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The treatment strategy of R0 resection in colorectal cancer with synchronous para-aortic lymph node metastasis

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Abstract

Background: Synchronous metastatic para-aortic lymph node (mPALN) dissectionin colorectal cancer has relatively good oncological outcomes, though many patients develop recurrence. Universal prognostic factor remain unclear and no definitive perioperative chemotherapy is available, making the treatment of mPALN controversial. In the present study, we aimed to establish a treatment strategy for synchronous mPALN.

Methods: This retrospective study involved 20 patients with pathological mPALN below the renal vein who underwent R0 resection. Long-term outcomes, recurrence type, and prognostic factors for survival were investigated.

Results: The 5-year overall survival and recurrence-free survival rates were 39% and 25%, respectively. Seventeen patients (85%) developed recurrence, including 13 (76%) within 1 year after surgery, and ~ 70% of all recurrences were multiple recurrences. Four patients (20%) survived > 5 years. Pathological T stage (p= 0.011), time to recurrence (p = 0.007), and recurrence resection (p = 0.009) were identified as prognostic factors for long-term survival.

Conclusions: R0 resection of synchronous mPALN in colorectal cancer resulted in acceptable oncological outcomes, though we found a high rate of early unresectable recurrence. If the recurrence occurs late or isolated, surgical resection should be considered for longer survival.

Keywords: Para-aortic lymph node metastasis, Synchronous, Colorectal cancer

Background

In colorectal cancer (CRC), the relatively rare occurrence of metastatic para-aortic lymph node (PALN) is categorized as stage IV disease [1, 2]. The reported incidence of isolated metastatic PALN is 1–2% [3, 4]. In stage IV patients, R0 resection is usually recommended for resectable liver or lung metastases [2, 5–7]. However, metastatic PALN remains highly controversial as no multicenter studies or randomized controlled trials have been performed on synchronous or metachronous PALN dissection (PALND).

A few studies have been published on metachronous metastatic PALN [8–11], and studies on synchronous metastatic PALN have shown that PALND below the renal veins can be performed safely, prolonging prognosis compared to non-surgical resection [12, 13]. Bae et al. [12] also demonstrated that PALND results in survival rates comparable to synchronous liver metastasectomy. However, although the 5-year overall survival (OS) rates for patients who underwent synchronous PALND reached 25–53%, approximately 80% of the patients experience recurrence [4, 12–15] and few studies have discussed the recurrence pattern [12] or treatment after

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recurrence. Furthermore, no definitive perioperative chemotherapy has been established.

Recently, three retrospective studies have shown updated prognostic factors for synchronous PALND, including R0 resection, histological type, number of PALN, other distant metastases, metastatic lateral pelvic lymph node, and preoperative CEA values [4, 15, 16]. However, the prognostic factors for synchronous PALN D identified in the previous studies are not yet universal.

These findings indicate that the treatment strategy for PALN remains highly controversial.

The aim of this study was to examine the prognostic factors, recurrence patterns, and long-term outcomes in CRC with synchronous metastatic PALN to establish the strategy for PALND.

Materials and methods

This was a single-center retrospective cohort study at Osaka International Cancer Institute, Osaka, Japan. The study protocol was approved by the institutional review board (No. 18033-2). Written informed consent was waived because of the retrospective design.

Study population

Between September 1998 and December 2018, we reviewed the medical records of patients who underwent PALND for clinical metastatic PALN in addition to resection of the primary CRC. Twenty-two patients had pathological metastatic PALN. Two patients who could not undergo R0 resection were excluded. R0 resection was defined as having no macroscopic or microscopic residual tumor. A total of 20 patients were included in the present study.

Indication for PALND

Tumors were pathologically diagnosed as CRC and classified according to the criteria of the World Health Organization and Union for International Cancer Control, 8th edition [17]. Clinical stage was assessed based on enhanced computed tomography (CT) and positron emission tomography (PET). Surgical treatment with CRC resection and PALND was performed based on the following criteria: metastatic PALN diagnosed as clinically positive by the colorectal surgery team and at least two radiologists based on PALN with a long-axis diameter ≥ 7 mm by CT and/or a high intensity spot on PET; metastatic PALN located only below the renal vein; and expectation of R0 resection, including synchronous metastasectomy or second stage metastasectomy, such as metachronous hepatectomy.

PALND

PALND was performed after primary tumor resection. PALND was defined as a dissection of all lymphatic and connective tissues around the abdominal aorta and inferior vena cava between the left renal vein and bifurcation of the iliac artery. If lymph node dissection was not performed in this area, it was defined as lymphadenectomy.

Follow-up

After surgery, all patients underwent general follow-up with examination of tumor markers every 3 months, as well as chest and abdominal CT every 6 months. A colonoscopy was performed every year for rectal cancer, and every other year for colon cancer. If recurrence was suspected during the follow-up, CT and/or PET was added immediately. Local recurrence was defined as recurrence within the pelvic cavity for rectal cancer or around the tumor area for colon cancer.

Statistical analysis

Data are presented as medians and ranges. The rates of OS and recurrence-free survival (RFS) were calculated using the Kaplan–Meier method, and the log-rank test was used to compare OS between the two groups. $P < 0.05$ was considered significant. Statistical analyses were performed using JMP version 8.0.2 software (SAS Institute, Cary, NC).

Results

Clinicopathological characteristics

The demographic and pathological characteristics of the 20 patients are given in Table 1.

Except for metastatic PALN, distant metastasis was confirmed in 4 patients (liver metastasis, $n = 2$; ovarian metastasis, $n = 1$; peritoneal dissemination, $n = 1$), all of which were resected synchronously. Adjuvant chemotherapy (AC) was performed in 12 patients (60%), 9 (75%) with camptothecin-11 or oxaliplatin, whereas neoadjuvant chemotherapy with oxaliplatin (NAC) was used in only 2 patients (10%).

Long-term outcomes and recurrence

The median follow-up duration was 24.8 months (6.6–248.1). The 5-year OS was 39% and 5-year RFS 25% (Fig. 1). Seventeen patients (85%) developed recurrence, including two cases of recurrence 8 years after surgery. Table 2 showed the pattern of first recurrence in the 17 patients.

Thirteen patients (76%) developed recurrence within 1 year after surgery. Almost all of these patients developed distant multiple recurrences that could not undergo surgical resection. However, four of the patients who developed recurrence 1 year after surgery had isolated recurrence, and three underwent surgical resection. The most common recurrence site was PALN (7/27, 26%), and three of the patients developed recurrence both above the renal vein and below the renal vein. Most patients who developed recurrent PALN also had other

Table 1 Clinicopathological characteristics

Clinicopathological characteristics	
Variables	Patients (n=20) N0.(%) or Median (Range)
Age (range)	60 (41-76)
Sex (%)	
Male	12 (60)
Female	8 (40)
Location (%)	
Right colon	4 (20)
Left colon	5 (25)
Rectum	11 (55)
Histology (%)	
Well/moderate	16 (80)
Mucinous/poor	4 (20)
CEA (range)	9.05 (1-80.9)
CA19-9 (range)	17.5 (2-148)
T stage	
T3	11 (55)
T4a	6 (30)
T4b	3 (15)
N stage	
N0	1 (5)
N1	5 (25)
N2	14 (70)
Metastasis to LPLN (%)	
Yes	3 (15)
No	17 (85)
Number of mPALNs (range)	2.5 (1-44)
PALND (%)	
PALND	11 (55)
Lymphadenectomy	9 (45)
M (%)	
M1a	16 (80)
M1b/M1c	4 (20)
Neoadjuvant chemotherapy (%)	
Yes	2 (10)
No	18 (80)
Adjuvant chemotherapy (%)	
Yes	11 (55)
No	9 (45)

CEA/CA19-9 values were at diagnosis (ng/ml)

LPLN, lateral pelvic lymph node; PALN, para aortic lymph node;

mPALN, metastatic PALN; PALND, para aortic lymph node dissection

CEA/CA19-9 values were at diagnosis (ng/ml)
LPLN, lateral pelvic lymph node; PALN, para aortic lymph node; mPALN, metastatic PALN; PALND, para aortic lymph node dissection

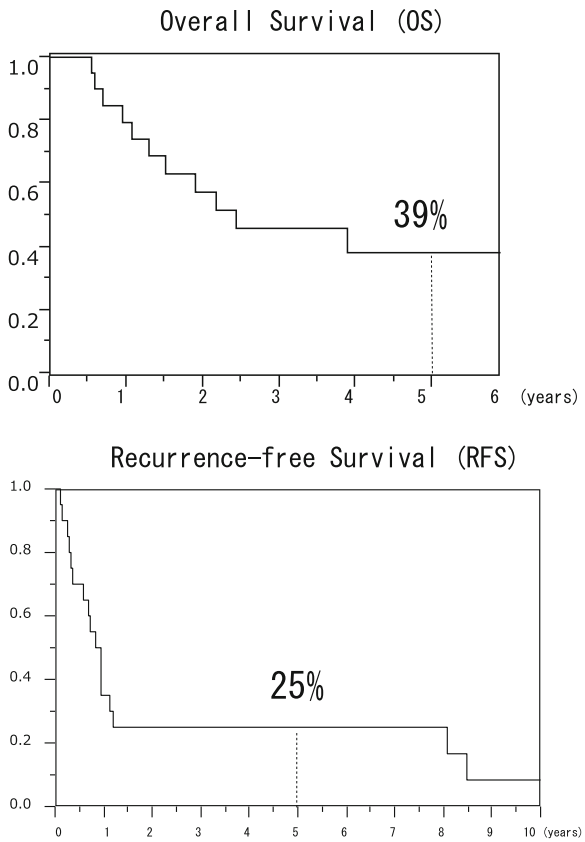

Fig. 1 Overall survival and recurrence-free survival for the patient with R0 PALND

distant metastases, but one patient developed only isolated PALN and was resected.

Long-term and short-term survivors

Table 3 shows the clinicopathological findings of four long-term survivors over 5 years and four short-term survivors within 1 year.

All short-term survivors developed early and multiple recurrences with no surgical indication. Two patients developed recurrence during AC, and the other two presented with recurrence before the introduction of AC. Long-term survivors also developed recurrence (3/4, 75%), but most were delayed and all were isolated recurrence that could be dissected curatively. Two patients who developed delayed recurrence had received AC for a long time.

Prognostic factors in patients with R0 PALND

Pathological T stage (p = 0.011), time to recurrence (p = 0.007), and recurrence resection (p = 0.009) were identified as prognostic factors (Table 4).

The 5-year OS in the four patients who could undergo resection of recurrence (metastatic PALN, n = 1; metastatic mediastinal LN, n = 3) was 100%. The number of metastatic PALNs (p = 0.686) and PALND (p = 0.743) were not

Table 2 Recurrence pattern after PALND

Recurrent cases	n=17 (%)			
time to recurrence (year)				
1≧	4 (24)	→	isolation	4 (100)
1<	13 (76)	→	isolation	1 (7)
			multiple metastases	12 (93)
type of recurrence				
Local	1 (6)			
Distant	16 (94)	→	isolation	5 (32)
			multiple metastases	11 (68)
First recurrence location				
Local	1 (4)			
Mediastinal lymph node	3 (11)			
Bone	4 (15)			
Liver	6 (22)			
Lung	6 (22)			
PALN	7 (26)			
		↳	below renal vein	4 (57)
			above and below renal vein	3 (43)

identified as prognostic factors. Distant metastasis (p = 0.143) was not identified as a risk factor, but no patients who had other distant metastases survived 5 years.

Discussion

This study was conducted to examine the oncological outcomes in CRC with synchronous PALN to establish the strategy for PALND. We found that PALND is associated with the potential for long-term survival, but also early unresectable recurrences. Pathological T stage, time to recurrence, and recurrence resection were prognostic factors for long-term survival. No previous reports have discussed recurrence, including the time to recurrence and site of recurrence, but the current findings

Table 3 Long and short survivors

Long and short survivors

Patient	Location	Histology	PALND	T	N	M	LPLN	number of PALNs	NAC (months)	AC (months)	Recurrence	Recurrence resection	RFS (days)	OS (days)
57 M	Sigmoid	tub2	PALND	3	2	M1a	-	18	0	48	isolated mediastinal LN	possible	3100	7442
50 M	rectum	tub2	PALND	4	2	M1a	positive	24	0	18	isolated mediastinal LN	possible	2942	5434
49 M	rectum	tub2	lymphadenectomy	3	1	M1a	negative	2	0	0	-	-	4612	4612
71 F	Sigmoid	por	lymphadenectomy	3	2	M1a	-	1	0	0	isolated PALN	possible	247	1836
55 F	Cecum	tub2	lymphadenectomy	4	1	M1c	-	1	0	3	multiple-bone	impossible	94	346
41 M	Sigmoid	tub2	PALND	4	2	M1a	-	44	0	4	multiple-organs	impossible	110	252
56 F	rectum	por	PALND	3	2	M1a	-	4	0	-	multiple-organs	impossible	35	214
76 F	rectum	tub2	lymphadenectomy	4	2	M1a	positive	2	3	-	multiple-organs	impossible	115	198

M, male; F, femal; tub2, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma, LPLN; lateral pelvic lymph node
NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy

M, male; F, female; tub2, moderately differentiated tubular adenocarcinoma; por, poorly differentiated adenocarcinoma, LPLN; lateral pelvic lymph node
NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy

Table 4 Univariate analysis for factors associated with overall survival

Univariate analysis for factors associated with overall survival			
Factors		5-year OS	P value
Age			0.131
<60	10	52.5	
≧60	10	23.3	
Sex			0.093
Male	12	38.5	
Female	8	15.6	
Location			0.709
Colon	9	40.0	
Rectum	11	38.4	
Histological type			0.935
Well/moderate	16	26.8	
Mucinous/poor	4	50.0	
CEA			0.700
<5	7	34.3	
≧5	12	46.9	
CA19-9			0.538
<37	14	33.1	
≧37	4	50.0	
pT stage			0.011
T3	11	63.6	
T4	9	11.1	
pN stage			0.572
N0/N1	6	66.7	
N2	14	29.4	
Metastasis to LPLN			0.498
Yes	3	50.0	
No	17	33.9	
Number of PALNs			0.686
≦2	10	37.5	
≧3	10	40.0	
PALND			0.743
Lymphadenectomy	9	38.9	
PALND	11	38.4	
Distant metastasis			0.143
M1a	16	50.1	
M1b/M1c	4	0.0	
Neoadjuvant chemotherapy			0.439
Yes	2	0.0	
No	18	36.4	
Adjuvant chemotherapy			0.555
Yes	11	49.1	
No	9	33.3	
time to recurrence (year)			0.007
<1	13	8.6	
≧1	7	100.0	
Recurrence resection			0.009
Possible	4	100.0	
Impossible	13	16.7	

LPLN; lateral pelvic lymph node

LPLN lateral pelvic lymph node

support treatment strategies for patients with synchronous metastatic PALN in CRC.

Our study was limited to patients who underwent R0 resection based on previous reports that R0 resection has a better prognosis than R1–2 resection [14, 15]. The 5-year OS and RFS rates in 20 patients with synchronous metastatic PALN who underwent PALND were 39% and 25%, respectively. These oncological outcomes are similar to what was reported in previous studies [4, 12–15], and relatively more favorable than general stage IV CRC (5-year OS 13.2 to 22 %) [14], which indicates that PALND can prolong prognosis.

In terms of recurrence, 55% of patients received AC, but the overall recurrence rate after PALND reached 85%, and most cases were early and multiple recurrences. Although four patients with isolated recurrences after PALND could undergo resection and experienced long-term survival [18], some patients developed unresectable recurrences before or during AC and died within 1 year after PALND. These findings show that a number of patients who underwent PALND had no indication for PALND in the first place.

We found that pathological T stage, time to recurrence, and recurrence resection are prognostic factors in patients undergoing R0 PALND, though these factors were only known postoperatively and not previously reported. First, though pathological T stage is common as a prognostic factor and useful in determining chemotherapy after resection of CRC without distant metastases [2, 7], in CRC with metastatic PALN, it may be not useful for considering the treatment strategy. We also showed a relationship between recurrence more than 1 year after PALND and long-term survival. Many of the recurrences 1 year after PALND were isolated recurrences, so a longer time to recurrence was more likely to be oncologically favorable. Therefore, it is reasonable that a long time to recurrence was associated with long-term survival from a biological perspective [19].

Resection of recurrence, especially after PALND, has been reported rarely and is highly controversial. Though resection of recurrence was performed in our study, all recurrences were isolated to distant lymph node, and most recurrences occurred more than 1 year after PALND. Thus, the indication for surgical resection was limited. However, considering the number of previous reports reporting prolonged prognosis with surgical resection for lymph node recurrence or repeat hepatic resection for liver re-recurrence [3, 10, 11, 20, 21], if the recurrence is resectable and not early, it would be valuable to perform resection for long-term survival, even after PALND.

In regards to other prognostic factors, distant metastasis and PALND did not have significant differences. However, the M1b/M1c patient did not achieve long survival, and distant metastasis has potential as a

prognostic factor [4, 14]. Though PALND was a statistically negative prognostic factor, it should be performed, if possible, because one patient after lymphadenectomy developed PALN recurrence and additional PALND provided long-term survival. Even with our results, universal prognostic factors for synchronous PALND have been unclear and at least a retrospective multi-institutional study is necessary.

Considering the treatment strategy for synchronous PALN, AC was a statistically negative prognostic factor for OS in the present study, though 75% of patients received intensive AC (camptothecin-11 or oxaliplatin), but two patients who developed delayed recurrence had received AC for a long time, indicating that AC had the potential to improve RFS. Although Nakai et al. [14] showed that AC is a prognostic factor after PALND, 94% of patients in their study underwent AC and requires careful interpretation. To interpret our results, it may be reasonable to refer to the previous randomized control study that showed AC (Uracil-tegafur and leucovorin) prolonged RFS, but not OS, after resection of liver metastasis [22].

Our study included only two patients who received NAC, and it was difficult to investigate NAC. However, considering that some oncologically poor patients developed unresectable early recurrences and few universal prognostic factors were available preoperatively, it may be reasonable to perform NAC. Though some studies have shown the efficiency of NAC for stage IV CRC [9, 20], there is little evidence for NAC in patients with metastatic PALN and further investigation is needed.

Some limitations must be considered when interpreting the results of this study. First, this study was a single-center, retrospective analysis. Second, this study covered 20 years and the background for treatment was different, especially chemotherapy. Third, this study had a selection bias, involving only patients with pathological PALN, but did not include the patients who underwent chemotherapy without PALND; therefore, not all PALN-positive patients were included.

Conclusions

Our results show that R0 synchronous PALND in CRC had relatively good oncological outcomes, and pathological T stage, time to recurrence, and recurrence resection were prognostic factors for PALND. Our results also revealed a high rate of early unresectable recurrences after PALND, but recurrence resection should be considered for longer survival in isolated late recurrence.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12957-020-02007-2.

Additional file 1.

Abbreviations

mPALN: Metastatic para-aortic lymph node; CRC: Colorectal cancer; PALN: Para-aortic lymph node; PALND: Para-aortic lymph node dissection; OS: Overall survival; CT: Computed tomography; PET: Positron emission tomography; RFS: Recurrence-free survival; AC: Adjuvant chemotherapy; NAC: Neoadjuvant chemotherapy; LPLN: Lateral pelvic lymph node

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Ethical approval and consent to participate
The study protocol was approved by the institutional review board (No. 18033-2). Written informed consent was waived because of the retrospective design.

Authors' contributions

HU, MY, and MO wrote the manuscript. NH, JN, KS, KY, HW, HT, and TO performed follow-up and collected the data. HM and ST revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed in this study are not publicly available (to maintain privacy) but are available from the corresponding author on reasonable request.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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References

1. Patriarca S, Ferretti S, Zanetti R. TNM Classification of malignant tumours - Eighth edition: which news? Epidemiol Prev. 2017;41(2):140–3.
2. Hashiguchi Y, Muro K, Saito Y, Ito Y, Ajioka Y, Hamaguchi T, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol. 2020;25(1):1–42.
3. Gagniere J, Dupre A, Chabaud S, Peyrat P, Meeus P, Rivoire M. Retroperitoneal nodal metastases from colorectal cancer: Curable metastases with radical retroperitoneal lymphadenectomy in selected patients. Eur J Surg Oncol. 2015;41(6):731–7.
4. Yamada K, Tsukamoto S, Ochiai H, Shida D, Kanemitsu Y. Improving selection for resection of synchronous para-aortic lymph node metastases in colorectal cancer. Dig Surg. 2019;36(5):369–75.
5. Morris EJ, Forman D, Thomas JD, Quirke P, Taylor EF, Fairley L, et al. Surgical management and outcomes of colorectal cancer liver metastases. Br J Surg. 2010;97(7):1110–8.
6. Iida T, Nomori H, Shiba M, Nakajima J, Okumura S, Horio H, et al. Prognostic factors after pulmonary metastasectomy for colorectal cancer and rationale for determining surgical indications: a retrospective analysis. Ann Surg. 2013;257(6):1059–64.
7. Provenzale D, Gupta S, Ahnen DJ, Markowitz AJ, Chung DC, Mayer RJ, et al. NCCN Guidelines Insights: Colorectal Cancer Screening, Version 1.2018. J Natl Compr Cancer Netw. 2018;16(8):939–49.
8. Wong JS, Tan GH, Teo MC. Management of para-aortic lymph node metastasis in colorectal patients: A systemic review. Surg Oncol. 2016;25(4):411–8.
9. Arimoto A, Uehara K, Kato T, Nakamura H, Kamiya T, Nagino M. Clinical significance of para-aortic lymph node dissection for advanced or

metastatic colorectal cancer in the current era of modern chemotherapy. Dig Surg. 2015;32(6):439–44.
10. Min BS, Kim NK, Sohn SK, Cho CH, Lee KY, Baik SH. Isolated paraaortic lymph-node recurrence after the curative resection of colorectal carcinoma. J Surg Oncol. 2008;97(2):136–40.
11. Sasaki K, Nozawa H, Kawai K, Hata K, Tanaka T, Nishikawa T, et al. Management of isolated para-aortic lymph node recurrence of colorectal cancer. Surg Today. 2019.
12. Bae SU, Han YD, Cho MS, Hur H, Min BS, Baik SH, et al. 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. 2016;23(5):1562–8.
13. Choi PW, Kim HC, Kim AY, Jung SH, Yu CS, Kim JC. Extensive lymphadenectomy in colorectal cancer with isolated para-aortic lymph node metastasis below the level of renal vessels. J Surg Oncol. 2010;101(1): 66–71.
14. Nakai N, Yamaguchi T, Kinugasa Y, Shiomi A, Kagawa H, Yamakawa Y, et al. Long-term outcomes after resection of para-aortic lymph node metastasis from left-sided colon and rectal cancer. Int J Color Dis. 2017;32(7):999–1007.
15. Sahara K, Watanabe J, Ishibe A, Suwa Y, Suwa H, Ota M, et al. Long-term outcome and prognostic factors for patients with para-aortic lymph node dissection in left-sided colorectal cancer. Int J Color Dis. 2019;34(6):1121–9.
16. Nakai N, Yamaguchi T, Kinugasa Y, Shiomi A, Kagawa H, Yamakawa Y, et al. Diagnostic value of computed tomography (CT) and positron emission tomography (PET) for paraaortic lymph node metastasis from left-sided colon and rectal cancer. Asian J Surg. 2019.
17. TNM classification of malignant tumours, 8th Edition, S. 272 (2017).
18. Matsuda Y, Yano M, Miyoshi N, Noura S, Ohue M, Sugimura K, et al. Solitary mediastinal lymph node recurrence after curative resection of colon cancer. World J Gastrointest Surg. 2014;6(8):164–8.
19. Nagata H, Ishihara S, Hata K, Murono K, Kaneko M, Yasuda K, et al. Survival and prognostic factors for metachronous peritoneal metastasis in patients with colon cancer. Ann Surg Oncol. 2017;24(5):1269–80.
20. Sato H, Maeda K, Morise Z, Takahashi H, Sugihara K, Japanese Study Group for Postoperative Follow-up of Colorectal C. Clinical outcomes of stage IV colorectal cancer after R0 resection: a multi-institutional retrospective analysis. Int J Clin Oncol. 2017;22(2):297–306.
21. Adair RA, Young AL, Cockbain AJ, Malde D, Prasad KR, Lodge JP, et al. Repeat hepatic resection for colorectal liver metastases. Br J Surg. 2012; 99(9):1278–83.
22. Hasegawa K, Saiura A, Takayama T, Miyagawa S, Yamamoto J, Ijichi M, et al. Adjuvant oral uracil-tegafur with leucovorin for colorectal cancer liver metastases: a randomized controlled trial. PLoS One. 2016;11(9):e0162400.

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