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ORIGINAL ARTICLE – COLORECTAL CANCER

Discrepancy Between Recurrence-Free Survival and Overall Survival in Patients with Resectable Colorectal Liver Metastases: A Potential Surrogate Endpoint for Time to Surgical Failure

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ABSTRACT

Background. Recurrence-free survival (RFS) may not be a surrogate for overall survival (OS) in patients with resectable colorectal liver metastases (CLM). We investigated whether a new composite tool—time to surgical failure (TSF)—is a suitable endpoint.

Methods. The medical records of consecutive patients who underwent curative resection for CLM at our center over a 17-year period were reviewed. Patients with liver-limited tumors ($n = 371$) who had not received previous treatment for metastasis were eligible for analysis. TSF was defined as the time until unresectable relapse or death. The correlations between TSF and OS, and between RFS and OS, were assessed for all the eligible patients.

Results. The median OS, TSF, and RFS were 5.7, 2.7, and 0.7 years, respectively, and the 5-year OS, TSF, and RFS rates were 52.6, 39.8, and 23.7 %, respectively, for all patients. The rates of first, second, and third relapse were 75.5, 77.6, and 70.8 %, respectively, and repeat resections were performed in 54.3 % (first relapses), 40.7 % (second relapses), and 47.1 % (third relapses) of patients. The concordance proportions of TSF and RFS for OS events were 0.83 and 0.65, respectively. The correlation between TSF and OS was stronger than that between RFS and OS in terms of the predicted probabilities.

Conclusions. The correlation between TSF and OS was stronger than that between RFS and OS after curative hepatic resection. TSF could be a suitable endpoint for CLM overall management.

Although colorectal liver metastases (CLM) are regarded as a distant metastatic status, surgical resection of R0 has been accepted as a potentially curative treatment since it can enable long-term survival, with a 5-year overall survival (OS) rate ranging between 33 and 56 % in relatively large and recent observational series.[1–3] However, an incidence of recurrence as high as 75 % even after curative surgical resection, with more than 50 % of recurrences occurring in the remnant liver only, remains an unsettled and severe problem.[3–5] To reduce this high relapse rate, hepatic resection combined with some form of adjuvant treatment has been proposed by several investigators.[6] Unfortunately, sufficient evidence for a standard adjuvant treatment has not been obtained.[7–9] In patients with stage III colorectal cancer, a short-term endpoint assessed after a 3-year median follow-up period, known as the disease-free survival (DFS) period, has been shown to be a valid surrogate marker for the standard 5-year OS endpoint.[10] This new paradigm has contributed to the development of adjuvant strategies, allowing faster completion of clinical trials, and has been accepted as a valid endpoint on which to base new standards of care in clinical practice.[11,12] On the other hand, in the absence of any evaluation of the use of earlier endpoints as optimal surrogates for OS in stage IV patients with resectable CLM, either the DFS period or the progression-free survival (PFS) period has usually been accepted as a primary endpoint in adjuvant setting trials. However, the negative

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results for long-term outcome in the pivotal EORTC 40983 phase III trial indicate that an improvement in PFS does not necessarily reflect the survival benefit.[13] In recent larger series, a survival discrepancy has seemed to exist between DFS and OS after resection for CLM.[1,3] Although OS can be regarded as an ultimate and robust endpoint in adjuvant setting clinical trials, it requires a long follow-up period and a large sample size, and can be affected by the use of second and further treatments for relapse. Thus, a clinically useful and reliable endpoint for validating the role of adjuvant treatments in patients with resectable CLM does not presently exist.

Why has a survival discrepancy existed between first relapse-related events (DFS or PFS) and OS in previous studies? One possible reason is that survival beyond relapse is prolonged by advanced chemotherapy for metastatic colorectal cancer, if a surgical approach cannot be selected. On the other hand, re-resections for recurrences in the remnant liver and/or lung have been accepted as providing a survival benefit.[4,14–16] As shown by the high repeat resection rate (more than 40 %) in patients with relapse in the EORTC 40983 trial, the first relapse-related event does not reflect long-term survival,[13] since a second or third re-resection can have curative potential in some patients with relapse. Therefore, we hypothesized that the possibility of repeat resection itself might have a prognostic impact on the overall management for resectable CLM. The time until development of an unresectable relapse, for which a repeat resection is impossible and which would be followed by a palliative therapeutic course, was investigated as a new endpoint. In the current study, we retrospectively investigated this hypothesis using data accumulated over a 17-year period at a single specialized center.

METHODS

Patients and Treatment

Data collected prospectively over a 17-year period (January 1994–December 2010) for 422 patients who underwent upfront hepatic resections for CLM at our center were reviewed. Fifty-one patients who were enrolled in an ongoing phase III trial to evaluate the efficacy of oral adjuvant chemotherapy using tegafur/uracil and leucovorin (UFT/LV) after surgery for CLM (UMIN-CTR: C000000013) were excluded from the present study.[17] The following data were available for curatively resected patients: sex, age, performance status, primary tumor site, histologic type, pathologic T and N stage according to the current TNM classification, characteristics of liver metastases, type of hepatic resection, surgical margin, date of resectable recurrence, date of re-resection, date of unresectable recurrence, and date of death or last visit. Table 1 shows the profiles for the study patients at baseline. All the resected liver metastases were diagnosed synchronously with the primary tumor in 188 patients (50.7 %). A major hepatic resection was defined as the resection of two or more segments, as described by Couinaud. Of the 371 liver resections that were performed, 83 patients (22.4 %) underwent a major hepatic resection with or without the combination of a partial resection, and 262 patients (70.6 %) underwent a partial resection only, with no surgery-related mortalities. All patients were assessed preoperatively using enhanced computed tomography (CT) with the following selection criteria applied for surgery: (1) the primary lesion must be resectable or must have been curatively resected; (2) all the liver metastases were amenable to resection with a negative surgical margin, leaving a remnant liver volume of at least 40 % without potentially ischemic or congested areas; and (3) no unresectable extrahepatic sites of disease. During the period of our investigation, our medical center's staff had the same policy toward hepatic resection for CLM: namely, a surgery-upfront approach was used regardless of the metastatic number, anatomic location, or extent of the liver metastases. Furthermore, all patients were assessed preoperatively using enhanced CT and magnetic resonance imaging (MRI) and the resectability criteria described above. Intraoperative ultrasonography was routinely performed to confirm the preoperative imaging and diagnosis. Patient follow-up included the serial measurement of tumor markers (carcinoembryonic antigen [CEA] and carbohydrate antigen 19-9 [CA19-9]) and a CT examination of the chest and abdomen performed every 3–6 months. Sufficient evidence regarding the efficacy of standard adjuvant treatment is lacking during the study period; therefore, the definitive efficacy of postoperative fluorouracil (FU)-based chemotherapy for 6 months remains unclear.[7,8] Hence, postoperative adjuvant chemotherapy was not routinely administered during the study period. The therapeutic regimens were as follows: bolus-based FU/LV ($n = 16$); UFT/LV ($n = 30$); capecitabine ($n = 12$); and oxaliplatin plus infusional and bolus FU/LV (FOLFOX) ($n = 22$). Preoperative chemotherapy was not performed for either the initial liver metastases or the recurrent diseases during this study period. The criterion for performing repeat resections for recurrent diseases was the likelihood of achieving a complete resection of all evident tumors. In cases with a recurrence in the remnant liver, a repeat hepatic resection was considered if an R0 resection and sufficient liver volume were feasible. In cases with recurrent pulmonary metastases, resectability was determined by an experienced thoracic surgeon based on whether a metastasectomy for three or fewer tumors, in principle, could be safely performed, regardless of their distribution. The

TABLE 1 Patient and tumor characteristics at baseline

Variable	Study patients ($n = 371$)
Sex (%)	
Male	67.4
Female	32.6
Age [years; median (range)]	62.5 (29–83)
ECOG PS (%)	
0	97.0
1	3.0
Primary tumor (%)	
Location	
Colon	57.1
Rectum	42.9
Histological differentiation	
Well	51.2
Moderate	46.9
Poor	1.9
pT stage	
T1	2.7
T2	5.1
T3	72.8
T4	19.4
pN stage	
N0	37.2
N1	34.2
N2	28.6
Initial liver metastases (%)	
Timing of diagnosis	
Synchronous	50.7
Metachronous	49.3
Tumor distribution	
Unilobar	61.2
Bilobar	38.8
Tumor number	
Single	40.7
Multiple	59.3
1–4	73.6
5–8	14.6
≥9	11.8
Size of largest tumor (cm)	
<2	19.1
2–5	49.0
≥5	31.9
Preoperative CEA (μg/L)	
>50	47.7
Type of hepatic resection (%)	
Major	22.4
Minor	77.6
Surgical margin (%)	
R0	89.2
R1	10.8
Postoperative adjuvant CT (%)	
FU/LV	4.3
UFT/LV	7.8
Cape	3.2
FOLFOX	5.9

ECOG PS Eastern Cooperative Oncology Group performance status, *well* well-differentiated adenocarcinoma, *moderate* moderately differentiated adenocarcinoma, *poor* poorly differentiated adenocarcinoma, *pT and pN* pathologic primary tumor (T) and regional lymph nodes (N) stage, *CEA* carcinoembryonic antigen, *CT* chemotherapy, *FU/LV* fluorouracil plus leucovorin, *UFT/LV* tegafur/uracil and leucovorin, *Cape* capecitabine, *FOLFOX* oxaliplatin plus infusional and bolus FU/LV

surgical policy of our institution is to always attempt to retain as much of the liver or pulmonary reserve as possible, since future repeat resections might be necessary. However, relapses to distant lymph nodes other than the primary (colorectal) local site or solitary and limited lesions were regarded as contraindications for a repeat resection. During the current study period, we regarded ablation therapy as a non-curative procedure and did not use this technique as a substitute for re-resection in patients with resectable recurrent disease since its efficacy for CLM is inferior to resection in terms of the rates of local recurrence and the 5-year OS.[4,18]

Definitions of Survival

OS was defined as the time interval from the initial surgery until death by any cause, while recurrence-free survival (RFS) was defined as the time interval from the initial surgery until the first recurrence of colorectal cancer or death as a result of any cause. In this study, the significance of repeat resection was evaluated using a composite endpoint, the time to surgical failure (TSF). This endpoint was defined as the time interval from the initial surgery until the first unresectable recurrence or death as a result of any cause (Fig. 1). While including the possibility of a repeat resection, the overall outcome in CLM patients was represented as the sum of each resectable RFS for sequential repeat resections plus palliative survival after the unresectable relapse event. Standard criteria for repeat resectability are difficult to specify as they depend on technical aspects that are related to the experience of the surgeon and the oncological question of whether the complete resection of the recurrences is likely to result in a potential cure. The current study was undertaken at a single institute where the selected staff had the same policy

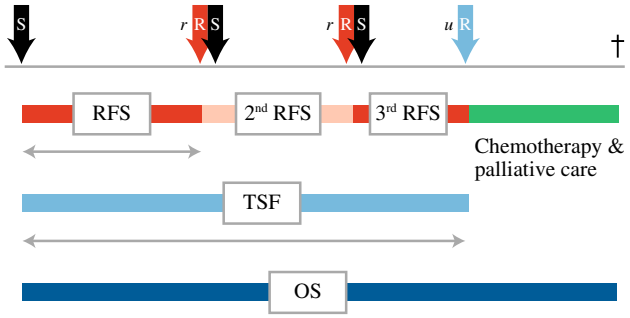


FIG. 1 Associations between each time-to-event (RFS, TSF, and OS) in the overall management of patients with resectable CLM. TSF was defined as the sum of the resectable RFS until the time of an unresectable relapse (surgical failure event). *RFS* recurrence-free survival, *TSF* time to surgical failure, *OS* overall survival, *CLM* colorectal liver metastasis, *rR* resectable relapse, *uR* unresectable relapse

toward the potential window for a cure, considering the possibility of repeat resections whenever possible from technical or oncological aspects; if a repeat resection was not feasible, the selection of optimal chemotherapy or other palliative therapy for unresectable relapse was considered.

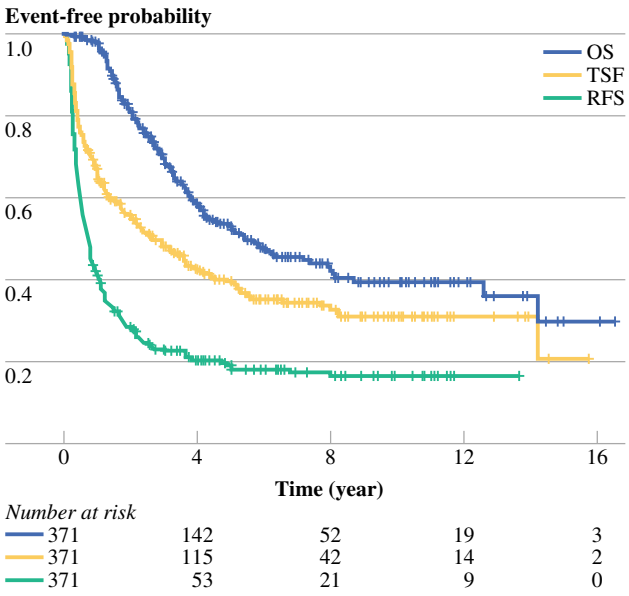
Statistical Analysis

The follow-up and survival periods were estimated using the Kaplan–Meier method, and were described using the median and 95 % confidence interval (CI). Significant differences were determined using the log-rank test, and $p < 0.05$ was considered significant. Surviving patients were censored at the time of the last follow-up. The correlations between RFS events and OS events, and between TSF events and OS events, were each evaluated using the concordance proportion. The Spearman rank correlation coefficient was used to estimate the correlations between the probabilities of RFS and OS, and between the probabilities of TSF and OS, as predicted using the Cox proportional hazards model in all the resected patients. To identify prognostic factors for TSF, a multivariate regression analysis was performed using the proportional hazard model with backward elimination for variables with $p < 0.1$ in the univariate analysis. All the statistical analyses were conducted using SAS, version 9.2 (SAS Institute, Cary, NC, USA). Statistical significance was set at $p < 0.05$.

RESULTS

Survival, Relapse, and Repeat Resections

The median OS, TSF, and RFS were 5.72 years (95 % CI 4.33–8.06 years), 2.68 years (95 % CI 1.98–3.66 years), and 0.66 years (95 % CI 0.54–0.78 years), respectively, for



		RFS		TSF	
		Event	Censored	Event	Censored
OS	Event	154	0	154	0
	Censored	131	86	63	154
Concordance proportion		0.65		0.83	

FIG. 2 Kaplan-Meier plots of OS, TSF, and RFS in all study patients ($n = 371$). The concordance proportions between RFS and OS, and between TSF and OS, are shown. *OS* overall survival, *TSF* time to surgical failure, *RFS* recurrence-free survival

all resected patients ($n = 371$; Fig. 2). The 5-year OS rate, 5-year TSF rate, and 5-year RFS rate was 54.3, 39.8, and 19.8 %, respectively. The 10-year OS rate, 10-year TSF rate, and 10-year RFS rate was 41.1, 32.4, and 17.1 %, respectively. As shown in Table 2, relapses occurred in 280 patients (75.5 %) after the initial hepatic resection, and repeat resections were performed in 152 patients (54.3 %). Of the 152 first repeat resections that were performed, second relapses occurred in 118 patients (77.6 %), and additional second repeat resections were performed in 48 patients (40.7 %). Of the 48 second repeat resections that were performed, third relapses occurred in 34 patients (70.8 %), and additional third repeat resections were performed in 16 patients (47.1 %). Of the 112 patients with a first recurrence to the liver only, 89 (79.5 %) underwent a repeat hepatic resection. The remaining 23 patients (20.5 %) did not undergo surgical treatment but did receive palliative chemotherapy. Among the 83 patients with a first recurrence to the lung only, 40 (48.2 %) underwent pulmonary resection, whereas the remaining 43 (51.8 %) received palliative chemotherapy. For first recurrence to the liver plus lung, 18 of 64 patients (28.1 %) underwent simultaneous or staged resections. As for the second and third recurrences, surgical resection was performed, if possible (Table 2).

TABLE 2 Entire history of relapse and repeat resection after initial hepatic resection

Variable	Study patients ($n = 371$)
First relapses (% of initial hepatic resection)	280 (75.5)
First relapse sites (% of first relapses)	
Liver only	112 (40.0)
Lung only	83 (29.6)
Liver plus lung	64 (22.9)
Others	21 (7.5)
First repeat resections (% of first relapses)	152 (54.3)
First repeat resections to site (% resection rates)	
Liver only	89 (79.5)
Lung only	40 (48.2)
Liver plus lung	18 (28.1)
Others	5 (23.8)
Type of first repeat resections [% of sites]	
Partial liver resection	80.7
Limited pulmonary resection	80.0
Second relapses (% of first repeat resections)	118 (77.6)
Second relapse sites (% of second relapses)	
Liver only	39 (33.1)
Lung only	33 (28.0)
Liver plus lung	28 (23.7)
Others	18 (15.2)
Second repeat resections (% of second relapses)	48 (40.7)
Second repeat resections to site (% resection rates)	
Liver only	22 (56.4)
Lung only	15 (45.5)
Liver plus lung	8 (28.6)
Others	3 (16.7)
Type of second repeat resections % of sites	
Partial liver resection	81.5
Limited pulmonary resection	91.3
Third relapses (% of second repeat resections)	34 (70.8)
Third relapse sites (% of third relapses)	
Liver only	12 (35.3)
Lung only	8 (23.5)
Liver plus lung	7 (20.6)
Others	7 (20.6)
Third repeat resections (% of third relapses)	16 (47.1)
Third repeat resections to site (% resection rates)	
Liver only	9 (75.0)
Lung only	5 (62.5)
Liver plus lung	2 (28.6)
Others	0 (0.0)
Type of third repeat resections [% of sites]	
Partial liver resection	81.8
Limited pulmonary resection	100.0
Actual 5-year survivors (1994–2008)	$n = 124$
Relapse episode (%)	75 (60.5)
Re-resections episode (%)	66 (53.2)
No. of times for re-resections	
Once	32
Twice	21
Thrice or more	13
Cancer-free status at 5 years (%)	87 (70.2)
Re-resections history (%)	49 (56.3)

'Others' includes metastatic site of primary local site, pedicular lymph nodes, celiac lymph nodes, para-aortic lymph nodes, adrenal gland, or peritoneum ±liver and/or lung

Correlation Between Recurrence-Free Survival and Overall Survival (OS), and Between Time to Surgical Failure and OS

The concordance proportions for RFS and OS, and for TSF and OS, were 0.65 and 0.83 for all patients, respectively (Fig. 2). The correlation between TSF and OS was stronger than that between RFS and OS. The Spearman rank correlation coefficients separately assessing the associations between the RFS, TSF, and OS events are shown in Fig. 3.

Multivariate Analysis

A multivariate analysis revealed that a recurrence-free interval <12 months was the only independent risk factor for TSF ($p = 0.04$; hazard ratio 1.98; 95 % CI 1.06–3.81), whereas a preoperative CEA value >50 μg/L, a metastatic number ≥3 tumors, a largest tumor size ≥5 cm, an intra- plus extra-hepatic relapse pattern, and no adjuvant CT were not statistically significant.

DISCUSSION

Our study demonstrated a survival discrepancy between RFS and OS in patients with resectable CLM. TSF, a newly defined time-to-event, seemed to be more strongly associated with OS and to be capable of reflecting the long-term outcome.

In this study, we proposed a new composite endpoint, TSF, as a surrogate for OS after the resection of CLM, taking the unique biological characteristics of colorectal cancer (in which the development of first relapse after an initial hepatic resection does not reflect surgical failure or non-curability) into consideration. This characteristic

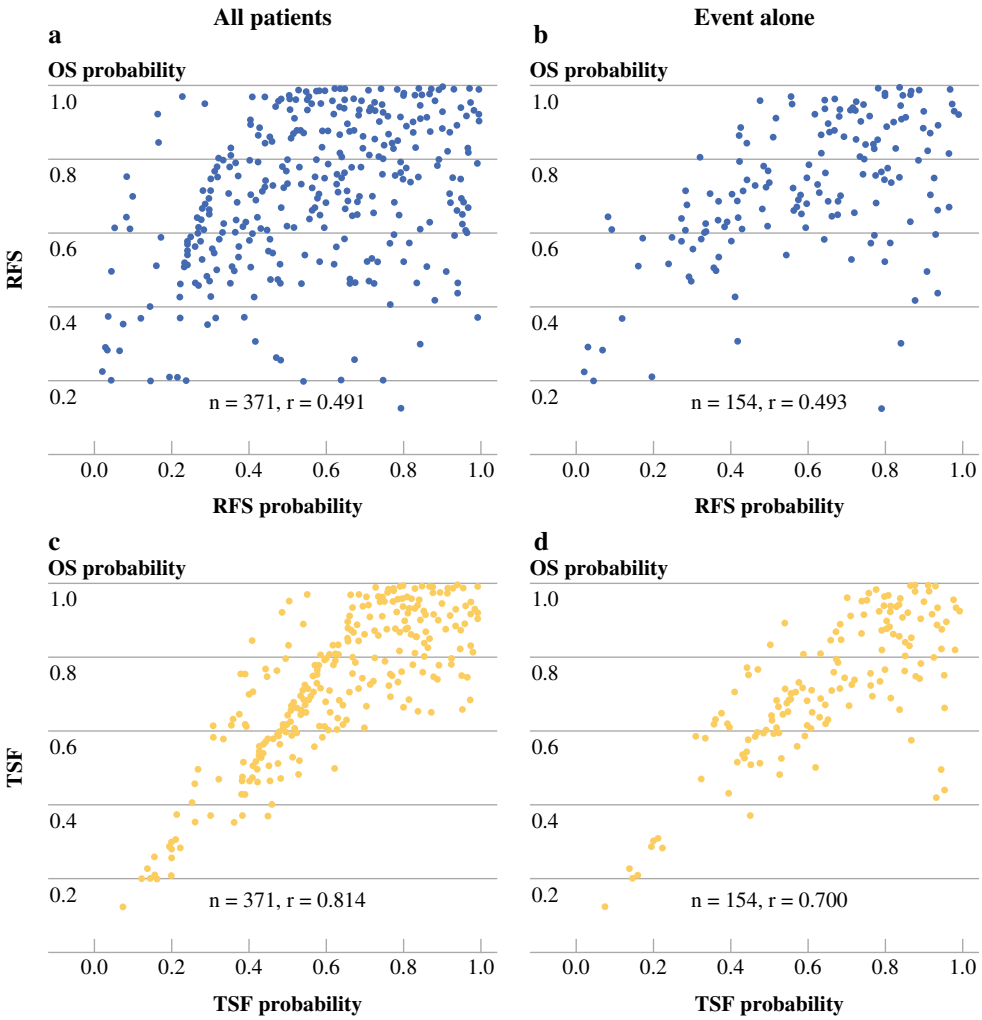


FIG. 3 Correlations between RFS and OS, and TSF and OS, in all patients (**a**, **c**) and event-alone patients (**b**, **d**). *RFS* recurrence-free survival, *OS* overall survival, *TSF* time to surgical failure

differs from other malignancies in which liver metastasis or a relapse event is directly associated with cancer-related death, although modern chemotherapy can prolong patient survival to a certain extent. Previous clinical trials in a CLM adjuvant setting have been judged using DFS or PFS as the primary endpoint, the improvement of which cannot be translated into the ultimate goal of a long-term survival benefit. The current study demonstrated that RFS, or the time to first recurrence, was not clinically associated with OS because of the sequential surgical management for recurrent diseases. Of the actual 5-year survivors ($n = 124$), 60.5 % ($n = 75$) developed recurrences within 5 years after their initial hepatectomy, and 53.2 % ($n = 66$) underwent repeat resections. Moreover, of the recurrence-free survivors at 5 years ($n = 87$), 56.3 % ($n = 49$) had previously developed recurrences and had achieved a cancer-free status after repeat resections (Table 2). Although recent effective chemotherapy has prolonged the OS of patients with recurrence, chemotherapy alone cannot realize the primary goal of a cure for patients with recurrences. Thus, the number of patients who could be cured even after a repeat resection was notable, and most patients received a survival benefit from repeat surgical management, even after a relapse event (Fig. 4). Using this new composite endpoint, the correlation between TSF and OS was shown to be much stronger than that between RFS and OS.

This study had several limitations. The first limitation is the difficulty in establishing standard criteria for repeat resections after relapse from technical or oncological perspectives, although our center's staff members have adopted a consistent policy using a multidisciplinary approach. The definition of 're-resectability' differs according to each institution's policy, and the new 'TSF' endpoint would be difficult to apply to conventional practice across multicenters. However, if 're-resectability' was to be determined by a central evaluation, TSF could be a promising surrogate endpoint for OS in future multicentric clinical trials. The most important points of this study are the unreliability of RFS and the clinical significance of repeat surgery. We believe that repeat resection should be regarded as an absolutely necessary strategy in the overall

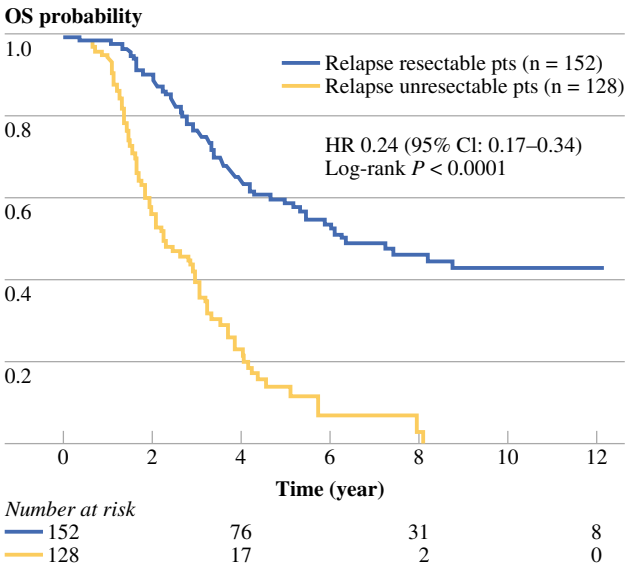


FIG. 4 Comparison of OS in all relapse patients ($n = 280$) after initial CLM resection: relapse resectable patients ($n = 152$) versus relapse unresectable patients ($n = 128$). *OS* overall survival, *CLM* colorectal liver metastasis

management of CLM, as the first relapse event after an initial hepatic resection does not necessarily indicate surgical treatment failure.

The second limitation concerns a problem in the study design, since our results are based on a retrospectively selected patient analysis and the correlations between the efficacy of adjuvant treatment and the TSF and the true endpoint cannot be measured.[19–21] However, the current study was based on prospectively collected data, and during the investigation period patients were treated using the same approach and the same perioperative management. Because our results represent a unified strategy at a single specialized center, our conclusion should be valid to some degree, although another prospective study is needed to confirm the validity of our results. If future adjuvant treatment truly prevents or delays the time to first relapse, to show that this efficacy translates into an OS benefit, the prolongation of the DFS or PFS could be accepted as a useful endpoint on its own.

CONCLUSIONS

The current study confirmed that the TSF, a new composite endpoint including the possibility of repeat resections, was associated with the OS and could be a potential surrogate for long-term outcome. Actually, the RFS does not clinically reflect the OS in the overall management of patients with resectable CLM, who could be candidates for a potential cure even if a recurrence has occurred.

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