Journal of Surgical Oncology

WILEY

Journal of SURGICAL ONCOLOGY

RESEARCH ARTICLE OPEN ACCESS

Recurrence Timing and Risk Following Curative Resection of Colorectal Liver Metastases: Insights From a Hazard Function Analysis

Jun Kawashima[1,2] | Miho Akabane[1] | Yutaka Endo[3] | Selamawit Woldesenbet[1] | Abdullah Altaf[1] | Andrea Ruzzenente[4] | Irinel Popescu[5] | Minoru Kitago[6] | George Poultsides[7] | Kazunari Sasaki[7] | Federico Aucejo[8] | Kota Sahara[2] | Itaru Endo[2] | Timothy M. Pawlik[1]

[1]Department of Surgery, The Ohio State University Wexner Medical Center and James Comprehensive Cancer Center, Columbus, Ohio, USA | [2]Department of Gastroenterological Surgery, Yokohama City University School of Medicine, Yokohama, Japan | [3]Department of Transplant Surgery, University of Rochester Medical Center, Rochester, New York, USA | [4]Department of Surgery, University of Verona, Verona, Italy | [5]Department of Surgery, Fundeni Clinical Institute, Bucharest, Romania | [6]Department of Surgery, Keio University, Tokyo, Japan | [7]Department of Surgery, Stanford University, Stanford, California, USA | [8]Department of General Surgery, Cleveland Clinic Foundation, Cleveland, Ohio, USA

Correspondence: Timothy M. Pawlik (Tim.Pawlik@osumc.edu)

Received: 22 October 2024 | **Accepted:** 29 October 2024

Funding: The authors received no specific funding for this work.

Keywords: colorectal liver metastases | curative resection | hazard function | recurrence

ABSTRACT

Introduction: There is no consensus on the optimal surveillance interval for patients undergoing resection of colorectal liver metastases (CRLM). We sought to assess the timing and intensity of recurrence following curative-intent resection of CRLM utilizing a recurrence-free survival (RFS) hazard function analysis.

Methods: Patients with CRLM who underwent curative-intent resection were identified from a multi-institutional database. The RFS hazard function was used to plot hazard rates and identify the peak of recurrence over time.

Results: Among 1804 patients, the median RFS was 19.9 months. In the analytic cohort, the RFS hazard curve peaked at 5.9 months (peak hazard rate: 0.054) and gradually declined, indicative of early recurrence. In subgroup analyses, patients with high and medium tumor burden scores (TBS) had RFS hazard peaks at 4.9 months (peak hazard rate: 0.060) and 5.8 months (peak hazard rate: 0.054), respectively. In contrast, patients with low TBS had a later peak at 7.5 months, with the lowest peak hazard rate of 0.047.

Conclusions: The recurrence peak for CRLM patients occurred approximately 6 months postsurgery, highlighting the need for intensified early postoperative surveillance. Patients with high TBS experienced earlier recurrence, underscoring the importance of close monitoring, particularly during the first 6 months after surgery.

1 | Introduction

Colorectal cancer (CRC) is a major contributor to cancer-related mortality worldwide, ranking as the second leading cause of cancer deaths in the United States [1]. Approximately 50% of patients with CRC develop colorectal liver metastases (CRLM), which poses a significant challenge in disease management [2]. Hepatic resection remains the cornerstone of curative-intent treatment for CRLM. However, recurrence rates following resection remain high with 50-75% of patients experiencing disease relapse even after successful resection [3, 4]. Recent advancements in surgical techniques and systemic chemotherapy have expanded

therapeutic options for recurrent disease, offering potential for improved outcomes, particularly with early intervention [5]. This underscores the importance of robust postoperative surveillance strategies to optimize timely treatment as it may improve prognosis for patients with recurrent CRLM [6].

To date, postoperative surveillance for CRLM typically involves cross-sectional imaging and serum carcinoembryonic antigen (CEA) monitoring [7–10]. However, there is no consensus on the optimal surveillance intervals [6]. For instance, the European Society for Medical Oncology (ESMO) guidelines recommend imaging measurements every 3 months for the first 2 years, while the National Comprehensive Cancer Network (NCCN) guidelines suggest imaging every 3-6 months [7, 8]. In contrast, the Japanese Society for Cancer of the Colon and Rectum (JSCCR) advises computed tomography (CT) scans every 6 months during the first 3 years, and the American Society of Colon and Rectal Surgeons (ASCRS) recommends imaging once every 12 months [9, 10]. These variations highlight the need to better understand recurrence trends over time and personalize postoperative surveillance strategies for patients.

To date, recurrence and survival outcomes have been analyzed using Kaplan-Meier analyses, which demonstrate the cumulative risk over time [11]. Although useful, these curves do not provide insight into the real-time risk of recurrence for patients who remain under observation [11]. In contrast, the hazard function offers a more dynamic perspective by estimating the instantaneous risk of recurrence at specific time points, allowing for a more detailed understanding of when patients are at the highest risk for recurrence [12]. Although this method has been used to evaluate recurrence timing in breast cancer, CRC, hepatocellular carcinoma, and intrahepatic cholangiocarcinoma, few studies have applied it to the field of CRLM [6, 11–15].

As such, the current study sought to examine the timing and intensity of recurrence after curative-intent resection of CRLM using the hazard function. We also investigated how clinical factors, including tumor burden score (TBS), Kirsten rat sarcoma oncogene (KRAS) mutation status, and the receipt of adjuvant chemotherapy, impacted the timing and intensity of peak recurrence. By identifying these factors, the data may inform more individualized follow-up strategies for patients with CRLM undergoing hepatic resection.

2 | Methods

2.1 | Study Population and Data Collection

An international, multi-institutional database was utilized to identify patients who underwent curative-intent liver resection for CRLM between 2000 and 2023 [16]. Patients who underwent palliative surgery, R2 resection, previous hepatectomy, or had extrahepatic metastases before liver resection were excluded. Additionally, records with missing data on tumor characteristics (i.e., tumor size and number) or long-term outcomes were also excluded. The study was approved by the Institutional Review Board of each participating institution.

2.2 | Variables and Outcomes of Interest

Patient clinicodemographic variables included age, sex, year of surgery (i.e., 2000–2010 or 2011–2023), receipt of preoperative systemic chemotherapy, primary tumor location (i.e., colon or rectum), T-category (i.e., T1/T2/T3 or T4) and lymph node involvement of primary tumor, KRAS mutational status, timing of CRLM diagnosis (i.e., synchronous or metachronous), disease-free interval (DFI) (i.e., < 12 months or ≥ 12 months), CEA levels at the time of CRLM diagnosis, the extent of hepatectomy (i.e., major or minor hepatectomy), tumor number, tumor size, TBS, pathological margin status, posthepatectomy severe complications, and receipt of adjuvant chemotherapy. The American Joint Committee on Cancer (AJCC) 8th edition staging manual was used for T-category classification [17]. Synchronous metastasis was defined as the presence of both a primary colorectal tumor and CRLM at the time of diagnosis [4]. TBS was computed using the formula: $\text{TBS}^2 = (\text{maximum CRLM diameter})^2 + (\text{number of CRLM})^2$ [18]. Patients were categorized into 3 groups (low TBS: < 3; medium TBS: ≥ 3 to < 9; high TBS: ≥ 9), as previously described [18]. DFI was defined as the duration from resection of primary tumor to liver metastasis [19]. Liver resection was defined as major (≥ 3 segments) or minor (≤ 2 segments) according to the "New World" terminology [20]. The severity of postoperative complications was defined according to the Clavien-Dindo classification system (grade I-V); severe complications were defined as Clavien-Dindo grade $\geq$ III [21].

The primary outcomes of interest included recurrence-free survival (RFS), defined as the time elapsed between the date of liver resection and the recurrence, either confirmed on biopsy or using evidence of a suspicious lesion on follow-up imaging. Overall survival (OS) was defined as the time interval between the date of hepatectomy for CRLM and the date of death or last follow-up. Following curative-intent hepatectomy, patients were monitored for recurrence based on serum tumor markers and imaging, such as CT, and/or magnetic resonance imaging. Patients were followed once every 3 to 4 months during the first 3 years, once every 6 months during the 4th and 5th years, and then annually [22]. The treatment of tumor recurrence was decided based on consensus among the multidisciplinary team at each institution.

2.3 | Statistical Analysis

Descriptive statistics were presented as median values with interquartile ranges (IQR) for continuous variables and as frequencies with percentages (%) for categorical variables. For the variables of interest, the RFS hazard function was applied to plot the hazard rates and the peak of recurrence over time. The kernel smoothing method provided estimates of hazard function from right-censored data [23]. Recurrence was defined as an event, and the units of measure for hazard rates were events per month. All statistical analyses were performed using R version 4.2.3 (R Project for Statistical Computing, Vienna, Austria).

3 | Results

3.1 | Baseline Cohort Characteristics

Among 1,804 patients who underwent curative-intent hepatectomy for CRLM, median age was 62 years (IQR: 53–69). Most patients were male ($n = 1089$, 60.4%), and the majority of surgical procedures were performed between 2011 and 2023 ($n = 1344$, 74.5%). Approximately one-third of patients received preoperative systemic chemotherapy ($n = 600$, 33.3%). The primary tumor was most frequently located in the colon ($n = 1270$, 70.4%) and were classified as T1–T3 disease ($n = 1614$, 89.5%). Lymph node metastases of primary tumor were present in 986 (54.7%) patients. KRAS mutations were identified in 266 (14.7%) patients, while 455 (25.2%) patients had wild-type KRAS. A total of 1117 (61.9%) patients had a short DFI of less than 12 months, and the median serum CEA level at the time of CRLM diagnosis was 10.0 ng/mL (IQR: 3.7–41.8). The median number of tumors was 2 (IQR: 1–3), and the median largest tumor size was 3.0 cm (IQR: 1.8–4.5), with a median TBS of 4.0 (IQR: 2.6–5.7). Most patients had a medium TBS ($n = 1081$, 59.9%), while fewer had low ($n = 577$, 32.0%) or high ($n = 146$, 8.1%) TBS. Less than one-half of patients underwent major hepatectomy ($n = 853$, 47.3%), and 551 (30.5%) patients had a positive resection margin (R1 resection). Additionally, 920 (51.0%) patients received adjuvant chemotherapy (Table 1).

TABLE 1 | Clinicopathological characteristics of the analytic cohort.

Characteristics	All patients $n = 1804$
Age, years, median (IQR)	62 [53, 69]
Sex, male, *n* (%)	1089 (60.4)
Year of surgery, 2011–2023, *n* (%)	1344 (74.5)
Preoperative systemic chemotherapy, *n* (%)	600 (33.3)
Location of primary tumor, rectum, *n* (%)	534 (29.6)
T category of primary tumor, *n* (%)	
T1/2/3	1614 (89.5)
T4	190 (10.5)
Lymph node metastases of primary tumor, *n* (%)	986 (54.7)
KRAS, *n* (%)	
Wild	455 (25.2)
Mutated	266 (14.7)
Unknown	1083 (60.0)
Timing of liver metastases, synchronous, *n* (%)	963 (53.4)
Disease-free interval, < 12 months, *n* (%)	1117 (61.9)
CEA, ng/mL, median (IQR)	10.0 [3.7, 41.8]
The extent of hepatectomy, major hepatectomy, *n* (%)	853 (47.3)
Tumor number, median (IQR)	2 [1, 3]
Largest tumor size, cm, median (IQR)	3.0 [1.8, 4.5]
Tumor burden score, median (IQR)	4.0 [2.6, 5.7]
Low, *n* (%)	577 (32.0)
Medium, *n* (%)	1081 (59.9)
High, *n* (%)	146 (8.1)
Margin status, R1, *n* (%)	551 (30.5)
Severe postoperative complications, *n* (%)	174 (9.6)
Adjuvant chemotherapy, *n* (%)	920 (51.0)
Recurrence after liver resection, *n* (%)	1009 (55.9)
Intrahepatic only	443 (24.6)
Extrahepatic recurrence	503 (27.9)
Unknown	61 (3.4)

Abbreviations: CEA, carcinoembryonic antigen; KRAS, Kirsten rat sarcoma oncogene.

3.2 | Hazard Functions of the Entire Cohort

After a median follow-up duration of 29.9 months (IQR: 14.8–51.4), the median RFS was 19.9 months (95% CI: 18.2–22.3) with a 5-year RFS of 30.8% (95% CI: 28.3–33.5). The median OS was 57.7 months (95% CI: 51.7–63.1) with a 5-year OS of 49.2% (95% CI: 46.3–52.4) (Figure 1). The hazard functions for RFS and OS of the entire cohort were evaluated. The RFS hazard curve peaked at 5.9 months (hazard rate: 0.054) and gradually declined with a long tail, indicative of relatively early recurrence. In contrast, the OS hazard curve remained relatively flat, with consistently low hazard rates throughout (Figure 2A). Among the 1,009 patients (55.9%) who experienced a recurrence, 443 patients (24.6%) had intrahepatic recurrence only, while 503 patients (27.9%) experienced extrahepatic recurrence (Table 1). RFS hazard curves, stratified by recurrence site, demonstrated similar recurrence patterns across different sites (Figure 2B).

3.3 | Hazard Functions Stratified by Clinical Factors

Hazard functions for disease recurrence stratified by TBS were examined. For patients with high and medium tumor burden, the RFS hazard curve peaked at 4.9 months (peak hazard rate: 0.060) and 5.8 months (peak hazard rate: 0.054), respectively. In contrast, the RFS hazard curve for patients with low TBS peaked at 7.5 months with the lowest peak hazard rate of 0.047 (Figure 3). RFS hazard functions were then analyzed based on KRAS mutation status. Among patients with KRAS wild-type status, the RFS hazard curve peaked at 5.6 months with a peak hazard rate of 0.052, whereas patients with KRAS mutations exhibited a higher peak hazard rate of 0.063 at a similar recurrence peak of 5.5 months (Figure S1).

Individuals who did not receive adjuvant chemotherapy experienced an earlier recurrence peak at 4.8 months with a higher peak rate of 0.058 versus individuals who received

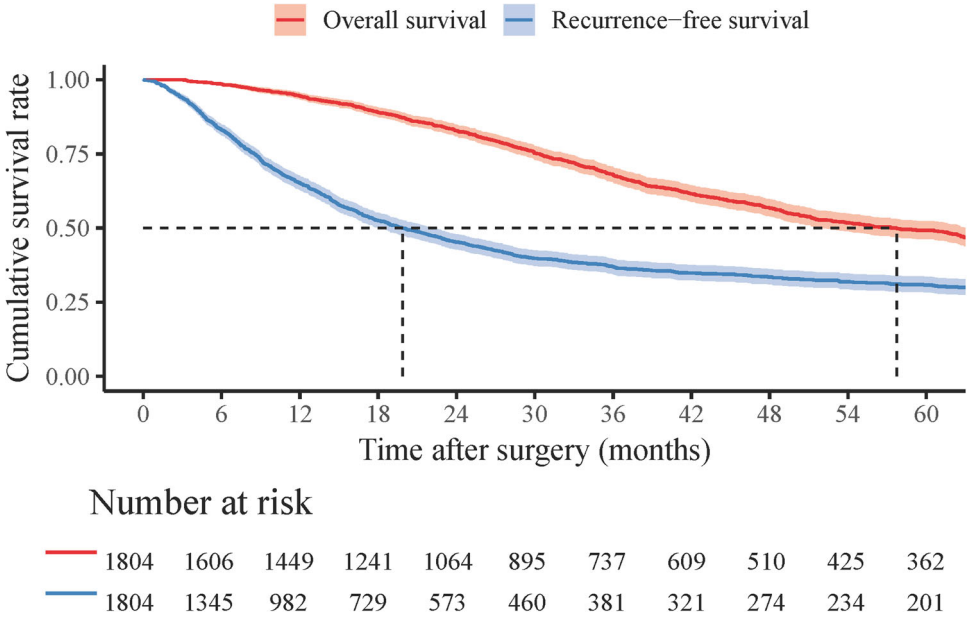

FIGURE 1 | Kaplan-Meier estimates of recurrence-free survival (RFS) and overall survival (OS) in all populations.

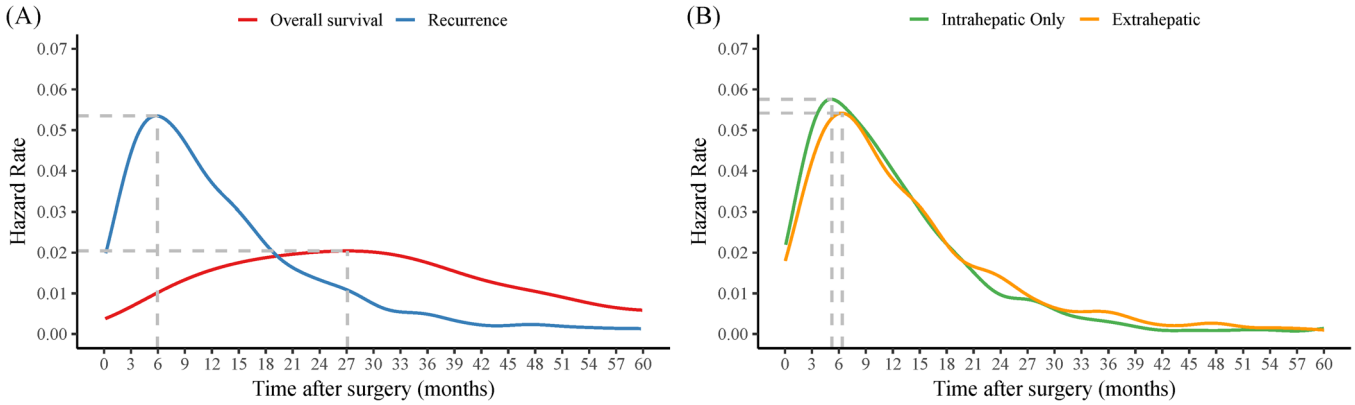

FIGURE 2 | (A) Smoothed hazard functions for recurrence and overall survival in the entire cohort. (B) Smoothed hazard functions for recurrence stratified by recurrence site (intrahepatic only and extrahepatic) among patients with recurrence.

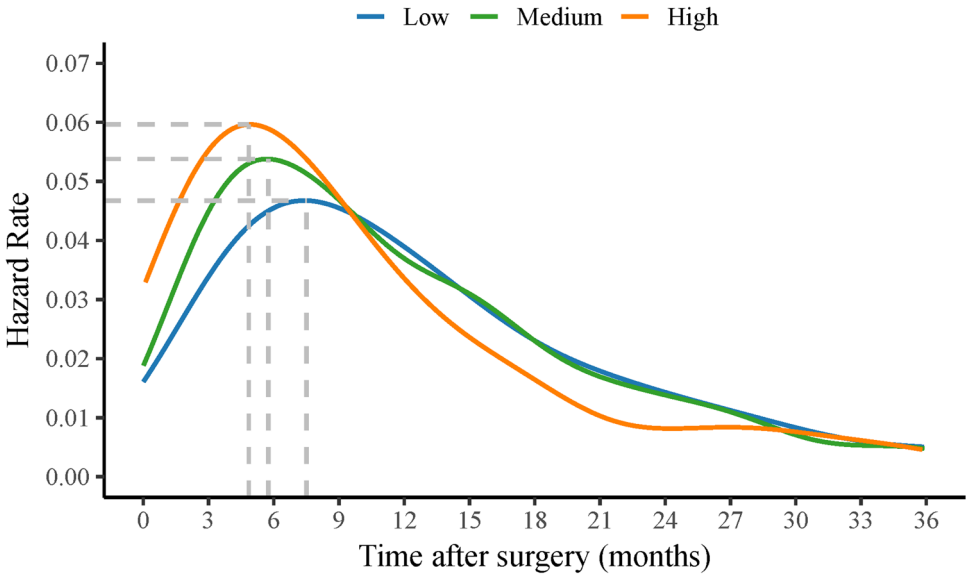

FIGURE 3 | Smoothed hazard functions for recurrence stratified by tumor burden score.

adjuvant chemotherapy (recurrence peak: 7.3 months, peak rate: 0.050). In contrast, the recurrence rate at 12 months postsurgery was lower among patients who did versus did not receive adjuvant chemotherapy (Figure 4). Recurrence hazard patterns were then examined relative to adjuvant chemotherapy stratified according to TBS (Figure S2). Of note, among patients with a high TBS, the hazard rate among individuals who did not receive adjuvant therapy peaked at 3.7 months (peak hazard rate: 0.069) versus 6.5 months (peak hazard rate: 0.054) among individuals who received adjuvant therapy (Figure S2A). Similarly, among patients with an intermediate TBS, the hazard rate in the non-adjuvant cohort peaked at 4.5 months (peak hazard rate: 0.063) compared with a peak at 7.5 months (peak hazard rate: 0.048) among patients who received adjuvant therapy (Figure S2B). In contrast, patients with a low TBS had similar hazard functions regardless of receipt of adjuvant chemotherapy (adjuvant vs. nonadjuvant chemotherapy: peak time: 8.4 vs. 7.1 months, peak hazard rate: 0.049 vs. 0.041) (Figure S2C).

4 | Discussion

Despite hepatic resection being the only curative-intent treatment option for CRLM, recurrence remains common ranging from 50% to 75% after curative-intent resection [3, 4]. To date, improvements in surgical techniques and chemotherapy have broadened treatment options for recurrent CRLM, giving some patients the opportunity for extended survival [5]. For instance, repeat hepatectomy and lung resection can be associated with improved outcomes in a subset of patients with recurrence after initial CRLM resection [4, 24–28]. Consequently, vigilant postoperative surveillance is crucial to ensure early detection of recurrence and to avoid missed opportunities for timely intervention [5, 6]. Although several guidelines recommend postoperative surveillance strategies for patients with stage IV colorectal cancer, including patients with CRLM, no uniform consensus exists on the optimal approach [7–10]. The inconsistency in surveillance recommendations is partly due to an incomplete understanding of the timing and patterns of recurrence risk, including when recurrence is most likely to occur after CRLM surgery. Therefore, the current study was important because we utilized a large, international, multi-institutional database to characterize the dynamic risk of recurrence after curative-intent resection of CRLM. Of note, through the use of hazard functions, the patients who underwent hepatectomy for CRLM peaked at 5.9 months, indicative of relatively early recurrence. In particular, patients with a higher tumor burden, and individuals who did not receive adjuvant chemotherapy had higher and earlier recurrence peaks within 5 months of surgery. In addition, recurrence hazard peak rates and peak timing were analyzed in relation to TBS and the administration of adjuvant chemotherapy. These findings help better understand the recurrence dynamics in CRLM, aiding in prediction, patient counseling, and guiding future management decisions regarding surveillance.

Survival calculated using the Kaplan-Meier analysis denotes the cumulative probability of an event for the entire cohort [29]. In contrast, hazard rates provide information about the risk of an event at a specific time point, making this approach more ideal for determining surveillance intervals [12, 29]. Findings in the current study demonstrated that the RFS curve declined sharply within the first 3 years after surgery but then reached a plateau with a more gradual decline. Hallet et al. reported that 89.1% of recurrences developed within 3 years in a retrospective multi-institutional cohort study of 2320 patients undergoing initial hepatectomy for CRLM [30]. Although major CRC guidelines from NCCN, ESMO, ASCR, and JSCCR have proposed surveillance protocols for resected stage IV CRC, the recommended intervals vary widely from 3 to 12 months [7–10]. Of note, in the current hazard function analysis, the recurrence risk peaked around 6 months after surgery and gradually declined over the next 3 years. These data suggest that intensified surveillance may be particularly important within the first 3 years, particularly around the 6-month mark, to detect early recurrences. In turn, reducing the intensity of surveillance after the third postoperative year is justified based on the data.

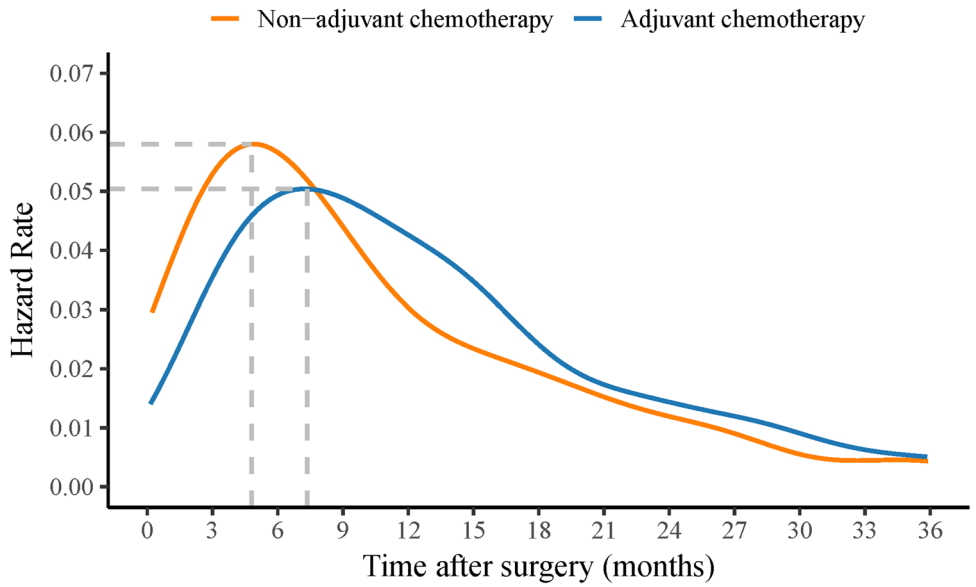

FIGURE 4 | Smoothed hazard functions for recurrence stratified by receipt of adjuvant chemotherapy.

Tumor morphology has been recognized as a key predictor of outcomes in patients with CRLM [19]. Several previous studies have incorporated morphologic characteristics, such as tumor size and number, to develop prediction models of oncological outcomes [31–34]. However, most models have incorporated tumor size and number as categorical variables based on arbitrary cut-off values [31–34]. Assessing CRLM size and number as continuous variables may, however, offer a more accurate reflection of overall tumor burden [35]. Notably, Sasaki and colleagues introduced and validated the "Tumor Burden Score" (TBS), which incorporates both tumor size and number into a composite continuous variable [18]. In fact, TBS outperformed binary tumor morphology categorizations used in other studies [18, 35, 36]. In the current study, individuals with higher tumor burden had earlier and higher recurrence peaks compared with patients who had a low tumor burden. Of note, among patients with high TBS, the recurrence peak was 4.9 months after surgery suggesting the importance of early surveillance after resection of high TBS CRLM. In turn, intensity of surveillance may be tailored relative to TBS, allowing for a more personalized approach and potentially minimizing unnecessary surveillance for patients at lower risk. Similarly, recent studies have highlighted the prognostic importance of KRAS mutation status among patients with CRLM [35, 37]. RAS mutations are detected in roughly 15%–35% of individuals with resectable CRLM and have been linked to worse OS and shorter RFS survival after surgical resection [35]. In the current study, among patients with KRAS wild-type status, the RFS hazard curve peaked at 5.6 months with a peak hazard rate of 0.052. In contrast, patients with KRAS mutations demonstrated a higher peak hazard rate of 0.063, with a similar recurrence peak at 5.5 months. Consistent with these results, a previous single-institution analysis had reported that patients with KRAS mutations had a higher recurrence risk, but the timing of recurrence was comparable [6]. These findings suggest that, while increasing the overall likelihood of recurrence, KRAS mutations may not alter the timing of recurrence.

Another important finding of the current study was the demonstration that the shape of hazard function curves differed among patients who did versus did not receive adjuvant chemotherapy. Although the peak recurrence time of patients who did not receive adjuvant chemotherapy was earlier than individuals who received adjuvant chemotherapy, the hazard rate was higher among individuals treated with adjuvant chemotherapy after around 9 months following surgery. This finding indicated that the primary effect of adjuvant chemotherapy may be to delay relapse. In turn, patients treated with adjuvant chemotherapy tend to relapse somewhat later than patients who did not receive adjuvant chemotherapy. This phenomenon may be one of the reasons why several clinical trials of CRLM adjuvant chemotherapy have demonstrated superiority in RFS but not in OS [38–40]. The current study also demonstrated that patients with medium or high TBS who did not receive adjuvant chemotherapy had an earlier and higher recurrence peak compared with individuals who received adjuvant chemotherapy. In contrast, patients with a low-TBS had similar recurrence patterns regardless of receipt of adjuvant chemotherapy. These results indicated that adjuvant chemotherapy had minimal impact on recurrence among patients in the low-TBS group. Indeed, several investigators have argued that patients who may benefit from adjuvant chemotherapy share very specific characteristics, including larger tumors or a greater number of metastases [41–43]. These findings suggest that TBS can serve as a useful criterion to select patients for adjuvant chemotherapy.

The findings of the current study should be interpreted with several limitations in mind. Although a strength, the multi-institutional nature of the database may have introduced heterogeneity into patient selection and surgical techniques among the participating centers. The criteria for administering postoperative adjuvant chemotherapy, along with variations in treatment duration and regimen, differed across centers and countries. While appropriate surveillance theoretically leads to early recurrence detection, timely therapeutic intervention, and improved prognosis, it remains unclear whether postoperative surveillance is associated with improved OS among patients with CRLM following curative surgery.

In conclusion, the application of the hazard function was used to assess risk, rates, and timing patterns of recurrence following curative-intent surgery for CRLM. The peak recurrence time among CRLM patients who underwent resection was around 6 months, underscoring the importance of early postoperative surveillance. In particular, patients with high TBS had earlier recurrence peaks, highlighting the need for close monitoring within the first 6 months after hepatic resection of CRLM.

Acknowledgments

The authors have nothing to report.

Disclosure

The authors have nothing to report.

Data Availability Statement

The data are not publicly available but can be made available in a deidentified manner upon reasonable request to the authors.

References

1. R. L. Siegel, N. S. Wagle, A. Cercek, R. A. Smith, and A. Jemal, "Colorectal Cancer Statistics, 2023," *CA: A Cancer Journal for Clinicians* 73 (2023): 233–254.

2. Y. Qian, Y. Li, and Y. Fu, "A Commentary on "Prognostic Value of Neutrophil-to-Lymphocyte Ratio in Colorectal Cancer Liver Metastasis: A Meta-Analysis of Results From Multivariate Analysis," *International Journal of Surgery (London, England)* 109 (2023): 2823–2824.

3. Y. Kitano, Y. Ono, K. Kobayashi, et al., "Neoadjuvant Chemotherapy for Borderline Resectable Colorectal Cancer Liver Metastases: A Single-Institution Retrospective Study," *HPB: The Official Journal of the International Hepato Pancreato Biliary Association* 26 (2024): 282–290.

4. Y. Endo, B. O. Rueda, S. Woldesenbet, et al., "The Impact of Recurrence Timing and Tumor Burden Score on Overall Survival Among Patients Undergoing Repeat Hepatectomy for Colorectal Liver Metastases," *Journal of Surgical Oncology* 128 (2023): 560–568.

5. J. Martin, A. Petrillo, E. C. Smyth, et al., "Colorectal Liver Metastases: Current Management and Future Perspectives," *World Journal of Clinical Oncology* 11 (2020): 761–808.

6. Y. Kawaguchi, S. Kopetz, H. A. Lillemoe, et al., "A New Surveillance Algorithm After Resection of Colorectal Liver Metastases Based on

Changes in Recurrence Risk and RAS Mutation Status," *Journal of the National Comprehensive Cancer Network* 18 (2020): 1500–1508.

7. A. Cervantes, R. Adam, S. Roselló, et al., "Metastatic Colorectal Cancer: ESMO Clinical Practice Guideline for Diagnosis, Treatment and Follow-Up," *Annals of Oncology* 34 (2023): 10–32.

8. National Comprehensive Cancer Network (2024) NCCN Clinical Practice Guidelines in Oncology Colon Cancer, version 5, 2024.

9. Y. Hashiguchi, K. Muro, Y. Saito, et al., "Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2019 for the Treatment of Colorectal Cancer," *International Journal of Clinical Oncology* 25 (2020): 1–42.

10. S. R. Steele, G. J. Chang, S. Hendren, et al., "Practice Guideline for the Surveillance of Patients After Curative Treatment of Colon and Rectal Cancer," *Diseases of the Colon & Rectum* 58 (2015): 713–725.

11. H. A. Lima, L. Alaimo, Z. J. Brown, et al., "Application of Hazard Functions to Investigate Recurrence After Curative-Intent Resection for Hepatocellular Carcinoma," *HPB: The Official Journal of the International Hepato Pancreato Biliary Association* 25 (2023): 260–268.

12. K. R. Hess and V. A. Levin, "Getting More Out of Survival Data by Using the Hazard Function," *Clinical Cancer Research* 20 (2014): 1404–1409.

13. M. Colleoni, Z. Sun, K. N. Price, et al., "Annual Hazard Rates of Recurrence for Breast Cancer During 24 Years of Follow-Up: Results From the International Breast Cancer Study Group Trials I to V," *Journal of Clinical Oncology* 34 (2016): 927–935.

14. N. Tomita, K. Kunieda, A. Maeda, et al., "Phase III Randomised Trial Comparing 6 vs. 12-Month of Capecitabine as Adjuvant Chemotherapy for Patients With Stage III Colon Cancer: Final Results of the JFMC37-0801 Study," *British Journal of Cancer* 120 (2019): 689–696.

15. L. Alaimo, Z. Moazzam, Z. J. Brown, et al., "Application of Hazard Function to Investigate Recurrence of Intrahepatic Cholangiocarcinoma After Curative-Intent Liver Resection: A Novel Approach to Characterize Recurrence," *Annals of Surgical Oncology* 30 (2023): 1340–1349.

16. A. Moro, R. Mehta, D. I. Tsilimigras, et al., "Prognostic Factors Differ According to KRAS Mutational Status: A Classification and Regression Tree Model to Define Prognostic Groups After Hepatectomy for Colorectal Liver Metastasis," *Surgery* 168 (2020): 497–503.

17. M. B. Amin, F. L. Greene, S. B. Edge, et al., "The Eighth Edition AJCC Cancer Staging Manual: Continuing to Build a Bridge From a Population-Based to a More "Personalized" Approach to Cancer Staging," *CA: A Cancer Journal for Clinicians* 67 (2017): 93–99.

18. K. Sasaki, D. Morioka, S. Conci, et al., "The Tumor Burden Score: A New "Metro-Ticket" Prognostic Tool for Colorectal Liver Metastases Based on Tumor Size and Number of Tumors," *Annals of Surgery* 267 (2018): 132–141.

19. Y. Fong, J. Fortner, R. L. Sun, M. F. Brennan, and L. H. Blumgart, "Clinical Score for Predicting Recurrence After Hepatic Resection for Metastatic Colorectal Cancer: Analysis of 1001 Consecutive Cases," *Annals of Surgery* 230 (1999): 309–318.

20. M. Nagino, R. DeMatteo, H. Lang, et al., "Proposal of a New Comprehensive Notation for Hepatectomy: The "New World" Terminology," *Annals of Surgery* 274 (2021): 1–3.

21. D. Dindo, N. Demartines, and P. A. Clavien, "Classification of Surgical Complications: A New Proposal With Evaluation in a Cohort of 6336 Patients and Results of a Survey," *Annals of Surgery* 240 (2004): 205–213.

22. J. Kawashima, O. P. Chatzipanagiotou, D. I. Tsilimigras, et al., "Preoperative and Postoperative Predictive Models of Early Recurrence for Colorectal Liver Metastases Following Chemotherapy and Curative-Intent One-Stage Hepatectomy," *European Journal of Surgical Oncology* 50 (2024): 108532.

23. H. G. Muller and J. L. Wang, "Hazard Rate Estimation Under Random Censoring With Varying Kernels and Bandwidths," *Biometrics* 50 (1994): 61–76.

24. W. Liu, J. M. Liu, K. Wang, H. W. Wang, and B. C. Xing, "Recurrent Colorectal Liver Metastasis Patients Could Benefit From Repeat Hepatic Resection," *BMC Surgery* 21 (2021): 327.

25. L. X. Luo, Z. Y. Yu, J. W. Huang, and H. Wu, "Selecting Patients for a Second Hepatectomy for Colorectal Metastases," *European Journal of Surgical Oncology (EJSO)* 40 (2014): 1036–1048.

26. S. J. Wang, X. Y. Si, Z. B. Cai, and Y. M. Zhou, "Survival After Repeat Hepatectomy for Recurrent Colorectal Liver Metastasis: A Review and Meta-Analysis of Prognostic Factors," *Hepatobiliary & Pancreatic Diseases International* 18 (2019): 313–320.

27. M. Gonzalez, J. H. Robert, N. Halkic, et al., "Survival After Lung Metastasectomy in Colorectal Cancer Patients With Previously Resected Liver Metastases," *World Journal of Surgery* 36 (2012): 386–391.

28. S. Salah, F. Ardissone, M. Gonzalez, et al., "Pulmonary Metastasectomy in Colorectal Cancer Patients With Previously Resected Liver Metastasis: Pooled Analysis," *Annals of Surgical Oncology* 22 (2015): 1844–1850.

29. Y. Kudose, D. Shida, Y. Ahiko, et al., "Evaluation of Recurrence Risk After Curative Resection for Patients With Stage I to III Colorectal Cancer Using the Hazard Function: Retrospective Analysis of a Single-Institution Large Cohort," *Annals of Surgery* 275 (2022): 727–734.

30. J. Hallet, A. Sa Cunha, R. Adam, et al., "Factors Influencing Recurrence Following Initial Hepatectomy for Colorectal Liver Metastases," *British Journal of Surgery* 103 (2016): 1366–1376.

31. D. Gomez and I. C. Cameron, "Prognostic Scores for Colorectal Liver Metastasis: Clinically Important or an Academic Exercise," *HPB: The Official Journal of the International Hepato Pancreato Biliary Association* 12 (2010): 227–238.

32. T. M. Pawlik, E. K. Abdalla, L. M. Ellis, J. N. Vauthey, and S. A. Curley, "Debunking Dogma: Surgery for Four or More Colorectal Liver Metastases is Justified," *Journal of Gastrointestinal Surgery* 10 (2006): 240–248.

33. M. W. Kattan, M. Gönen, W. R. Jarnagin, et al., "A Nomogram for Predicting Disease-Specific Survival After Hepatic Resection for Metastatic Colorectal Cancer," *Annals of Surgery* 247 (2008): 282–287.

34. Y. Kanemitsu and T. Kato, "Prognostic Models for Predicting Death After Hepatectomy in Individuals With Hepatic Metastases From Colorectal Cancer," *World Journal of Surgery* 32 (2008): 1097–1107.

35. D. I. Tsilimigras, M. J. Hyer, F. Bagante, et al., "Resection of Colorectal Liver Metastasis: Prognostic Impact of Tumor Burden vs Kras Mutational Status," *Journal of the American College of Surgeons* 232 (2021): 590–598.

36. Y. Endo, L. Alaimo, Z. Moazzam, et al., "Postoperative Morbidity After Simultaneous Versus Staged Resection of Synchronous Colorectal Liver Metastases: Impact of Hepatic Tumor Burden," *Surgery* 175 (2024): 432–440.

37. J. N. Vauthey, G. Zimmitti, S. E. Kopetz, et al., "RAS Mutation Status Predicts Survival and Patterns of Recurrence in Patients Undergoing Hepatectomy for Colorectal Liver Metastases," *Annals of Surgery* 258 (2013): 619–627.

38. Y. Kanemitsu, Y. Shimizu, J. Mizusawa, et al., "Hepatectomy Followed by mFOLFOX6 Versus Hepatectomy Alone for Liver-Only Metastatic Colorectal Cancer (JCOG0603): A Phase II or III Randomized Controlled Trial," *Journal of Clinical Oncology* 39 (2021): 3789–3799.

39. G. Portier, D. Elias, O. Bouche, et al., "Multicenter Randomized Trial of Adjuvant Fluorouracil and Folinic Acid Compared With Surgery Alone After Resection of Colorectal Liver Metastases: FFCD ACHBTH AURC 9002 Trial," *Journal of Clinical Oncology* 24 (2006): 4976–4982.

40. K. Hasegawa, A. Saiura, T. Takayama, et al., "Adjuvant Oral Uracil-Tegafur With Leucovorin for Colorectal Cancer Liver Metastases: A Randomized Controlled Trial," *PLoS One* 11 (2016): e0162400.

41. N. N. Rahbari, C. Reissfelder, H. Schulze-Bergkamen, et al., "Adjuvant Therapy After Resection of Colorectal Liver Metastases: The Predictive Value of the MSKCC Clinical Risk Score in the Era of Modern Chemotherapy," *BMC Cancer* 14 (2014): 174.

42. K. Takeda, Y. Kikuchi, Y. Sawada, et al., "Efficacy of Adjuvant Chemotherapy Following Curative Resection of Colorectal Cancer Liver Metastases," *Anticancer Research* 42 (2022): 5497–5505.

43. Y. Endo, L. Alaimo, Z. Moazzam, et al., "Optimal Policy Tree to Assist in Adjuvant Therapy Decision-Making After Resection of Colorectal Liver Metastases," *Surgery* 175 (2024): 645–653.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.