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ORIGINAL ARTICLE

Factors affecting survival in patients with isolated liver-metastatic colorectal cancer treated with local ablative or surgical treatments for liver metastasis

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Summary

Purpose: *Local treatments for isolated synchronous or metachronous liver metastases in colorectal cancer (CRC) have been shown to improve overall survival (OS). The aim of this study was to investigate the factors affecting OS in CRC patients with isolated liver metastasis in whom the primary tumor and corresponding liver metastasis were treated with curative intent using local ablative or surgical methods.*

Methods: *A total of 47 CRC patients presenting with an initial or subsequent isolated liver metastasis, who were treated with local surgical or ablative treatment for liver metastasis with curative intent, were enrolled in this study between 2007 and 2017. The possible factors affecting OS were analyzed.*

Results: *Out of the 47 patients, 35 (74.5%) were male. The median age was 61 (25-80) years. Thirty-four (72.3%) patients underwent liver metastasectomy, while 13 (27.7%) patients were treated with non-surgical local ablative therapies (NSLAT) for liver metastasis. Median OS (mOS) could not be reached in patients who underwent metastasectomy at the time of diagnosis compared to 55 months in those undergoing metastasectomy following a chemotherapy period (p=0.03). Patients treated with NSLAT had a mOS of 60 months compared to "not reached" in those who underwent liver metastasectomy (p=0.45). mOS was higher in patients with pT4 stage vs. <pT4 stages (28 months vs. not reached, p=0.02, respectively). Multivariate regression analysis revealed that undergoing liver metastasectomy at the time of diagnosis (HR 0.10; 95%Cl: 0.01-0.82) and pT4 stage (HR 4.365; 95%Cl: 1.27 - 14.98) were the most important independent factors affecting OS.*

Conclusion: *This study demonstrated that CRC patients with isolated liver metastasis, <pT4 stage and curative liver metastasectomy achieved the best survival outcomes.*

Key words: *colorectal cancer, liver metastasis, metastasectomy, survival, local ablative treatments*

Introduction

Colorectal cancer (CRC) is the second most common cancer in women and the third most common cancer in men worldwide. It is the third most common cause of cancer-related death in women and the second most common cause in men. Although CRC mortality has fallen gradually since 1990, the incidence rate in those < 50 years of age has increased steadily by 2.1% per year from 1992 to 2012 [1-4].

Liver metastasis from CRC is an important therapeutic challenge. Approximately 50% of patients with CRC develop liver metastasis during

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the course of disease, with only 20-35% of these patients having sole liver metastasis [3,5]. Liver metastasis is the main cause of mortality in CRC, with an average 5-year survival rate ranging from 25% to 40% [6-8]. However, less than 10% of patients with metastatic CRC have resectable disease at the time of diagnosis [9].

For patients with isolated liver-metastatic CRC, local treatment approaches for liver metastasis can be considered an alternative treatment option to systemic chemotherapy (CT) as being applied in combination with CT. Current regional treatment options for liver metastasis in CRC include surgical resection or non-surgical local ablative therapies (NSLAT) including local thermal ablation, regional hepatic intra-arterial CT, chemoembolization, radioembolization, neoadjuvant chemotherapy, and radiation therapy (RT) such as stereotactic RT [3,10].

Performing metastasectomy for synchronous or metachronous liver metastasis in CRC has been shown to improve survival rates in well-selected patient groups [11]. Surgery remains the gold standard approach out of the above-mentioned treatment options. However, theoretically, newer technologies such as stereotactic RT may provide similar long-term benefits in some patients. Although the optimal treatment approach for metastatic liver lesions appears to be surgical resection, only 7%-20% of cases can be candidates for curative resection due to large tumor size, multifocal lesions, advanced patient age, comorbid diseases, and insufficient hepatic reserve [12]. However, there is no standard consensus regarding the optimal timing of metastasectomy, type of metastasectomy, and ideal CT combination given before or after metastasectomy in patients undergoing curative resection. The aim of this analysis was to investigate the factors affecting survival in curatively-operated CRC patients who underwent metastasectomy or NSLAT for isolated liver metastasis.

Methods

Study population

Medical records of patients with CRC, who were followed up and treated in our oncology center between 2007 and 2017, were reviewed retrospectively. Patients having any of the following criteria were excluded from the study: being < 18 years of age, not undergoing curative surgery, having metastasis outside the liver, being ineligible for ablative or surgical therapies for liver metastasis, history of secondary primary cancer, and missing data. Finally, a total 47 patients who met the criteria above were included for analysis. The study was approved by the Ethics Committee of the University of Health Sciences, Okmeydani Training and Research Hospital, on February 26, 2018.

Data collection

Patient clinicopathological features including age, gender, presence of ileus at the time of diagnosis, Eastern Cooperative Oncology Group Performance Status (ECOG PS), time of metastasectomy (at diagnosis or at follow-up), localization of primary tumor, pathological tumor stage (pT), pathological nodal stage (pN), RAS and BRAF mutation status, type of treatment for liver metastasis (surgery vs. NSLAT), systemic treatments administered in the 1st, 2nd, and 3rd line setting, and patient final status were obtained from archive files. The patients were divided into two groups based on the treatments performed for liver metastasis: as metastasectomy or NSLAT (radiofrequency ablation, microwave ablation, transarterial chemoembolization, and radio-embolization). The treatment regimens were as follows: 5-fluorouracil (5-FU)-based treatments [FOLFOX (oxaliplatin+5-FU + folinic acid), FOLFIRI (5-FU + irinotecan + folinic acid), XELOX (oxaliplatin+capecitabine), XELIRI (irinotecan + capecitabine), FUFA (5-FU + folinic acid), capecitabine], anti-vascular endothelial growth factor (anti-VEGF; bevacizumab or aflibercept) therapy, anti-epidermal growth factor receptor (anti-EGFR; panitumumab or cetuximab) therapy, and regorafenib. The pT stage was grouped as T2-3 and T4 while the pN status was grouped as N0 and N1-2. Cecum, appendix, ascending colon and hepatic flexure tumors were defined as "right CRC", while splenic flexure, descending colon, rectosigmoid colon and rectum tumors were defined as "left CRC''. Overall Survival (OS) was calculated as the time from the date of diagnosis to the date of the last follow-up or death.

Statistics

Statistical Package for the Social Sciences 22.0 for Windows software (Armonk NY, IBM Corp. 2013) was used for the statistical analysis. The comparison of the rates between the groups was performed by chi-square analysis. Monte Carlo simulation was applied if conditions could not be met. Survival analyses were performed using Kaplan-Meier method and log-rank test. Determinant factors were examined through Cox regression analysis. Backward stepwise model was used with parameters having a p value below 0.1. An overall 5% alpha error level was used to infer statistical significance.

Results

The study included 47 patients, 35 (74.5%) men and 12 (25.5%), women. The median age of the patients was 61 years (range, 25-80). Out of the 47 patients, 11 (23.4%) had ileus at the time of diagnosis. Thirty-four (72.3%) patients underwent metastasectomy, while 13 (27.7%) patients underwent NSLAT. Surgical metastasectomy or NSLAT could be performed at the time of diagnosis in 16 (34.0%) patients, whereas 31 (66.0%) patients initially received CT followed by local ablative therapies or metastasectomy for liver metastasis (Table 1).

Table 1. Patient, disease and treatment characteristics

Characteristics	*Patients* (n=47) n (%)	*Surgical Metastasectomy (n=34) n (%)*	*NSLAT (n=13) n (%)*	*p*
Gender				0.269
Male	35 (74.5)	27 (79.4)	8 (61.5)	
Female	12 (25.5)	7 (20.6)	5 (38.5)	
Age (years)				0.084
Median (min-max)	61.0 (25-80)	66.5 (25-80)	58.0 (45-69)	
Emergency surgery				0.647
No	36 (76.6)	26 (76.5)	10 (76.9)	
Yes	11 (23.4)	8 (23.5)	3 (23.1)	
ECOG PS				0.519
0	45 (95.7)	32 (94.1)	13 (100.0)	
1	2 (4.3)	2 (5.9)	0 (0.0)	
Time of metastasectomy				0.090
At diagnosis	16 (34.0)	14 (41.2)	2 (15.4)	
At follow-up	31 (66.0)	20 (58.8)	11 (84.6)	
Localization of primary tumor				0.933
Ascending colon	6 (12.8)	5 (14.7)	1 (7.7)	
Transverse colon	1 (2.1)	1 (2.9)	0 (0.0)	
Descending colon	5 (10.6)	4 (11.8)	1 (7.7)	
Sigmoid colon	19 (40.4)	12 (35.3)	7 (53.8)	
Rectum	12 (25.5)	9 (26.5)	3 (23.1)	
Recto-sigmoid	4 (8.5)	3 (8.8)	1 (7.7)	
pT stage				0.413
T2-3	39 (83.0)	27 (92.3)	12 (79.4)	
T4	8 (17.0)	7 (7.7)	1 (20.6)	
pN stage				0.111
N0	23 (48.9)	14 (41.2)	9 (69.2)	
N1-2	24 (51.1)	20 (58.8)	4 (30.8)	
RAS mutation status				**0.025**
Wild	21 (44.7)	12 (35.3)	9 (69.2)	
Mutant	9 (19.1)	6 (17.6)	3 (23.1)	
Unknown	17 (36.2)	16 (47.1)	1 (7.7)	
BRAF mutation status				0.237
Wild	9 (19.1)	5 (14.7)	4 (30.8)	
Unknown	38 (80.9)	29 (85.3)	9 (69.2)	
1st line				0.004
5-FU-based+ anti VEGF	13 (27.7)	6 (17.6)	7 (53.8)	
5-FU-based	14 (29.8)	19 (55.9)	1 (7.7)	
5-FU-based+ anti-EGFR	20 (42.6)	9 (26.5)	5 (38.5)	
2nd line				0.768
5-FU-based+ anti VEGF	13 (65.0)	7 (63.6)	6 (66.7)	
5-FU-based	3 (15.0)	2 (18.2)	1 (11.1)	
5-FU-based+ anti-EGFR	4 (20.0)	2 (18.2)	2 (22.2)	
3rd line				0.193
5-FU-based+anti-VEGF	7 (58.3)	5 (83.3)	2 (33.3)	
5-FU-based+anti-EGFR	2 (16.7)	0 (0.0)	2 (33.3)	
Regorafenib	3 (25.0)	1 (16.7)	2 (33.3)	
Final status				0.713
Dead	12 (25.5)	8 (23.5)	4 (30.8)	
Alive	35 (74.5)	26 (76.5)	9 (69.2)	

ECOG PS:, Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; FU: 5- fluorouracil; pN: Pathological lymph node stage; PNI: Perineural invasion; pT: Pathologic tumor stage; VEGF: vascular endothelial growth factor; NSLAT: non-surgical local ablative treatment. Bold number denotes statistical significance

The number of patients and treatment regimens in the 1st, 2nd, and 3rd line were as follows:
1st Line: 13 patients (27.7%); 5-FU-based + Anti-VEGF, 14 patients (29.8%); 5-FU-based, and 20 (42.6%) patients; 5-FU-based + anti-EGFR.
2nd Line: 13 (65.0%) patients; FU-based + Anti-VEGF, 3 (15.0%) patients; 5-FU-based, and 4 (20%) patients; 5-FU-based + anti-EGFR.
3rd Line: 7 (58.3%) patients; 5-FU-based + Anti-VEGF, 2 (16.7) patients; 5-FU-based + Anti-EGFR, and 3 (25%) patient;regorafenib.

There were no statistically significant differences between the patients undergoing surgical metastasectomy and those treated with NSLAT in terms of age, gender, ileus at presentation, time of curative local therapy for liver metastasis, primary

Table 2. The survival rates (%) of patients at 12, 36, and 60 months

Months	*Patients (%)*	*Surgery (%)*	*NSLAT (%)*	*At diagnosis*	*At follow-up*	*pT2-3 (%)*	*pT4 (%)*	*pN0 (%)*	*pN1-2 (%)*
12	97.8	96.9	88.9	100	96.7	96.9	85.7	95.7	95.2
36	75.0	78.9	61.0	92.3	64.0	81.9	42.9	84.5	66.2
60	58.3	64.7	30.5	92.3	35.5	62.8	42.9	63.4	56.7

pN: Pathologic lymph node stage; pT: Pathologic tumor stage; NSLAT: non-surgical ablative local treatment

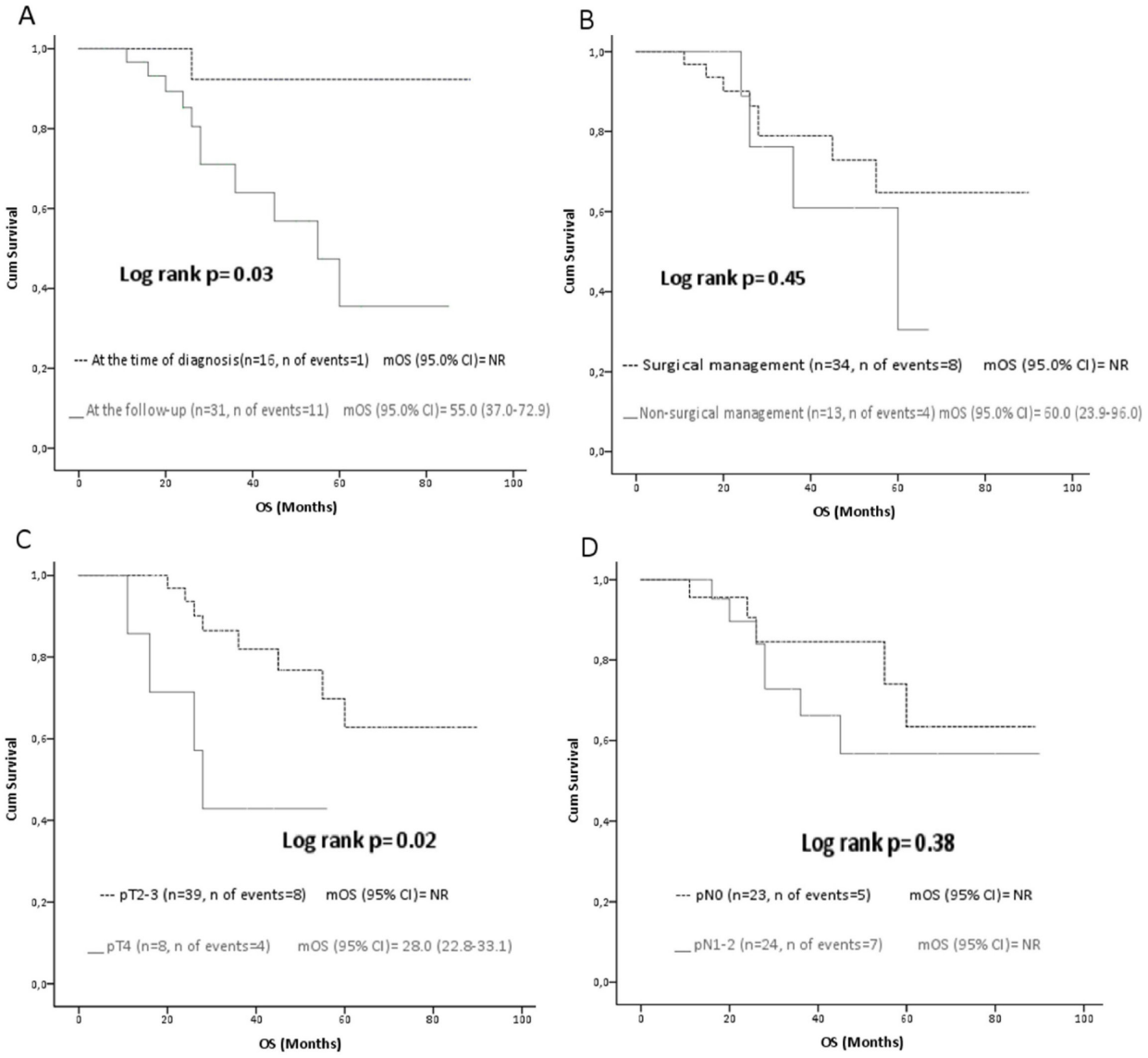

Figure 1. Survival according to Kaplan Meier method. **A:** Survival according to the time of metastasectomy; **B:** Survival according to the type of local treatment methods for liver metastasis; **C:** Survival according to the pathologic tumor stage; **D:** Survival according to the pathologic nodal stage. pN: Pathologic lymph node stage; PNI: Perineural invasion; pT: Pathologic tumor stage

Table 3. Univariate and multivariate analysis of potential associations between patient characteristics and survival

Univariate analysis for OS	*HR*	*95.0% CI*	*p*
Age at diagnosis (years)			0.628
<65	1	-	
≥65	1.013	0.961-1.068	
Gender			0.708
Female	1	-	
Male	1.259	0.376-4.208	
Emergency surgery			0.634
Yes	1	-	
No	0.691	0.151-3.160	
Time of metastasectomy			**0.034**
At follow-up	1	-	
At diagnosis	0.115	0.015-0.897	
Primary tumor localization			0.427
Left	1	-	
Right	2.302	0.294-18.015	
pT stage			**0.022**
T2-3	1	-	
T4	3.834	1.108-13.265	
pN stage			0.387
N0	1	-	
N1-2	1.669	0.523-5.326	
RAS mutation status			
Wild	1	-	0.179
Mutant	0.323	0.140-2.601	0.288
Unknown	0.556	0.265-1.999	0.150
Treatment type of metastasis			0.453
Surgical	1		
NSLAT	1.576	0.472-5.252	
1st line chemotherapy			
5-FU-based+ anti-VEGF	1	-	0.209
5-FU-based	2.552	0.591-11.015	0.715
5-FU-based+ anti-EGFR	0.756	0.168-3.395	0.871
2nd line chemotherapy			
5-FU-based+ anti-VEGF	1		
5-FU-based	2.687	0.247-9.264	0.459
5-FU-based+ anti-EGFR	2.121	0.127-35.39	0.600
3rd line chemotherapy			
5-FU-based+anti-VEGF	1	-	
5-FU-based+anti-EGFR	1.729	0.267-11.168	0.565
Regorafenib	3.397	0.431-26.764	0.246
Multivariate analysis for OS	*HR*	*95.0% CI for HR*	*p*
Timing of treatment for metastasis			**0.031**
At follow-up	1	-	
At diagnosis	0.106	0.013-0.826	
pT stage			**0.019**
pT2-T3	1	-	
pT4	4.365	1.272-14.982	

ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; FU: 5- fluoro-uracil; pN: Pathologic lymph node stage; PNI: Perineural invasion; pT: Pathologic tumor stage; VEGF: vascular endothelial growth factor; NSLAT: non-surgical local ablative treatment Bold numbers denote statistical significance

tumor localization, pT, pN, RAS and BRAF mutation status, 2nd and 3rd line treatment regimens, and death rates. The use of 5-FU-based treatment was statistically significant in the 1st line setting in those undergoing metastasectomy (p=0.004) (Table 1).

At a median follow-up time of 34 months (range, 6-90 months), 12 (25.5%) patients died (Table 2). According to the Kaplan Meier analysis, median overall survival (mOS) could not be reached in patients who underwent metastasectomy at the time of diagnosis compared to 55 months in those undergoing metastasectomy following chemotherapy (95% CI, 37.0-72.9, Log rank p=0.03). Patients treated with NSLAT for liver metastasis had a mOS of 60 months (95% CI, 23.9-96.0) compared to "not reached" in those who underwent liver metastasectomy (p=0.45). When considering the primary tumor stage, mOS was 28 months (95% CI, 22.8-33.1) in patients with pT4 stage vs. not reached in those with pT2 or pT3 stages (p=0.02). mOS could not be reached in patients with pN0 and pN1-2 (log rank p=0.38) (Figure 1).

In univariate analysis, time of metastasectomy and pT stage were found to be factors affecting survival (p=0.034, p=0.022, respectively). Likewise, multivariate analysis revealed that undergoing liver metastasectomy at the time of diagnosis (HR 0.10 Cl, 0.01-0.82, p=0.031) and pT4 stage (HR 4.365 Cl, 1.27-14.98, p=0.019) were the most important independent factors affecting survival (Table 3).

Discussion

In this study, we aimed to investigate the factors affecting survival in curatively-operated CRC patients with sole liver metastasis who underwent metastasectomy or NSLAT for liver metastasis. The best results were observed in those undergoing metastasectomy at the time of diagnosis as well as in patients with early pathological tumor stage. The treatment of liver metastases in CRC has gradually improved in recent years. Proper patient selection and optimal perioperative care progressively decreased the morbidity and mortality rates in CRC [13,14]. In addition, indications of surgical metastasectomy in CRC continue to develop. Although the presence of multiple (bilobar) metastases used to be a contraindication to surgery, it is currently no longer considered a contraindication to metastasectomy. The main purpose of surgical metastasectomy is to yield R0 resection leaving sufficient residual liver volume. Strategies for identifying patients more likely to benefit from metastasectomy also continue to evolve [15,16].

The 5-year survival rate in patients who underwent surgical metastasectomy for isolated liver-metastatic CRC ranged from 28% to 57.7% [17-19]. In a study by Hayashi et al. including 83 CRC patients with sole liver metastasis treated with surgical metastasectomy at the time of diagnosis, mOS was reported to be 25 months, with a 5-year survival rate of 57.5%. While the depth of primary tumor invasion was found to be a significant parameter in univariate analysis, it was not statistically significant in multivariate analysis [17]. Similarly, Rees et al. reported a 5-year survival rate of 36% in their study consisting of 80 patients who underwent surgical metastasectomy for liver-metastatic CRC, indicating that tumor invasion depth and lymph node involvement were found to be independent negative factors for survival [18].

In our study, the 5-year survival rate was 64.7% in patients undergoing surgical metastasectomy and mOS could not be reached. In addition, the depth of tumor invasion at the time of diagnosis significantly affected survival. Having a pT4 stage increased the mortality risk by 4.3 times. In non-metastatic CRC, the invasion depth of the primary tumor is known to affect survival independently. In fact, while the 5-year survival rate is 76.3% and 58.8% in stage IIB (pT4aN0M0) and IIC (pT4bN0M0) disease, respectively, this rate is around 83% in stage IIIA (pT3N1M0) disease [20]. This condition may apply to the CRC patients with liver metastasis who underwent curative surgical metastasectomy. Although tumor laterality is important in many cancers [21] and colon cancer [4], in our study, laterality was not a more prominent factor than metastasectomy and pT stage.

The optimal timing of metastasectomy in CRC patients with synchronous liver metastasis is still under debate. Hayashi et al. showed no difference between the timing of metastasectomy (at diagnosis vs. at follow-up) [17]. However, in our study, performing metastasectomy at the time of diagnosis was found to reduce the risk of mortality significantly. The favorable survival rates in patients who underwent surgical metastasectomy at the time of diagnosis may be due in large part to low tumor burden in these groups.

Over the last few decades, a variety of ablative techniques has been developed, with each technique having its own advantages and disadvantages depending on the patient's clinical situation. Ablative treatment techniques for liver-metastatic CRC have emerged as a safe and effective alternative treatment method to hepatic resection. Randomized studies and case series showed that ablative techniques could almost yield similar clinical results to those achieved by resection [22,23]. Bale et al. reported a 5-year survival rate of 27% in 63 patients with liver-metastatic CRC who underwent

NSLAT [24]. Similarly, Hamada et al. found a 5-year survival rate of 21% in their study including 101 isolated liver-metastatic CRC patients treated with NSLAT [22]. In CRC patients with sole liver metastasis treated with NSLAT, the 5-year survival rate ranges between 14% and 33% [22,24-28]. In our study, the 5-year survival rate in patients treated with NSLAT was found to be 30%, with mOS of 60 months.

Although our study was conducted on a specific patient group and the follow-up period was long, it was single-centered and retrospective. In addition, the number of cases in our study was low and there were some missing data regarding the number of liver metastasis, location of metastasis in the liver, size of metastasis, and distance of the resection margin. In addition, as the number of patients undergoing NSLAT was low in our study, patients could not be divided into subgroups according to treatment types for liver metastasis.

In conclusion, in patients with liver-metastatic CRC, performing metastasectomy at the time of diagnosis significantly prolonged survival compared to a subsequent metastasectomy at follow-up. In addition, pT4 stage at the time of diagnosis significantly shortened survival compared to pT2-pT3 stages. In CRC patients with isolated liver metastasis, we recommend, if possible, surgical metastasectomy or NSLAT at the time of diagnosis. Nevertheless, prospective studies with greater sample size are needed to verify these findings.

Author contributions

Concept: AS, SC; Design: MMA, SA, SS; Supervision: AA, SC, AS, SA; Resources: NY, CG, FA; Materials: AS, NY, CD; Data Collection and/or Processing: AS ,NY ,CG; Analysis and/or Interpretation: SC, FK, AS; Literature Search: CD, MMA, SS, SA, FK; Writing Manuscript: SS;AS; Critical Review: SC, SS, CD; Other: CG, AA,FK.

Conflict of interests

The authors declare no conflict of interests.

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