

Effect of high ligation on survival of patients undergoing surgery for primary colorectal cancer and synchronous liver metastases

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Background: Although R0 surgery is recommended for stage IV colorectal cancer, the degree of required lymphadenectomy has not been established. The aim of this study was to investigate the prognostic impact of high ligation (HL) of the feeding artery and the number of retrieved lymph nodes after R0 surgery for colorectal cancer and synchronous colorectal cancer liver metastasis (CRLM).

Methods: This was a multi-institutional retrospective analysis of patients with colorectal cancer and synchronous CRLM who had R0 surgery between January 1997 and December 2007. Clinical and pathological features were compared in patients who underwent HL and those who had a low ligation (LL). Kaplan–Meier analysis was performed to estimate the effect of HL on overall survival (OS). The impact of several risk factors on survival was analysed using the Cox proportional hazards model.

Results: Of 549 patients, 409 (74.5 per cent) had HL. Median follow-up was 51.4 months. HL significantly improved the 5-year OS rate (58.2 per cent *versus* 49.3 per cent for LL; $P = 0.017$). Multivariable analysis revealed HL to be a significant prognostic factor compared with LL (5-year mortality: hazard ratio (HR) 0.68, 95 per cent c.i. 0.51 to 0.90; $P = 0.007$). In subgroup analysis, the positive effect of HL on OS was greatest in patients with lymph node metastasis.

Conclusion: HL of the feeding artery was associated with improved OS in patients with colorectal cancer and synchronous CRLM after R0 surgery.

Funding information

No funding

Paper accepted 3 February 2020

Published online 3 April 2020 in Wiley Online Library (www.bjsopen.com). DOI: 10.1002/bjs5.50274

Introduction

An anatomical approach to surgical procedures has drawn global attention recently. In patients with colorectal cancer, complete mesocolic excision^{1,2} and total mesorectal excision^{3,4} involve mobilization of the mesocolon and mesorectum respectively along their anatomical layers. A concomitantly performed high ligation (HL)^{5,6} involves transection of the artery at the root of its feeding artery. These procedures allow the surgeon to perform *en bloc* dissection of blood vessels, lymphatic vessels and lymph nodes (LNs). These procedures now constitute the standard technique to prevent postoperative recurrence^{5,7}.

The liver is one of the commonest sites of metastasis of colorectal cancer. The 5-year survival rate following curative resection of colorectal cancer liver metastases (CRLM) is reportedly 39.2 per cent⁸. Consequently, several recent

guidelines^{9–11} have recommended attempting R0 surgery for the treatment of colorectal cancer with liver metastases.

Combining curative resection of CRLM with the newer technique of anatomical resection of primary colorectal lesions might be the most effective procedure to prevent postoperative recurrence of synchronous CRLM. Few studies, however, have addressed the impact of this combined technique. In particular, the efficacy of performing radical lymphadenectomy during removal of the primary colorectal lesion remains unclear, and consequently there is no standard procedure for lymphadenectomy. Moreover, the number of LNs to be retrieved has not been validated. Given that extended radical operations are closely associated with the occurrence of postoperative complications^{12,13}, many surgeons question their feasibility in patients with CRLM.

The objectives of this study were to clarify the impact of both HL and the number of dissected LNs on post-operative survival after curative resection in patients with primary colorectal cancer and synchronous CRLM.

Methods

This study involved a multi-institutional retrospective analysis of patients with colorectal cancer and synchronous CRLM who underwent R0 surgery between January 1997 and December 2007. The patients were registered by the Japanese Study Group for Postoperative Follow-up of Colorectal Cancer (JFUP-CRC), which was founded in 2001 to establish an appropriate surveillance protocol for colorectal cancer and comprises 18 institutions, including academic medical centres or local base major hospitals. 'Liver-first' surgery for hepatic metastasis in colorectal cancer was not performed in Japan during the study period, and so this cohort did not include patients treated with liver-first surgery.

Inclusion criteria for the study were as follows: patients with a diagnosis of colorectal cancer with synchronous CRLM; no metastases other than those involving the liver; and R0 resection of all CRLM performed less than 3 months after excision of the primary lesion. Exclusion criteria were: radiotherapy or chemotherapy administered before resection of the primary tumour or before liver resection in the case of staged surgery; cancer associated with ulcerative colitis, Crohn's disease or familial adenomatous polyposis; and presence of any other active malignancy.

Definition of the level of arterial ligation

HL was defined as ligation of the feeding artery at its root. The HL technique was applied as follows: for right-sided colonic tumours, the ileocolic artery and the right colic artery (if present) were ligated at their respective points of origin from the superior mesenteric artery; for transverse colonic cancers, the root of the middle colic artery was ligated; and for left-sided colonic tumours and rectal cancers, the root of the inferior mesenteric artery (IMA) was ligated.

Classification of the extent of hepatic metastasis

The extent of CRLM was determined using the H-factor scale according to the Japanese Classification of Colorectal Carcinoma from the Japanese Society for Cancer of the Colon and Rectum¹⁴. The H factor is determined by the number and maximum diameter of metastatic tumours: H1, one to four metastatic lesions with a maximum diameter of 5 cm or less; H2, metastases not included in the

H1 or H3 subclassification; H3, more than four metastatic lesions with a maximum diameter greater than 5 cm.

Outcomes of interest

The primary outcome was overall survival (OS), defined as the time from curative resection of the primary lesion to death from any cause. Patients who were lost to follow-up and those who were alive at the time of their last follow-up visit were censored at the date of last contact.

Statistical analysis

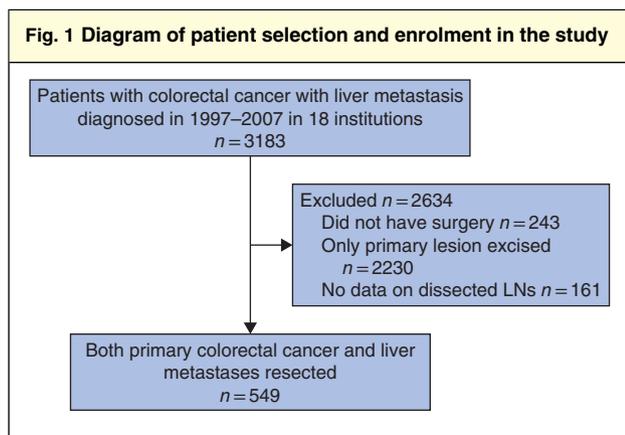
Univariable analysis was performed using Student's *t* test and χ^2 analysis for continuous and categorical variables respectively. Kaplan–Meier curves were employed for survival analyses, and the log rank test was used to assess differences between patients who underwent HL and those who had low ligation (LL). Cox proportional hazards models were also used to determine the association between predictor variables and the time-to-event outcome (OS). The final multivariable model was created using the forced entry method of co-variable elimination, and included only significant co-variables ($P < 0.050$).

The relationship between the number of retrieved LNs (continuous) and the risk of death was explored using a fractional polynomial predictive plot with 95 per cent c.i. and a non-parametric regression model, based on a cubic spline with four internal knots. In subgroup analysis, hazard ratios (HRs) for the interaction between treatment effect and any subgroup variable were visualized using a forest plot. Statistical significance was indicated by $P < 0.050$. All statistical analyses were performed using Stata[®] version 12 (StataCorp, College Station, Texas, USA).

Results

A total of 3183 patients with stage IV colorectal cancer treated between January 1997 and December 2007 were analysed retrospectively. Of these, 710 patients who had undergone resection of both the primary colorectal lesion and CRLM were enrolled in the study; 161 patients were then excluded owing to insufficient data regarding the number of LNs removed at operation. A total of 549 patients with colorectal cancer met all inclusion criteria (*Fig. 1*). Patients' background characteristics are summarized in *Table 1*.

The patients were categorized into the HL (409 patients) or LL (140 patients) group according to the level at which the artery feeding the colorectal cancer had been ligated. The groups differed significantly with respect to mean(s.d.) age (61.8(10.5) years in the HL group *versus*



LN, lymph nodes.

63.3(10.6) years in the LL group; $P=0.006$), possibly indicating a preference for less invasive surgery in older patients. There was also a significant difference between the groups with regard to the primary cancer being located in the rectum (23.2 versus 39.3 per cent respectively; $P<0.001$). Other clinical variables were comparable between the groups (Table 1). The mean(s.d.) number of

LN retrieved differed significantly: 26.0(14.8) in the HL group versus 20.9(18.8) in the LL group ($P<0.001$).

Survival analysis

Median follow-up was 51.4 (range 0.6–188) months. The 5-year OS rate was significantly higher in the HL group than in the LL group (58.2 versus 49.3 per cent respectively; $P=0.017$) (Fig. 2).

In univariable analysis of prognostic factors predictive of survival after curative surgery, a significantly lower 5-year mortality rate was found in the HL group (HR 0.72, 95 per cent c.i. 0.54 to 0.94; $P=0.018$). This association was confirmed in the subsequent multivariable analysis (HR 0.68, 0.51 to 0.90; $P=0.007$) (Table 2).

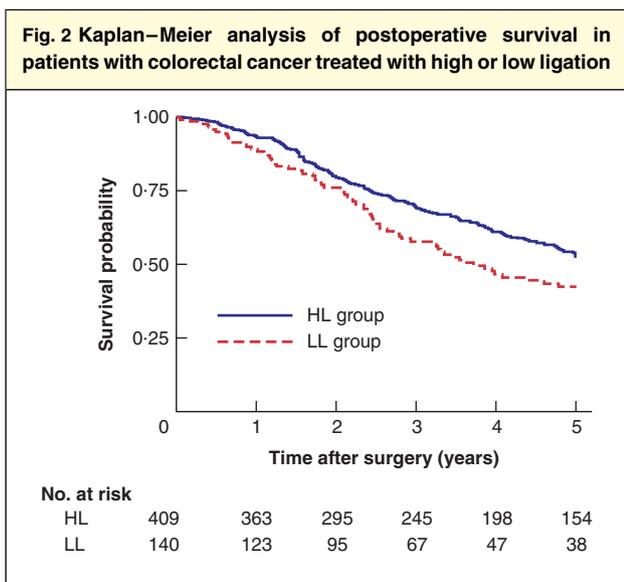
Influence of number of retrieved lymph nodes on prognosis

A fractional polynomial analysis was conducted to evaluate the dose–response relationship between the number of retrieved LNs and OS. In Fig. 3, the curve for the relative HR of 5-year mortality falls gradually to the right, indicating that the dissected LN count was positively associated with OS.

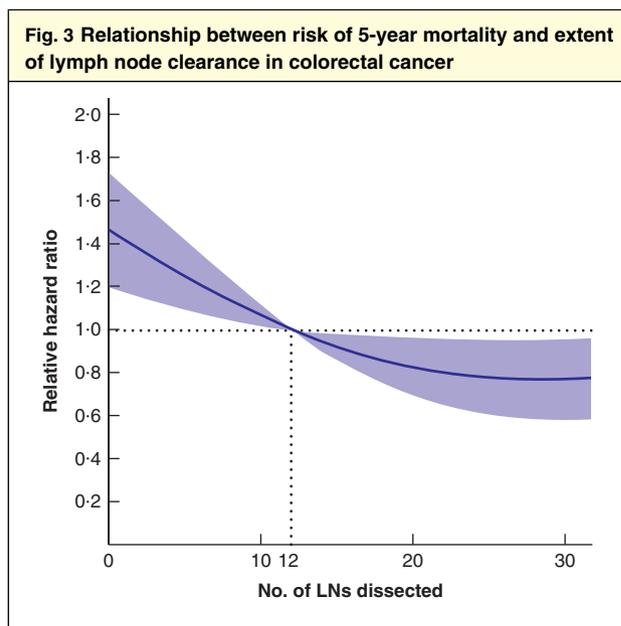
Table 1 Demographic characteristics of study patients

| | Total (n = 549) | HL group (n = 409) | LL group (n = 140) | P‡ |
|--|-------------------|--------------------|--------------------|----------|
| Age (years)* | 62.2(10.5) | 61.8(10.5) | 63.3(10.6) | 0.006§ |
| Sex ratio (M : F) | 348 : 201 | 250 : 159 | 98 : 42 | 0.060 |
| Tumour location | | | | < 0.001 |
| Colon | 399 (72.7) | 314 (76.8) | 85 (60.7) | |
| Rectum | 150 (27.3) | 95 (23.2) | 55 (39.3) | |
| Histology | | | | 0.098 |
| Well or moderately differentiated tubular adenocarcinoma | 518 (94.4) | 382 (93.4) | 136 (97.1) | |
| Other | 31 (5.6) | 27 (6.6) | 4 (2.9) | |
| Depth of tumour | | | | 0.641 |
| T2 | 23 (4.2) | 18 (4.4) | 5 (3.6) | |
| T3 | 323 (58.8) | 236 (57.7) | 87 (62.1) | |
| T4 | 203 (37.0) | 155 (37.9) | 48 (34.3) | |
| No. of retrieved LNs* | 24.7(16.1) | 26.0(14.8) | 20.9(18.8) | < 0.001§ |
| LN metastasis | 162 (29.5) | 117 (28.6) | 45 (32.1) | 0.428 |
| Invasion of lymph vessel | 114 (20.8) | 79 (19.3) | 35 (25.0) | 0.152 |
| Invasion of vascular channel | 64 (11.7) | 43 (10.5) | 21 (15.0) | 0.153 |
| Classification of hepatic metastasis | | | | 0.470 |
| H1 | 401 (73.0) | 296 (72.4) | 105 (75.0) | |
| H2 | 104 (18.9) | 82 (20.0) | 22 (15.7) | |
| H3 | 44 (8.0) | 31 (7.6) | 13 (9.3) | |
| Preoperative serum CEA level (ng/ml)† | 17.2 (0.4–25 000) | 15.5 (0.5–25 000) | 21.3 (0.4–7680) | 0.301§ |
| Postoperative chemotherapy | 154 (28.1) | 116 (28.4) | 38 (27.1) | 0.942 |
| Simultaneous liver resection | 161 (29.3) | 112 (27.4) | 49 (35.0) | 0.143 |

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) and †median (range). HL, high ligation; LL, low ligation; LN, lymph node; CEA, carcinoembryonic antigen. ‡ χ^2 test, except §Student's *t* test.



HL, high ligation; LL, low ligation. $P=0.017$ (log rank test).



The shaded area represents 95 per cent confidence intervals. The value of 12 is marked on the x -axis as the least number of lymph nodes (LNs) to be resected to attain the standard for 5-year mortality.

Subgroup analyses of the effect of high ligation on prognosis

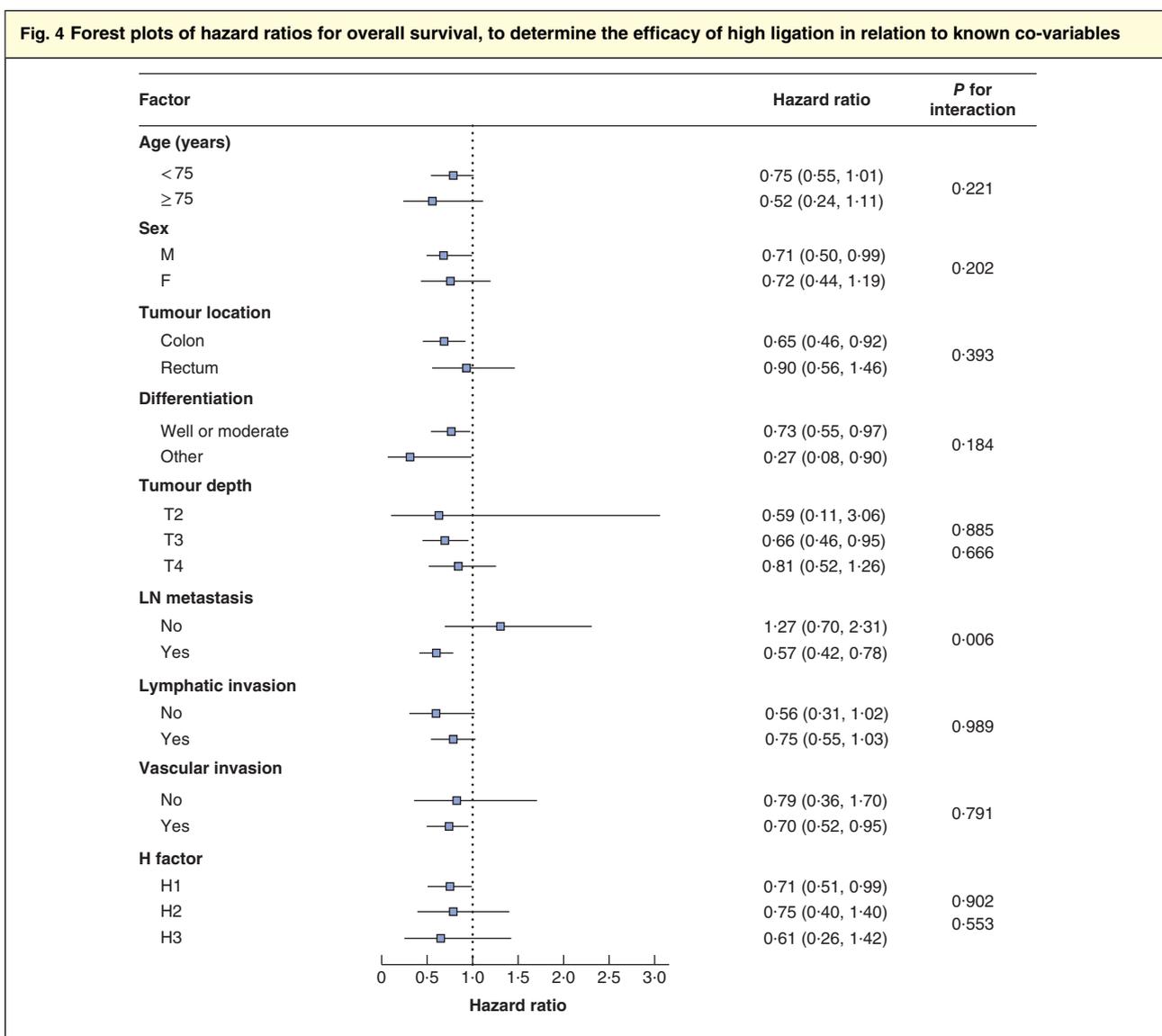
Subgroup analyses were conducted to explore other co-variables affecting the HR for OS (Fig. 4). Several co-variables demonstrated significant effects of HL on

prognosis. The association between OS and co-variables was significantly stronger in the presence of LN metastasis (HR with no LN metastasis 1.27, 95 per cent c.i. 0.70 to

Table 2 Univariable and multivariable analysis of risk factors for death after colorectal cancer surgery

| | Univariable analysis | | Multivariable analysis | |
|---|----------------------|-------|------------------------|-------|
| | Hazard ratio | P | Hazard ratio | P |
| Age | 1.17 (0.78, 1.74) | 0.452 | | |
| Female sex | 1.04 (0.80, 1.36) | 0.745 | | |
| Rectal location | 1.19 (0.90, 1.57) | 0.217 | | |
| Tumour differentiation (well or moderate) | 0.58 (0.34, 0.99) | 0.044 | 0.57 (0.33, 0.98) | 0.042 |
| Depth of tumour | | | | |
| T2 | 1.00 (reference) | | | |
| T3 | 1.49 (0.70, 3.19) | 0.301 | | |
| T4 | 2.05 (0.95, 4.42) | 0.072 | | |
| LN metastasis | 1.38 (1.04, 1.84) | 0.027 | 1.36 (1.02, 1.82) | 0.036 |
| Invasion of lymph vessel | 1.21 (0.88, 1.67) | 0.235 | | |
| Invasion of vascular channel | 0.98 (0.67, 1.45) | 0.938 | | |
| With HL | 0.72 (0.54, 0.94) | 0.018 | 0.68 (0.51, 0.90) | 0.007 |
| No. of LNs dissected | 1.00 (0.99, 1.01) | 0.387 | | |
| Classification of liver metastasis | | | | |
| H1 | 1.00 (reference) | | 1.00 (reference) | |
| H2 | 1.46 (1.08, 1.99) | 0.024 | 1.48 (1.09, 2.00) | 0.012 |
| H3 | 1.41 (0.91, 2.18) | 0.121 | 1.33 (0.86, 2.08) | 0.195 |
| High preoperative serum CEA level (> 5 ng/ml) | 1.12 (0.85, 1.48) | 0.431 | | |
| Postoperative chemotherapy | 1.01 (0.77, 1.33) | 0.932 | | |
| Simultaneous liver resection | 1.02 (0.78, 1.34) | 0.873 | | |

Values in parentheses are 95 per cent confidence intervals. LN, lymph node; HL, high ligation; CEA, carcinoembryonic antigen.



Values in parentheses are 95 per cent confidence intervals. LN, lymph node.

2.31; HR with positive nodes 0.57, 0.42 to 0.78; $P=0.006$ for interaction).

Influence of high ligation on recurrence

Recurrence occurred in 331 patients: 248 of 409 patients in the HL group (60.6 per cent) *versus* 83 of 140 in the LL group (59.3 per cent) ($P=0.778$). Although disease-free survival did not differ significantly between the groups, the 5-year cumulative liver recurrence rate was significantly higher in the LL group: 42.1 per cent (59 of 140) *versus* 31.5 per cent (129 of 409) in the HL group ($P=0.022$). There was no significant difference in distant

metastases, such as lung metastasis or peritoneal dissemination, between the groups (15.6 per cent (64 of 409) in the HL group *versus* 15.0 per cent (21 of 140) in the LL group; ($P=0.855$), or in local recurrence (4.2 per cent (17 of 409) *versus* 2.9 per cent (4 of 140) respectively; $P=0.489$).

In further analysis focused on the extent of liver metastasis, HL appeared to decrease liver recurrence only in patients with H1 liver metastases (HR 0.85, 95 per cent c.i. 0.69 to 0.99; $P=0.041$). Thus, the prognostic impact of HL was greater in patients with one to four hepatic metastatic lesions with a maximum diameter of 5 cm or less.

Discussion

The role of lymphadenectomy in patients with colorectal cancer and synchronous CRLM has been unclear. The results of this study suggest that HL can improve OS in these patients. Furthermore, the number of retrieved LNs was associated with survival. These findings suggest the benefit of more aggressive lymphadenectomy to prevent postoperative recurrence in patients with colorectal cancer and CRLM.

This study has indicated that HL is an independent prognostic factor after curative resection of both the primary lesion and CRLM. The results may be explained partially by the clearance of micrometastases within the mesentery. Recent advanced colorectal surgical procedures, such as HL and complete mesocolic excision, have gained acceptance as they help to maximize the number of LNs harvested at operation and improve subsequent prognosis. These techniques significantly improve long-term outcomes in patients with stage I–III colonic cancer without increasing the rate of major postoperative complications^{1,5}. Approximately 20 per cent of patients with no apparent LN metastasis have been reported to have nodal micrometastases, detected after surgery on haematoxylin and eosin staining^{15,16}. Radical LN resection appears to reduce the risk of missing residual cancer cells from regional LNs, subsequently preventing cancer recurrence in patients with colorectal cancer and CRLM. Although the incidence of locoregional recurrence was comparable in the LL and HL groups, use of the HL technique was found to suppress CRLM significantly.

The findings of this study demonstrate that radical resection of LNs, as defined by the degree of dissection and number of nodes extracted, is important to improve survival in patients with colorectal cancer and CRLM. This raises intriguing questions regarding whether it is necessary to define the degree of excision or the number of LNs to be excised. Anatomical studies^{17,18} have revealed significant differences between the ascending and sigmoid colon in terms of LN distribution. Furthermore, neoadjuvant chemoradiotherapy significantly reduces mesorectal LN counts¹⁹. However, many anatomical and clinical co-variables may influence the extent of LN involvement. Future studies are recommended to determine these factors.

The subgroup analysis also demonstrated several important findings. First, a clear association was observed between degree of LN metastasis and OS, suggesting that patients with nodal metastases may have improved survival benefit from radical lymphadenectomy than those without. As it is difficult accurately to detect LN metastasis before surgery, an R0 resection with radical lymphadenectomy

should be attempted, if possible, in all patients with colorectal cancer and CRLM. Second, HL ligation was more efficacious in colonic cancer than in rectal cancer, which may be attributable to the differences in lymphatic drainage of the colon and the rectum. The rectum has two lymphatic drainage channels^{20,21}. Lymphatic drainage of the upper third of the rectum occurs along the inferior mesenteric vein, following the portal vein, whereas that of the lower third of the rectum is lateral to the iliac nodes via lymphatic channels within the lateral ligaments. Rectal tumour cells that have spread to the lateral nodes can be missed if only LNs along the inferior mesenteric artery are dissected. The surviving tumour cells could then metastasize to other organs, such as the lungs or brain. These findings support the use of other treatments in addition to HL, to decrease the number of malignant cells left behind.

This study has some limitations. First, it was a retrospective study, and thus may be affected by selection bias with respect to patient enrolment. In view of the heterogeneity of CRLM, although an RCT may not be feasible, a large cohort study might be useful to draw a more definite conclusion. Second, the indications for surgery for stage IV colorectal cancer may differ between institutions; for example, simultaneous excision of CRLM along with the primary lesion is performed in some institutions. The influence of the timing of hepatectomy on survival remains unclear. A 2015 review²² of available treatment strategies for synchronous CRLM discussed following four approaches used in clinical practice: primary tumour resection; simultaneous resection; a chemotherapy-first approach; and upfront hepatectomy. The review²² concluded that no single method was superior, and advised careful appraisal on a case-by-case basis before selecting an approach. The observation period of the present study was before publication of the liver-first surgical approach by Mentha and colleagues²³, although liver-first surgery combined with the watch-and-wait strategy for rectal cancer may be a future approach for rectal cancer liver metastases. Finally, there is a lack of information on the efficacy of postoperative chemotherapy. Recent advances in chemotherapy for colorectal cancer have improved the survival of patients with recurrent or advanced disease²⁴. Although the value of postoperative adjuvant chemotherapy for liver metastases has not been demonstrated in phase III trials^{25,26}, the postoperative chemotherapeutic induction rate and its impact on OS should be compared between patients undergoing HL and LL in future studies.

The findings of this study show that HL could improve OS in patients with colorectal cancer and synchronous resectable CRLM. However, future prospective RCTs are indicated to validate these findings.

Acknowledgements

The authors completed this study in collaboration with the following: I. Takemasa (Sapporo Medical University), K. Hakamada (Hiroshima University), H. Kameyama (Niigata University), K. Hase (National Defence Medical College), H. Ozawa (Tochigi Cancer Centre), S. Ishihara (University of Tokyo), T. Masaki (Kyorin University), M. Itabashi (Tokyo Women's Medical University), K. Takahashi (Tokyo Metropolitan Cancer and Infectious Disease Centre), H. Yano (International Medical Centre of Japan), Y. Kinugasa (Tokyo Medical and Dental University), Y. Hashiguchi (Teikyo University), K. Hanai (Fujita Health University), K. Komori (Aichi Cancer Centre), Y. Sakai (Kyoto University) and Y. Akagi (Kurume University).

The authors thank Editage (www.editage.jp) for English-language editing.

Disclosure: The authors declare no conflict of interest.

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