DFS: 20.54 ± 3.82 months versus 38.97 ± 1.56 months, hazard ratio [HR]: 6.615, 95% CI: 2.930–14.934, $P < 0.001$ and OS: 34.32 ± 3.16 months versus 43.83 ± 0.80 months, HR: 10.563, 95% CI: 2.044–54.588, $P = 0.005$).

Discussion

The present study revealed APN metastasis as a strong independent predictor of distant metastases with a 13.9-times high risk, and the identification of APN metastasis through anatomical classification may provide additional prognostic information for the risk stratification of DFS and OS in patients with stage III CRC following standard treatments. Notably, APN metastasis was significantly more important than regional lymph node metastasis considering distant metastases in patients with stage III CRC.

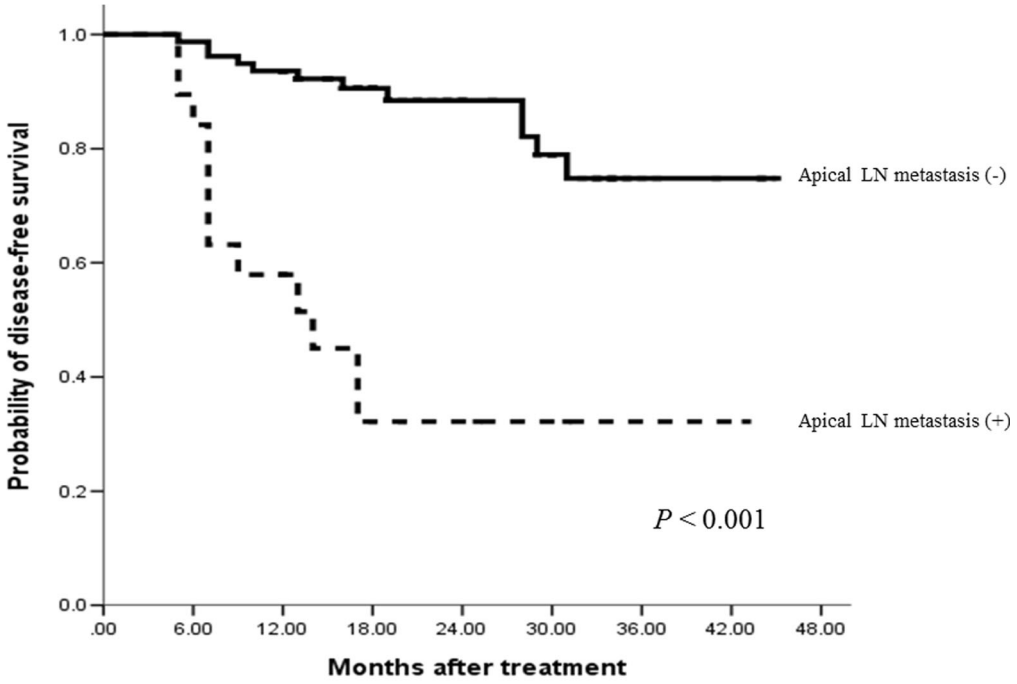
In the 1987 version of the American Joint Committee on Cancer (AJCC) staging system, the APN status was an indicator of the N3 category [16]. However, the revised version of the TNM classification excludes this N3 category because some clinicians found no difference in the survival of patients with N2 and N3 tumors [17]. The number of positive nodes, but not the topography of nodes, is considered a significant prognostic factor [18]. Our study suggests, for stage III CRC at least, that APN metastasis is a crucial factor in the AJCC staging guidelines. In the current study, only the N2 stage influenced the APN metastasis. Contrastingly, Chen et al. reported a significant association of T3 and T4 stages and poor differentiation with APN metastasis in 578 consecutive patients with CRC [19]. The difference might be that we only focused on patients with curatively treated and adequate lymph node-retrieved stage III CRC with subsequent FOLFOX adjuvant chemotherapy, which is the treatment strategy in clinical practice.

The incidence of APN metastasis in this study (19.6%) is similar to that in a previous study [12]. Although the specific role and prognostic value of the APN status in CRC remains debatable [8, 20–24], most studies have reported that APN metastasis is significantly associated with poor prognosis [7, 8]. Our results indicate that APN metastasis is an independent prognostic factor for poor oncological outcomes in patients with stage III CRC; however, this is not consistent with the findings of Yi et al.

Table 5 Correlations between the apical lymph nodes metastases and tumor stage. The common sites of distant metastases in adequate retrieved lymph nodes and FOLFOX adjuvant treated stage III colorectal cancer patients with APNs[a] metastases

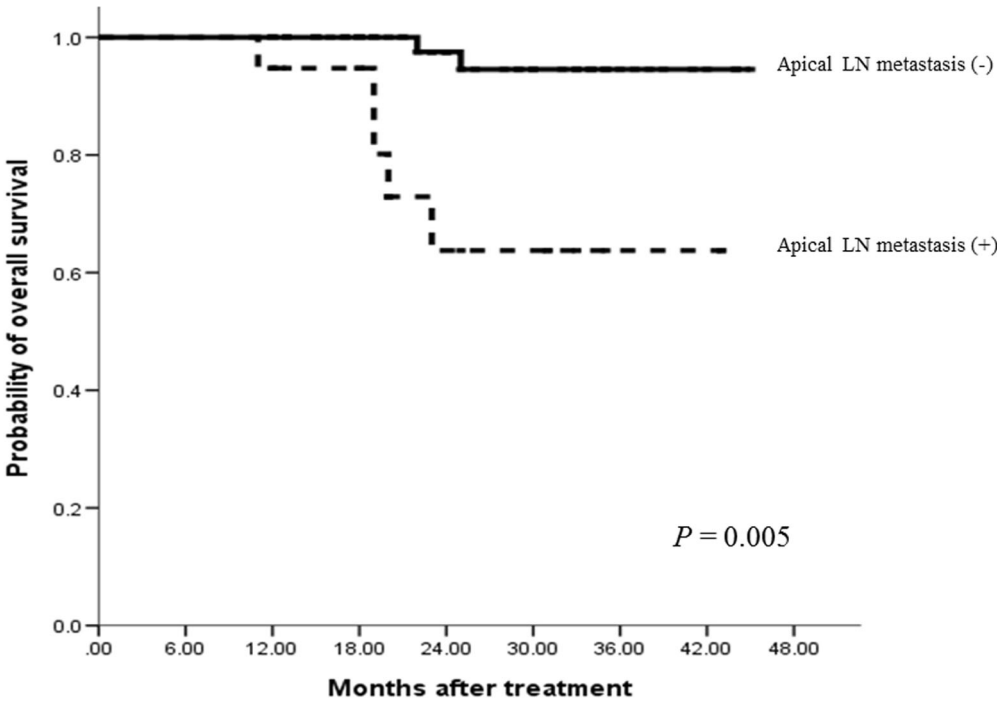
Event	Apical lymph node metastases (+) (n=19) (%)	Apical lymph node metastases (-) (n=78) (%)	*P*-value
Stage III			0.141
IIIA	2 (10.5)	14 (18.0)	
IIIB	9 (47.4)	48 (61.5)	
IIIC	8 (42.1)	16 (20.5)	
Distant metastatic sites			
Liver	6 (31.6)	4 (5.2)	
Peritoneum	3 (15.7)	3 (3.7)	
Lung	1 (5.3)	4 (5.2)	
Lung + Peritoneum	1 (5.3)	0 (0)	
Para-aortic lymph node	1 (5.3)	0 (0)	

[a] APNs: Apical lymph nodes



No. at risk								
Apical LN metastasis (+)	19	17	11	5	3	2	1	1
Apical LN metastasis (-)	78	77	73	49	32	23	7	4

Fig. 1 Cumulative disease-free survival (DFS) rates for the APN metastasis group (dotted line) and APN no metastasis group (solid line) were analyzed using the Kaplan–Meier method, with differences compared using the log-rank test. The APN metastasis group had a poorer DFS rate than did the APN no metastasis group (HR: 6.615; 95% CI: 2.930–14.934, $P < 0.001$)



No. at risk								
Apical LN metastasis (+)	19	19	18	15	7	6	2	2
Apical LN metastasis (-)	78	78	78	56	36	27	10	5

Fig. 2 Cumulative overall survival (OS) rates for the APN metastasis group (dotted line) and APN no metastasis group (solid line) were analyzed using the Kaplan–Meier method, with differences compared using the log-rank test. The APN metastasis group had a lower OS rate than did the APN no metastasis group (HR: 10.563, 95% CI: 2.044–54.588, $P = 0.005$)

[24]. Two reasons must be considered. First, our study included stage III right- and left-sided colon and rectal cancers, but Yi et al. only described stage III sigmoid colon or rectal cancer. Second, compared with patients in Yi et al.'s study, our patients had adequate lymph node retrieval with standard FOLFOX adjuvant chemotherapy. According to our review of relevant literature, the influence of APN metastasis on the distant metastases of curatively resected stage III CRC with adequate lymph node retrieval and FOLFOX adjuvant chemotherapy has not been reported previously. However, our results revealed a higher association between tumors with APN metastasis and postoperative distant metastases. Furthermore, APN metastasis was observed to be more important than regional lymph node metastasis in the distant metastases of stage III CRC with adequate lymph node retrieval and FOLFOX adjuvant treatment. The liver remained the most common site of distant metastasis in patients with APN metastasis.

Skip metastasis is an important concern that should be considered in lymph node evaluation. The location of metastatic lymph nodes has been widely evaluated in Asia according to the Japanese general rules for clinical and pathological studies on cancer of the colon, rectum, and anus [25]. Skip metastases were common in CRC specimens, with an incidence of 3.7%–18.2% [26]. In our study, 3 (3.1%) of the 97 patients had positive APNs without metastasis in the regional lymph nodes. Although APN-related skip metastasis has been found to be rare in most studies [26–28], reporting the APN status may still be important for a more accurate staging of patients.

We acknowledge that our study involved a relatively small number of patients. Despite this limitation, we provide valuable evidence for the clinical practice of oncology regarding the importance of APN as a negative independent prognostic factor for survival and distant metastasis. This highlights the importance of harvesting the APN and evaluating its pathology in CRC surgery. We also revealed that patients with APN metastasis had a poorer DFS and OS despite receiving standard FOLFOX adjuvant chemotherapy.

In conclusion, APN metastasis appears to be a strong independent, negative prognostic factor in patients with stage III CRC following FOLFOX adjuvant chemotherapy. High-tie surgery and thorough extensive lymphadenectomy should be routinely performed in surgery for patients with CRC to incorporate APNs for accurate staging.

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Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflicts of interest.

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