Recurrence-free survival versus overall survival as a primary endpoint for studies of resected colorectal liver metastasis: a retrospective study and meta-analysis

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Summary

Background Recurrence-free survival has been used as a surrogate endpoint for overall survival in trials involving patients with resected colorectal liver metastases. We aimed to assess the correlation between recurrence-free survival and overall survival after resection of colorectal liver metastases to determine the adequacy of this surrogate endpoint.

Methods In this retrospective study and meta-analysis, we compiled an institutional cohort of consecutive patients who had complete resection of colorectal liver metastases from the Memorial Sloan Kettering Cancer Center (New York, NY, USA) prospective database. Patients were eligible for inclusion if they were aged 18 years or older, and underwent hepatectomy, with or without operative ablation, between Jan 1, 1991, and April 30, 2019. We estimated overall survival and recurrence-free survival probabilities at various timepoints using the Kaplan-Meier method, and we assessed pairwise associations between these endpoints using Spearman's rank correlation. We also did a meta-analysis of adjuvant phase 3 clinical trials for colorectal liver metastases to assess the correlation between hazard ratios (HRs) for recurrence-free survival and overall survival. We searched MEDLINE for articles of phase 3 randomised controlled trials analysing adjuvant treatment strategies for resected colorectal metastases from database inception to Jan 1, 2022. The titles and abstracts of identified studies were screened before full-text screening and summary data were either recalculated or extracted manually from the published Kaplan-Meier curves (depending on data availability).

Findings Data were available for 3299 patients in the institutional database, of whom 2983 were eligible for inclusion in our cohort. Median follow-up was 8·4 years (95% CI 7·9–9·1) , during which time there were 1995 (67%) disease recurrences and 1684 (56%) deaths. Median recurrence-free survival was 1·3 years (95% CI 1·3–1·4) and median overall survival was 5·2 years (95% CI 5·0–5·5). 1428 (85%) of 1684 deaths were preceded by recurrence, and median time from recurrence to death was 2·0 years (IQR 1·0–3·4). Pairwise correlations between recurrence-free survival and overall survival were low to moderate, with a correlation estimate ranging from 0·30 (SD 0·17) to 0·56 (0·13). In the meta-analysis of adjuvant clinical trials, the Spearman's correlation coefficient between recurrence-free survival HR and overall survival HR was r=0·20 (p=0·71).

Interpretation We found a minimal correlation between recurrence-free survival and overall survival after resection of colorectal liver metastases. Recurrence-free survival is an inadequate surrogate endpoint for overall survival in this disease setting.

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Introduction

A surrogate endpoint is a substitute of a primary endpoint expected to predict the clinical benefit, harm, or absence of an intervention.[1] In oncology, recurrence-free survival is widely used in trial design as a surrogate endpoint for overall survival.[2–4] Although overall survival is usually considered the most clinically meaningful endpoint, a surrogate endpoint such as recurrence-free survival typically requires shorter follow-up time and can hasten trial completion, improving the feasibility, efficiency, cost, and delivery of new therapeutics.

For the post-surgical management of patients with colorectal liver metastases, all randomised controlled trials to date assessing the clinical value of adjuvant chemotherapy[5–8] have used recurrence-free survival as the primary endpoint. However, recurrence-free survival has not been validated as a surrogate endpoint for overall survival in this setting. A previous meta-analysis included both perioperative and adjuvant chemotherapy trials, thus introducing treatment heterogeneity to the analysis, and included only two published randomised controlled trials of adjuvant chemotherapy.[9] Although recurrence-free survival and overall survival are highly correlated in

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Research in context

Evidence before this study

Recurrence-free survival and overall survival have been shown to be highly correlated in patients with non-metastatic colorectal treated in phase 3 adjuvant trials. Such data have been used to justify the use of recurrence-free survival as a surrogate endpoint for overall survival in trials involving patients with resected colorectal liver metastases. The adequacy of recurrence-free survival as a surrogate endpoint for this clinical context needs further validation. A previous meta-analysis included both perioperative and adjuvant chemotherapy trials, thus introducing treatment heterogeneity to the analysis, and included only two published randomised controlled trials of adjuvant chemotherapy.

Added value of this study

To our knowledge, this is the largest comparative analysis of recurrence-free versus overall survival in patients with resected colorectal liver metastases after curative-intent hepatectomy. In an institutional series of patients who underwent complete resection of colorectal liver metastases, pairwise correlations between recurrence-free survival and overall survival probabilities were low to moderate. Similarly, in a meta-analysis of six phase 3 randomised clinical trials of adjuvant chemotherapy in this disease context, recurrence-free survival was found to be a poor surrogate for overall survival.

Implications of all the available evidence

After resection of colorectal liver metastases, there is minimal correlation between recurrence-free survival and overall survival. Recurrence-free survival is an inadequate surrogate for overall survival in this disease context and novel trial endpoints are needed if overall survival is not feasible.

patients with non-metastatic colorectal cancer treated in phase 3 adjuvant trials,[3,4] whether or not this correlation persists in patients with resected colorectal liver metastases has not yet been assessed. Because recurrence after resection of colorectal liver metastases can be effectively salvaged with additional locoregional therapies and systemic chemotherapy,[10] and considering that longer survival after recurrence reduces the association between recurrence-free survival and overall survival,[11] we hypothesised that recurrence-free survival might not be a reliable surrogate endpoint for overall survival in this patient population. Ongoing clinical trials for the management of patients after resection of colorectal liver metastases are using recurrence-free survival as a primary endpoint;[12] therefore, establishing the appropriateness of this surrogate endpoint for overall survival is urgently needed.

We used a robust, prospectively collected, single-institution database of consecutive patients who underwent complete resection of colorectal liver metastases and for whom recurrence-free survival and overall survival data was available to assess the correlation between these two endpoints at the patient level.[13] Subsequently, we assessed the correlation of these endpoints at the trial level[13] via a meta-analysis of all adjuvant randomised controlled trials for the management of patients after the resection of colorectal liver metastases.

Methods

Study design and participants

For this retrospective study, we identified consecutive patients who underwent complete resection of colorectal liver metastases as part of their standard-of-care management between Jan 1, 1991, and April 30, 2019, from the prospectively collected institutional database at the Memorial Sloan Kettering Cancer Center (MSKCC), a cancer centre in New York, NY, USA. Patients eligible for our analyses were aged 18 years or older and underwent complete resection of colorectal liver metastases, with or without operative ablation. Patients without overall survival or recurrence-free survival data were excluded. Major hepatectomy was defined as resection of at least three contiguous segments. Patients who were not disease-free at the time of hepatic resection (ie, non-treated primary cancer, unresected extrahepatic disease, or gross [R2] residual hepatic disease) were excluded. Additionally, patients were excluded if they received operative ablation without concomitant resection or if they died within 90 days of their surgery. Patients with unresectable colorectal liver metastases at presentation were included if they eventually had a complete resection after downstaging. For patients who received systemic therapy, modern chemotherapy was defined as any regimen containing oxaliplatin, irinotecan, or targeted therapy.

We began collecting patient information from this database after institutional review board approval (reference #16-1588). Individual patient consent was waived because there was minimal risk to participants.

Search strategy and selection criteria

For the meta-analysis portion of this work, we searched MEDLINE for articles reporting on phase 3 randomised controlled trials of adjuvant treatment strategies for resected colorectal liver metastases published from database inception to Jan 1, 2022, using a combination of keywords and Medical Subject Headings terms related to the terms "adjuvant", "colorectal", "liver metastases", and "randomized controlled trial". Two authors (BLE and MID) independently filtered the articles by screening the

titles and abstracts, followed by a full-text review. Discrepancies were resolved by consensus between BLE and MID. We excluded articles that reported non-randomised studies, phase 1 or 2 trials, unpublished studies, or studies not written or translated into English. Additionally, trials using perioperative chemotherapy regimens[14,15] were excluded, because at the time of randomisation the patient was not disease-free and thus the study endpoint could be considered to be a compound of progression-free and recurrence-free survival.

This meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for its synthesis.[16] The meta-analysis was not prospectively registered.

Data analysis

Overall survival was calculated from the date of liver resection to the date of death from any cause. Patients who were alive at last follow-up were censored at the date of last follow-up. Recurrence-free survival was calculated from the date of liver resection to the date disease recurrence was detected or the date of death of any cause. Patients without recurrence and alive at last follow-up were censored at the date of last follow-up. If recurrence status was not known at the time of death (eg, extracted from social security death index), the patient was censored at last follow-up. Postoperative surveillance for disease recurrence included: medical history and physical examination, serum carcinoembryonic antigen (CEA) concentration, and CT scan of the chest, abdomen, and pelvis at least twice annually for at least 5 years, in accordance with National Comprehensive Cancer Network guidelines. Scans were either done centrally or locally, and centralised review of cross-sectional imaging was done at MSKCC.

For the subset of patients who had recurrence, we categorised recurrence-free survival into half-year intervals for the first year, 1-year intervals between years 1 and 5, and then 5 years or longer (ie, 0 to <0·5, 0·5 to <1, 1 to <2, 2 to <3, 3 to <4, 4 to <5, and ≥5 years). For this subset of patients, survival after recurrence was calculated as the time from recurrence to death or last follow-up. For patients who underwent two-stage hepatectomy, survival analyses were initiated from the date of second liver resection, when the patient was rendered free of disease.

For our meta-analysis, we recalculated the Kaplan-Meier curves, along with the risk tables, from patient-level data when available.[5,6,17] When authors of eligible studies were unavailable to provide primary data, we extracted summary data (treatment group, overall survival probabilities along the curve and the corresponding time points, and recurrence-free survival probabilities along the curve and corresponding times points) from the published Kaplan-Meier curves using DigitizeIT. Duplicate data were not encountered. We did not do a formal assessment of heterogeneity among studies because of the small number of included studies and the potential bias of the heterogeneity statistic.[18]

Statistical analysis

For our retrospective study, we calculated median follow-up (95% CI) using the reverse Kaplan-Meier method. We estimated overall survival and recurrence-free survival probabilities using the Kaplan-Meier method. Overall survival and recurrence-free survival times were visually compared using a scatterplot stratified by vital status of patients at last data updated (Sept 15, 2019). For each set of pairwise timepoints, we calculated Spearman's rank correlations between the respective probabilities. To mimic previous analyses of independent trials,[2–4] we randomly split our single-institution database of patients treated with standard-of-care surgery into 30 groups of approximately 100 patients per group to calculate a correlation matrix of overall survival and recurrence-free survival at varying timepoints. To account for the variability in randomly assigning patients into subgroups, we repeated the splitting process 1000 times and we summarised the resulting 1000 correlation matrices using mean (SD) and violin plots. For each of the 1000 splits, we estimated the overall survival and recurrence-free survival probabilities of each group in 1-year increments (between 2 to 10 years for overall survival, and 1 to 5 years for recurrence-free survival). The pairwise timepoint of 3-year recurrence-free survival and 5-year overall survival was a pair of interest because of its established role as a surrogate endpoint in non-metastatic colorectal cancer trials.[3] Such analyses were repeated in several prespecified subsets, which were: early treatment era (1991–2000), contemporary treatment era (2001–19), left-sided primary tumour, right sided primary tumour, and after excluding patients who received hepatic artery infusion of floxuridine or patients with resected extrahepatic disease.

For patients who had a recurrence, we assessed the rate of salvage surgery as a clinically relevant proxy for severity.[19] To examine whether recurrence-free survival affects the subsequent survival after recurrence, we analysed recurrence-free survival versus survival after recurrence using a scatterplot. We calculated the Kaplan-Meier estimate of survival after recurrence, stratified by recurrence-free survival categories.

For the meta-analysis, we estimated the overall survival and recurrence-free survival hazard ratios (HRs) for treatment group versus control group using the methods developed by Tierney and colleagues.[20] The 5-year overall survival and 3-year recurrence-free survival estimates were estimated either from the recalculated Kaplan-Meier curves when patient-level data were available, or from the extracted data from the DigitizeIT software. We assessed the associations among the pairs of recurrence-free survival and overall survival HRs and the pairs of 3-year recurrence-free survival and 5-year overall survival estimates using

For the **DigitizeIT website** see https://www.digitizeit.xyz/

	Patients (n=2983)
Demographics	
Age, years	60 (50–68)
Sex	
Male	1687 (57%)
Female	1296 (43%)
Race	
White	2248 (75%)
Black	136 (5%)
Asian or Pacific Islander	110 (4%)
Other	30 (1%)
Missing	459 (15%)
Primary tumour characteristics	
Primary tumour location	
Right colon	821 (28%)
Left colon	1374 (46%)
Rectum	688 (23%)
Missing	100 (3%)
T classification	
T1–T2	377 (13%)
T3	1928 (65%)
T4	392 (13%)
Missing	286 (10%)
N classification	
Negative	1097 (37%)
Positive	1857 (62%)
Missing	29 (1%)
Liver metastases characteristics	
Number of lesions	
Median	2 (1–3)
1	1280 (43%)
2	601 (20%)
3	388 (13%)
4	238 (8%)
5–9	353 (12%)
≥10	62 (2%)
Missing	61 (2%)
Size of largest tumour, cm	
Median	3 (2–5)
<5	2147 (72%)
≥5	769 (26%)
Missing	67 (2%)
Synchronous metastases	
Yes	1664 (56%)
No	1318 (4%)
Missing	1 (<1%)
Less than 1 year from diagnosis of colorectal cancer until detection of colorectal liver metastasis	
Yes	1537 (52%)
No	1432 (48%)
Missing	14 (<1%)

(Table 1 continues in next column)

	Patients (n=2983)
(Continued from previous column)	
Carcinoembryonic antigen >200 ng/mL	
Yes	226 (8%)
No	2345 (79%)
Missing	412 (14%)
Clinical risk score	
Low (0–2)	1779 (60%)
High (3–5)	1204 (40%)
Surgical management	
Extent of hepatectomy	
Minor	1416 (47%)
Major	1348 (45%)
Missing	219 (7%)
Concurrent ablation	
Yes	387 (13%)
No	2595 (87%)
Missing	1 (<1%)
Two-stage hepatectomy	
Yes	107 (4%)
No	2875 (96%)
Missing	1 (<1%)
Hepatic arterial infusion pump	
Yes	850 (28%)
No	2129 (71%)
Missing	4 (<1%)
R1 margin	
Yes	344 (12%)
No	2620 (88%)
Missing	19 (1%)
Resection of extrahepatic disease	
Yes	352 (12%)
No	2631 (88%)
Missing	0
Systemic therapy use	
Any systemic therapy	2724 (91%)
Modern systemic therapy*	1966 (66%)
None	212 (7%)
Missing	47 (2%)

Data are median (IQR) or n (%). R1=microscopic margin involvement. *Missing data for 289 patients.

Table 1: **Clinical and demographic characteristics of resected colorectal liver metastasis cohort**

Spearman's correlation coefficients and weighted linear regression, with weights equal to the sample size of the trial from which the data were derived.

Descriptive statistics are presented as frequencies for categorical variables and median (IQR) for continuous variables. We used Pearson's χ^2 test or Fisher's exact test to analyse categorical variables and the Wilcoxon rank-sum test to analyse continuous variables.

In post-hoc analysis, we assessed temporal trends in mean clinical risk score, rate of re-resection for

recurrence, and use of CT versus MRI during the study period.

p values of less than 0·05 were determined to be significant. We did all analyses using R software (version 4.0.1).

Role of the funding source

The funder had no role in the study design, conduct of the study, data collection, data management, data analysis, data interpretation, or writing of the report.

Results

Data were available for 3299 patients in the MSKCC prospective liver resection database, of whom 243 were excluded for either having intact primary tumour (n=51), unresected extrahepatic disease (n=139), or liver metastasis not fully resected (n=184), or a combination of these variables, yielding a total of 3056 patients who underwent curative-intent hepatectomy for colorectal liver metastases during the study period. After exclusion of two patients without vital status and 71 patients who died within 90 days of surgery, the final study cohort comprised 2983 patients. 40 patients had unknown recurrence status at the time of death (eg, extracted from social security death index) and were censored at last follow-up. Patient demographic and clinical characteristics are summarised in table 1. 1416 (47%) patients underwent minor hepatectomy, 234 (17%) with ablation and 1182 (83%) without ablation, and 1348 (45%) underwent major hepatectomy, 96 (7%) with ablation and 1252 (93%) without ablation. Resection was combined with placement of a hepatic arterial infusion pump in 850 (28%) patients and two-stage hepatectomy was rarely used (107 [4%] patients). 352 (12%) patients underwent complete resection of extrahepatic disease, which included lymph nodes (109 [31%] of 352), lung (98 [28%]), peritoneal metastases (45 [13%]), local recurrence (36 [10%]), and others (84 [24%]; appendix pp 2–3).

The median follow-up was 8·4 years (95% CI 7·9–9·1). There were 1995 (67%) disease recurrences and 1684 (56%) deaths. Median recurrence-free survival was 1·3 years (95% CI 1·3–1·4) and median overall survival was 5·2 years (95% CI 5·0–5·5). 1428 (85%) of 1684 deaths were preceded by recurrence, and median time from recurrence to death was 2·0 years (range 0·0–23·4; IQR 1·0–3·4). 5-year overall survival probability was 51% (95% CI 50–54) and 10-year overall survival probability was 33% (30–35). Repeat resection or ablation of any recurrence was done in 864 patients (29% of the overall cohort; 43% of those who recurred). Specific management of recurrent disease is summarised in the appendix (p 4). Patients who had a recurrence within 1 year were less likely to undergo repeat resection, ablation, or both, than were those who had a recurrence more than 1 year after resection (410 [38%] of 1091 *vs* 454 [50%] of 904; p<0·0001).

The correlation between recurrence-free survival and overall survival event times for patients who had a recurrence is shown in figure 1. The scatterplot suggests low correlation between time to recurrence and overall survival, as shown by the high variability in survival time regardless of the time to recurrence. Pairwise Spearman's rank correlation coefficients between recurrence-free survival and overall survival probabilities after resection are shown in table 2. At the estimated pairs of timepoints, the mean Spearman's rank correlation coefficient between the endpoints ranged from 0·30 (SD 0·17) to 0·56 (0·13), suggesting low-to-moderate correlation. For the comparison between 3-year recurrence-free survival and 5-year overall survival, which is highly correlated in patients with non-metastatic colorectal cancer, the Spearman's rank correlation was 0·49 (SD 0·15).

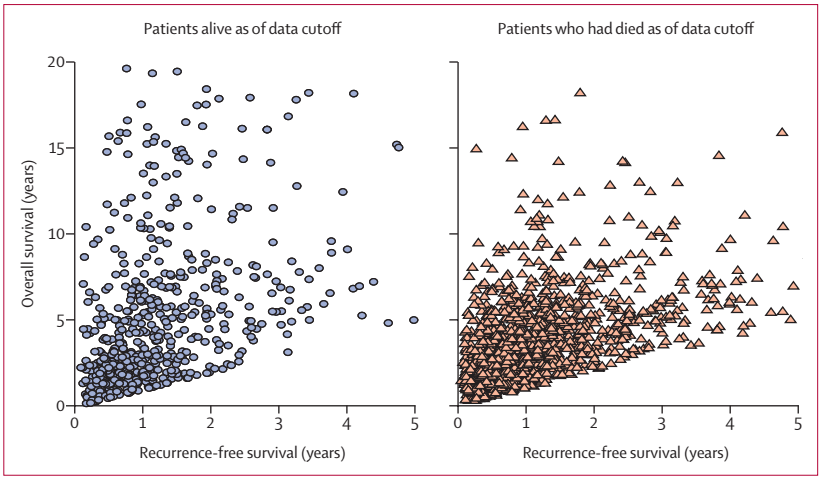


Figure 1: **Scatterplot of overall survival versus recurrence-free survival for patients with recurrence (n=1995) in the resected colorectal liver metastasis cohort**

Data are shown by vital status at data cutoff (Sept 15, 2019). Only data for recurrence-free survival of 5 years or less and overall survival of 20 years or less are shown.

We found high variability in the estimated correlations from the 1000 runs for the Spearman's rank correlation coefficients (appendix p 5), indicating high uncertainty in the mean correlation estimates and suggesting that recurrence-free survival was not only a weak correlate of overall survival, but also an unreliable one.

To interrogate the potential effect of different treatment eras, in prespecified analyses, the study cohort was divided into an early era (1991–2000) and a contemporary era (2001–19),[21] with 833 (28%) patients in the early era and 2150 (72%) in the contemporary era. We found similar recurrence-free survival between the early and contemporary eras, and improved overall survival in the contemporary era compared with the early era (appendix p 6). At the estimated pairs of timepoints for each era, the mean Spearman's rank correlation coefficient between the endpoints ranged from 0·29 (SD 0·35) to 0·66 (0·24) for the early era and from 0·31 (0·21) to 0·49 (0·19) for the contemporary era, suggesting low-to-moderate correlation (appendix p 7). In post-hoc analyses, we found no temporal trends in mean clinical risk score, rate of re-resection for

See Online for appendix

	2-year overall survival	3-year overall survival	4-year overall survival	5-year overall survival	6-year overall survival	7-year overall survival	8-year overall survival	9-year overall survival	10-year overall survival
1-year recurrence-free survival	0·37 (0·16)	0·42 (0·16)	0·42 (0·16)	0·40 (0·16)	0·38 (0·17)	0·37 (0·16)	0·33 (0·17)	0·31 (0·17)	0·30 (0·17)
2-year recurrence-free survival	..	0·40 (0·16)	0·44 (0·16)	0·46 (0·16)	0·47 (0·16)	0·46 (0·16)	0·44 (0·16)	0·42 (0·16)	0·40 (0·16)
3-year recurrence-free survival	..	..	0·44 (0·16)	0·49 (0·15)	0·51 (0·15)	0·51 (0·15)	0·49 (0·15)	0·48 (0·15)	0·46 (0·15)
4-year recurrence-free survival	..	..	..	0·49 (0·15)	0·52 (0·14)	0·54 (0·14)	0·52 (0·14)	0·52 (0·14)	0·51 (0·14)
5-year recurrence-free survival	..	..	..	..	0·54 (0·13)	0·56 (0·13)	0·55 (0·13)	0·55 (0·13)	0·54 (0·14)

Data are mean (SD). Estimates are calculated from 1000 random sample runs, and at each sample run, correlations of overall survival and recurrence-free survival probabilities at the specified time pairs were estimated for 30 randomly assigned groups.

Table 2: **Pairwise Spearman's correlation estimates of overall survival versus recurrence-free survival in the resected colorectal liver metastasis cohort**

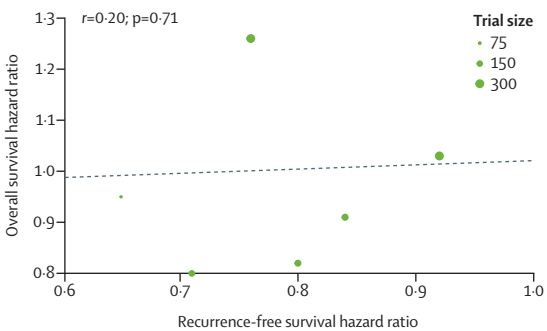


Figure 2: **Weighted linear regression fit of overall survival versus recurrence-free survival hazard ratios**
Data are shown for patients with resected colorectal liver metastasis, by trial (n=6). The horizontal dashed line shows the weighted linear regression fit. The key of trial sizes is for reference only; a summary of each study, including participant size, is shown in the appendix (p 15).

recurrence, or use of CT and MRIs during the study period (appendix pp 8–10).

The rate of salvage surgery (a clinically relevant proxy for severity[19]) did not vary by treatment era (181 [32%] of 569 patients who had a recurrence during the early era *vs* 432 [30%] of 1426 during the contemporary eta; p=0·51).

In additional prespecified subset analyses in which patients receiving hepatic arterial infusion of floxuridine (appendix p 11) or with extrahepatic disease (appendix p 12) were excluded, the Spearman's rank correlations between recurrence-free survival and overall survival for the various sets of pairwise timepoints remained low to moderate. Similarly, the measured correlations between recurrence-free survival and overall survival remained low for the subset of patients with left-sided as well as right-sided primary tumours (appendix p 13).

To assess the degree of correlation between recurrence-free survival and overall survival in phase 3 randomised controlled trials for resected colorectal liver metastases, we did a literature search of the MEDLINE database. The initial search yielded 142 articles. After screening, six studies (published between Dec 30, 1999, and Dec 1, 2021) were included in the meta-analysis (appendix p 14).[5–8,17,22] Only phase 3 randomised trials for the study of adjuvant treatment regimens (and not perioperative sequencing regimens) were included to avoid introducing treatment heterogeneity to analysis. A summary of the studies included in the meta-analysis is in the appendix (p 15).

In our meta-analysis, we first assessed association between overall survival and recurrence-free survival HRs across the six trials of adjuvant chemotherapy, which included of 1185 patients (figure 2). We found no significant correlation between overall and recurrence-free survival HRs (Spearman's rank correlation r=0·20; SE=0·58; p=0·71). In a subsequent trial group meta-analysis, we assessed correlation between 3-year recurrence-free survival and 5-year overall survival (appendix p 16). For the analysis of 3-year recurrence-free survival versus 5-year overall survival, one study[8] was omitted because trial results were reported only up to 48 months. Again, the Spearman's correlation coefficient was low to moderate (r=0·43; SE=0·39; p=0·22; appendix p 16).

The correlation between recurrence-free survival and overall survival depends on the patterns of survival after recurrence. Because recurrence-free survival was not strongly correlated with overall survival in either our institutional cohort or our meta-analysis of randomised clinical trials, we sought to explore the association between survival after recurrence for varying recurrence-free survival intervals. In the subset of patients who had disease recurrence in our institutional cohort (n=1995), we assessed the association between recurrence-free survival and survival after recurrence using a scatterplot (figure 3), from which we found little association between the length of the recurrence-free interval and subsequent time from recurrence to death.

Next, we calculated Kaplan-Meier estimates of survival after recurrence stratified by recurrence-free survival intervals (figure 4). Patients who recurred early had the worst survival after recurrence, with a median survival after recurrence of 1·9 years (95% CI 1·7–2·2) in those with a recurrence-free survival of less than 6 months and 2·4 years (2·2–2·7) in those with a recurrence-free survival of 6 months to less than 12 months; whereas the patients who recurred late had the longest survival after recurrence, with a median survival after recurrence of 4·5 years (3·8–11·7) in patients with a recurrence-free survival of 5 years or

longer. The Kaplan-Meier estimates of survival after recurrence for the intervening time periods overlapped and we could not identify any apparent pattern (median survival after recurrence for the four groups ranged from 3·1 to 3·4 years; appendix p 17).

Discussion

To our knowledge, this study is the largest comparative analysis of recurrence-free versus overall survival after curative-intent hepatectomy. We found low-to-moderate correlation between recurrence-free survival and overall survival at all assessed time points. Although most deaths (1428 [85%] of 1684) were preceded by tumour recurrence, there was a wide range of time intervals (0·0–23·4 years) from recurrence to death, thus limiting the value of recurrence-free survival as a surrogate endpoint for overall survival. Moreover, in a meta-analysis of adjuvant randomised controlled trials in this setting, the correlation between recurrence-free survival and overall survival was also found to be low to moderate. Surrogate validation is a demanding process that must be done for each clinical context and the data we present here do not support the use of recurrence-free survival as a surrogate endpoint for overall survival at the patient level or the trial level for resected colorectal liver metastasis.

Long-term cure (ie, alive and free of disease) is an important reported outcome for patients with cancer.[23–25] The goal of improving long-term cure rates supports the use of overall survival as the primary endpoint for clinical trials assessing therapies for patients with resected colorectal liver metastases. However, the use of overall survival as a primary endpoint can require substantially more follow-up resources and longer times to event, as we found in our institutional database, with a difference of 3·9 years between median recurrence-free survival and overall survival estimates. For these data, the highest correlation between the two endpoints was 0·56 (SD 0·13), observed between 5-year recurrence-free survival and 7-year overall survival among the 35 tested pairwise timepoints, but this correlation was still only moderate.

Originally, the use of recurrence-free survival as a surrogate endpoint for overall survival was derived from analyses of the Adjuvant Colon Cancer Endpoints (known as ACCENT) database—a pooled database of randomised clinical trials of fluorouracil-based adjuvant therapy for non-metastatic colorectal cancer—which relied on 3-year recurrence-free survival as a surrogate for 5-year overall survival.[3] However, in the analysis of recurrence-free survival versus overall survival for patients with non-metastatic colon cancer by Sargent and colleagues,[3] the R^2 value from the weighted linear regression of 5-year overall survival on 3-year recurrence-free survival was 0·85 and the corresponding Spearman's rank correlation coefficient was 0·88, which is substantially higher than the correlations found in our study. Furthermore, by direct comparison using the same timepoints (3-year recurrence-free survival and 5-year overall survival), we estimated the correlation for patients with resected metastatic disease was 0·49 (SD 0·15), and similarly 0·43 (SE 0·39) from the randomised clinical trial data; a substantially weaker degree of correlation than was found in patients with non-metastatic colon cancer.

Surrogate endpoints should have a scientifically plausible link to the true endpoint and be embedded within the causal pathway to the true endpoint.[26] From our institutional database of patients, we found that 85% of deaths were preceded by disease recurrence, a rate very similar to that observed in the non-metastatic

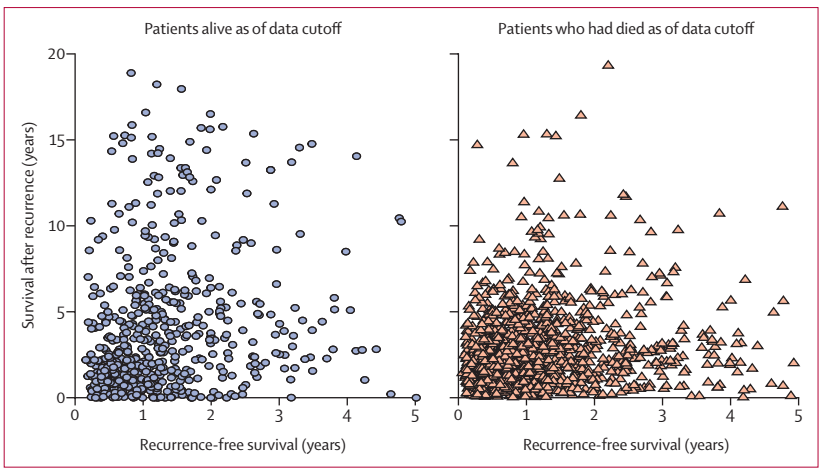
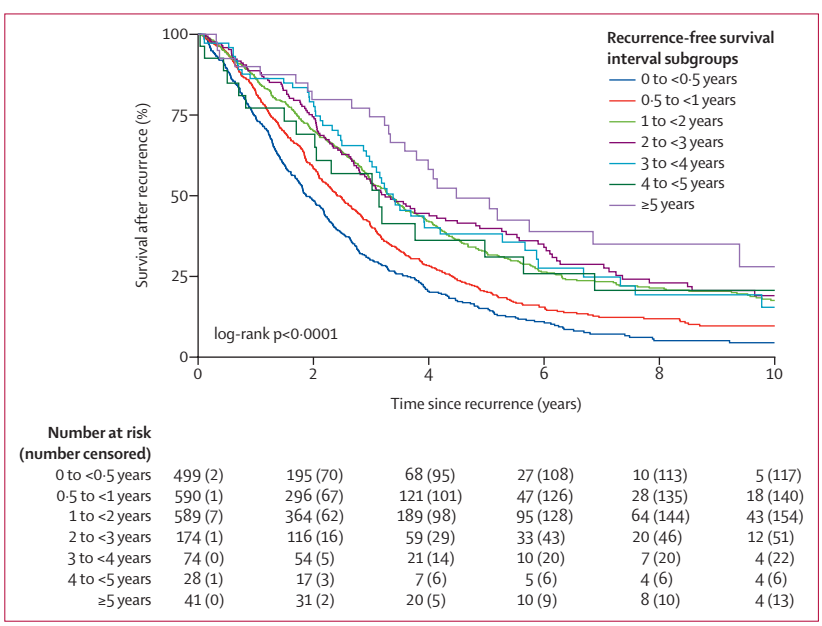


Figure 3: **Scatterplot of survival after recurrence versus recurrence-free survival for patients with recurrence (n=1995) in the resected colorectal liver metastasis cohort**
Data are shown by vital status at data cutoff (Sept 15, 2019). Only data for recurrence-free survival of 5 years or less and overall survival of 20 years or less are shown.



Number at risk (number censored)						
0 to <0·5 years	499 (2)	195 (70)	68 (95)	27 (108)	10 (113)	5 (117)
0·5 to <1 years	590 (1)	296 (67)	121 (101)	47 (126)	28 (135)	18 (140)
1 to <2 years	589 (7)	364 (62)	189 (98)	95 (128)	64 (144)	43 (154)
2 to <3 years	174 (1)	116 (16)	59 (29)	33 (43)	20 (46)	12 (51)
3 to <4 years	74 (0)	54 (5)	21 (14)	10 (20)	7 (20)	4 (22)
4 to <5 years	28 (1)	17 (3)	7 (6)	5 (6)	4 (6)	4 (6)
≥5 years	41 (0)	31 (2)	20 (5)	10 (9)	8 (10)	4 (13)

Figure 4: **Kaplan-Meier estimates of survival after recurrence for subsets of patients with recurrence (n=1995) in the resected colorectal liver metastasis cohort**
Data are stratified by recurrence-free intervals and truncated to the first 10 years after recurrence. The p value corresponds to the log-rank test of difference among the survival curves.

colorectal cancer setting at 84%,[2] and reaffirming recurrence-free survival as an almost certain causal link to overall survival. However, by contrast with the non-metastatic setting, we found that time to recurrence did not reliably predict the survival outcome. Moreover, when stratified by time to recurrence intervals, there were long-term survivors at all intervals assessed.

The degree to which recurrence-free survival is a reliable surrogate endpoint for overall survival might depend on the pattern of recurrence and the salvage treatment options. Potentially curative salvage surgery is a therapeutic possibility for approximately 27–54% of patients after hepatectomy, of whom approximately 22–42% will have a long-term cure.[19,27] In the case of colorectal liver metastases, the improving safety of liver surgery, coupled with locoregional therapies, might support its more widespread use and possibly high rate of curability[28] to salvage disease recurrence. The importance of the type of recurrence, and thus eligibility for local salvage treatment, has been found in several international studies.[10,29] In a case series of 371 patients at the University of Tokyo (Tokyo, Japan) by Oba and colleagues,[27] patients with resectable patterns of recurrence had substantially improved survival (and long-term cure rates) compared with patients with unresectable recurrences.[27] Oba and colleagues introduced the concept of time to surgical failure, defined as the time from surgery to unresectable relapse or death, and found this endpoint to correlate more strongly with overall survival than with recurrence-free survival. Similarly, in a Dutch series of 1374 patients with colorectal liver metastases who underwent curative-intent resection, the disease-free interval between resection of the colorectal primary cancer and diagnosis of colorectal liver metastases was associated with recurrence-free survival, but not with overall survival after resection of colorectal liver metastases.[29] Importantly, the authors of the Dutch series noted that eligibility for local salvage treatment was independent of the disease-free interval between resection of the colorectal primary cancer and diagnosis of colorectal liver metastases, which might explain why differences in recurrence-free survival did not translate to differences in overall survival. In our institutional cohort, salvage surgery was used for 864 (43%) of 1995 patients who had a recurrence, which is very similar to the rate of salvage surgery (40% and 46% in two treatment groups) in the EORTC 40983 trial of perioperative chemotherapy, another study in which early improvements in recurrence-free survival (in eligible patients) receiving FOLFOX (leucovorin, fluorouracil, and oxaliplatin) did not translate to any differences in overall survival.[15] In summary, the relevant issue might be the pattern of recurrence and how such recurrence is treated, rather than if a patient has a recurrence at all.

Our findings have two important implications for clinical management and research trial design. First, recurrence-free survival should not be used as a surrogate endpoint for overall survival in this clinical context. In a series of all oncology trials that received US Food and Drug Administration (FDA) approval between 2009 and 2013, overall survival was used as the primary endpoint in less than a third of studies.[30] A failure of a surrogate endpoint in the case of bevacizumab for metastatic breast cancer highlights the danger of this approach.[31] More specifically, bevacizumab received provisional FDA approval, in 2008, for the treatment of metastatic breast cancer on the basis of an improvement in progression-free survival.[32,33] However, approval was subsequently withdrawn 3 years later, after additional trials found a lower improvement in progression-free survival than expected and no improvements in overall survival.[34] Overall survival has not routinely been the primary endpoint in trials for patients with resected colorectal liver metastases.[5,6,14,15] Our findings support overall survival as the ideal primary endpoint in future trial design, or call for the establishment of novel endpoints that more reliably correlate with survival. Given the importance of salvage surgery for this disease context, time to surgical failure might be a trial endpoint to consider, pending its assessment in external datasets.

Second, although recurrence-free survival is not an appropriate surrogate endpoint for overall survival, it can still be used to guide prognostication for patients with resected colorectal liver metastases. We found distinct prognostic groups for early (ie, <1 year after resection) and late onset of recurrence (ie, ≥5 years after resection), with worse survival observed for patients who had early recurrence onset. Early recurrence has been previously identified as a poor prognostic factor,[35,36] although the differential prognosis between disease-free intervals shorter than 6 months and of 6–12 months is a novel finding of our study. The highest disease-free interval of 5 years or longer was associated with the highest rate of cure (>25% survival at 10 years). However, because only patients who had extremes of recurrence-free survival (<1 year or ≥5 years) had noticeably different survival probabilities, the overall association between recurrence-free survival and overall survival (accounting for all patients, inclusive of those with recurrence-free survival at 1–5 years after resection) showed substantial heterogeneity; hence, in the context of clinical trials, recurrence-free survival would not be an appropriate surrogate of overall survival.

Recurrence-free survival could still be considered a valuable trial endpoint, considering that improvements in recurrence-free survival will lead to improvements in cancer-related symptoms. The assumption that supports this hypothesis is that patients who live longer without disease recurrence will have improved health-related quality of life (HRQoL), even without longer overall survival. However, in a meta-analysis of contemporary oncological randomised controlled trials that reported both progression-free survival and HRQoL, the authors found no association between the two endpoints.[37] The specific association between recurrence-free survival and

HRQoL, particularly for this disease context, is yet to be established. Alternatively, therapies to improve recurrence-free survival without concurrent improvements in overall survival or HRQoL might still be preferred by patients. Again, the data are limited to studies of progression-free survival, in which most patients who are surveyed are receiving palliative chemotherapy and would not exchange the possibility of increased adverse events for isolated improvements in progression-free survival.[22] We are exploring patient attitudes about isolated improvements in recurrence-free survival at our centres.

Several limitations of these analyses warrant emphasis. First, there are concerns that arise from a long study period during which patient management might have varied—for instance, indications for surgery might have changed. However, we found no substantial temporal trends in the mean clinical risk score or rate of re-resection for recurrence in our institutional cohort; thus, our results appear to represent a unified surgical strategy at a single specialised centre. Moreover, we observed low-to-moderate correlation between the two endpoints for the subsets of early and contemporary eras of systemic therapy. There were likely additional changes in the clinical management of recurrence over the study period, and a future publication exploring the varying strategies for recurrent colorectal liver metastases and their effect on survival is being planned. Second, the association between recurrence-free survival and overall survival can be affected by the timing and quality of assessment for recurrence. Despite the absence of protocol-defined follow-up, small variabilities in imaging timing (measured in weeks) are unlikely to explain the low correlation between recurrence-free survival and overall survival in either study era. Additionally, the nearly identical Spearman's rank correlation coefficient obtained from institutional data and the meta-analysis of randomised trials (for which assessment of recurrence was protocolised) suggest that these small differences in patient surveillance and management might not have an effect on the low correlation between these two study endpoints. Regarding types of imaging for recurrence, we found no temporal trends in the use of CT compared with MRI imaging during the study period. Third, the introduction of more effective treatments for recurrent disease in the contemporary era might improve survival after recurrence and thus further weaken any association between recurrence-free survival and overall survival. We observed similar recurrence-free survival between the early and contemporary eras, and improved overall survival in the contemporary era compared with the early era, suggesting that survival after recurrence might be improved in the contemporary era. Still, the poor association between recurrence-free survival and overall survival persisted in the early treatment era. Nevertheless, delaying first recurrence is an important clinical objective for patient benefit, barring the toxic side-effects of treatment. Fourth, we did not assess the correlation between recurrence and overall survival in the context of perioperative chemotherapy, because this analysis was limited to patients and phase 3 randomised controlled trials in which the patient was rendered disease-free at baseline. In the EORTC 40983 trial of perioperative chemotherapy,[15] patients were not disease-free at the time of randomisation, and thus the study endpoint is a compound of progression-free and recurrence-free survival. Nevertheless, improvements in their primary endpoint in eligible patients receiving FOLFOX did not translate to any differences in overall survival,[15] suggesting that this context might be similar to that in our analyses. Fifth, because the institutional database spanned many years, some individual datapoints were not available for every patient, particularly in the earlier years of data collection. Because the weak correlation between recurrence-free survival and overall survival persisted in the contemporary era (2001–19), when missing data were rare (data not shown), we believe that missing data was not a major form of bias in our analyses. Sixth, definitions of technical so-called resectability might have changed over the study period, in line with changes in biological selection and technical expertise. Thus, we did not exclude patients who were deemed unresectable at presentation. Despite this potential source of bias, the Spearman's rank correlation coefficient derived from our data and from the meta-analysis of adjuvant trials, which included precise definitions of resectability, were very similar. Finally, recurrence-free survival events included death without recurrence, which matches standard definitions in most related clinical trials. This definition favours an increased correlation between recurrence-free survival and overall survival when compared with censoring death events. Yet, despite this fact, the observed correlation remained low to moderate.

This study includes, to our knowledge, the largest series of patients who have undergone complete resection of colorectal liver metastases with detailed long-term outcomes of recurrence and overall survival, and we provide evidence that the correlation between recurrence-free survival and overall survival in this disease context is minimal. Furthermore, we found poor correlation between these two endpoints in a meta-analysis of all phase 3 randomised clinical trials of adjuvant chemotherapy in this disease context. The development of first relapse after an initial hepatic resection did not reflect non-curability, with variable survival lengths and even long-term cures at all intervals of recurrence. Recurrence-free survival is an inadequate surrogate for overall survival and novel endpoints, such as time to surgical failure, are needed to guide future trial planning if overall survival is not a feasible endpoint at the time of design.

Contributors

BLE, JL, MG, and MID contributed to study conceptualisation. BLE, JL, LVS, FEB, TA, KH, BGK, NK, YM, and GP contributed to data curation. JL and MG did the formal analysis. JAD, WRJ, MG, and MID acquired the study funding. JL and MG contributed to the study methodology.

BLE, VPB, JAD, WRJ, NEK, TPK, LBS, KCS, ACW, MG, and MID contributed to project administration. VPB, JAD, KH, WRJ, NEK, TPK, BGK, NK, YM, GP, LBS, KCS, ACW, MG, and MID contributed study resources. JL and MG contributed software. MG and MID were study supervisors. JL designed the figures. BLE, JL, MG, and MID wrote the original draft of the manuscript and all authors contributed to the revision of the manuscript. JL and MG accessed and verified the underlying study data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JL, LVS, VPB, JAD, WRJ, NEK, TPK, LBS, KCS, ACW, MG, and MID are affiliated with Memorial Sloan Kettering Cancer Center, New York, NY, USA, which is supported by funding from the National Cancer Institute (P30 CA008748). All other authors declare no competing interests.

Data sharing

Individual participant data from Memorial Sloan Kettering Cancer Center will not be made available. The meta-analysis used data from published studies; data are available from these individual published studies.

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