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BRIEF COMMUNICATION

Selection criteria related to long-term survival following liver transplantation for colorectal liver metastasis

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Patients with nonresectable colorectal cancer receiving palliative chemotherapy have a 5-year overall survival rate of about 10%. Liver transplant provided a Kaplan-Meier–estimated 5-year overall survival of up to 83%. The objective of the study was to evaluate the ability of different scoring systems to predict long-term overall survival after liver transplant. Patients with colorectal cancer with nonresectable liver-only metastases determined by computed tomography (CT)/magnetic resonance imaging/positron emission tomography (PET)-CT scans from 2 prospective studies (SECA-I and -II) were included. All included patients had previously received chemotherapy. PET-CT was performed within 90 days of the liver transplant. Overall survival, disease-free survival, and survival after relapse based on the Fong Clinical Risk Score, total PET liver uptake (metabolic tumor volume), and Oslo Score were compared. At median follow-up of 85 months for live patients, Kaplan-Meier overall survival rates at 5 years were 100%, 78%, and 67% in patients with Fong Clinical Risk Score 0 to 2, metabolic tumor volume–low group, and Oslo Score 0 to 2, respectively. Median overall survival was 101, 68, and 65 months in patients with Fong Clinical Risk Score 0 to 2, metabolic tumor volume–low, and Oslo Score 0 to 2. These selection criteria may be used to obtain 5-year overall survival rates comparable to other indications for liver transplant.

KEYWORDS

cancer/malignancy/neoplasia, cancer/malignancy/neoplasia: metastatic disease, clinical research/practice, clinical trial, liver disease: malignant, liver transplantation/hepatology

1 | INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy worldwide.[1] About half of the patients have metastases at time of diagnosis or will develop metastases later. The liver is the most frequent metastatic site, and liver resection is considered the only curative treatment option in colorectal liver metastases (CRLMs). Overall survival (OS) after liver resections has been shown to be related to

Abbreviations: CEA, , carcinoembryonic antigen; CRC, colorectal cancer; CRLM, colorectal cancer liver metastasis; DFS, disease-free survival; FCRS, Fong Clinical Risk Score; 18F-FDG, 18F-fluorodeoxyglucose; HCC, hepatocellular carcinoma; KM, Kaplan-Meier; LT, liver transplant; MTV, metabolic tumor volume; OS, overall survival; PET, positron-emission tomography.

metachronous disease (metastatic disease detected >12 months from diagnosis), >1 liver lesion, size of largest liver metastases of ≥5 cm, carcinoembryonic antigen (CEA) levels >200 μg/L, and lymph node–positive primary colorectal tumor (Fong Clinical Risk Score [FCRS][2]). About 20% of the patients with CRLMs are candidates for liver resections,[3] but about 60% to 70% have recurrence within 3 years.[4] Palliative chemotherapy is therefore the treatment option for the majority of patients with CRLMs. The median OS from start of first-line chemotherapy is about 2 years and 5-year OS is about 10%, although longer median OS has been obtained in selected patients with good performance status (ECOG 0 or 1), no *(K)RAS* or *BRAF* mutations, and left-sided tumors.[5-9]

Liver transplant (LT) is the standard of care for selected patients with malignant liver tumors such as hepatocellular carcinoma (HCC) and liver metastases from low-grade neuroendocrine tumors.[10,11] In the 1990s, LT in patients with CRC was abandoned because of a 5-year OS of <20%.[12] In 2006, we started a pilot study (SECA-I) reexamining LT in patients with CRC with nonresectable liver-only metastases. The results in 21 cases were reported in 2013 when the first included patient had been observed for 5 years and the estimated 5-year OS was 60%.[13] Pretransplant maximal tumor diameter >5.5 cm, level of CEA before LT > 80 μg/L, failing response on chemotherapy, and an interval from resection of the primary tumor to transplant of <2 years were all factors associated with decreased survival. We used ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) in combination with computed tomography (CT) to exclude extrahepatic metastases; further, patients with high liver PET uptake had reduced 5-year OS after LT.[14] We showed elsewhere that patients with response to chemotherapy, lower CEA levels at time of LT, and smaller and fewer liver metastases have a Kaplan-Meier (KM)-estimated 5-year OS of 83%.[15]

The aim of the present study was to investigate how 3 different clinical scoring systems could predict long-term survival after LT of patients with CRC with nonresectable liver only metastases.

2 | METHODS

This report is based on 2 prospective clinical trials that included patients with nonresectable CRC liver-only metastases (Clinical Trials.gov NCT01311453, SECA-I; Clinical Trials.gov NCT01479608, SECA-II). The SECA-I study included 23 patients from November 2006 to April 2012; the SECA-II study started in April 2012 and is ongoing. To standardize the pretransplant PET/CT evaluation and avoid underestimation of possible disease progression in cases with a long interval between PET/CT and transplant, only patients having a PET/CT scan within 90 days of LT were included. Nineteen patients (14 and 5 patients from the SECA-I and SECA-II trails, respectively) met these inclusion criteria. The end of follow-up was March 3, 2019. Both studies were approved by the regional ethics committee and institutional review board. The inclusion and exclusion criteria have been reported previously.[13] The main inclusion criteria were nonresectable liver-only disease determined by a multidisciplinary liver meeting with HPB surgeons, liver transplant surgeons, radiologists, and oncologist; no extrahepatic disease determined by CT and PET/CT scans; previous chemotherapy; and good performance status (ECOG 0 or 1). Some of the included patients had previously had liver resection. The criteria for resectable disease vary between surgeons and institutions, and there was a development during the study period. The immunosuppression protocol consisted of induction with basiliximab, sirolimus (mTOR inhibitor), or tacrolimus the first 4 to 6 weeks and then conversion to sirolimus (SECA-II study).[15] Glucocorticoids and mycophenolate mofetil were administered from day 0; steroids were tapered to 0 during the first 3 to 6 months. None of the patients received adjuvant chemotherapy after LT.

Patients had follow-up every month during the first year, every 3 months during the second year, and every 6 months thereafter for up to 10 years. CT scans were performed every 3 months during the first 2 years and then every 6 months. Follow-up and treatment at time of relapse were at the discretion of the responsible physician.

Disease-free survival (DFS) was defined as time from LT to suspected metastatic lesions or local relapse described by CT/magnetic resonance imaging/PET-CT scans, occurrence of new CRC primary, or diagnosis of other malignant disease. OS was calculated from date of LT to the end of follow-up. OS from time of relapse was calculated as OS minus DFS.

From the pretransplant ^{18}F-FDG PET/CT examination, metabolic tumor volume (MTV) was measured and calculated for all liver metastases.[14] MTV (cm^3) was defined as the tumor volume with ^{18}F-FDG uptake segmented by a fixed threshold of 40% of the maximum standardized uptake value in the volume of interest. Total MTV was calculated by adding the values from all metastases for each patient. Liver background was measured by placing a region of interest of 3 cm in the right liver lobe. If the metastases were not visible compared with the liver background, an MTV value of 0 was given.

Tumor location from the cecum to the transverse colon was defined as right-sided primary. Risk stratification of the candidates was done by means of the FCRS and the Oslo Score. In FCRS, 0 to 5 points were calculated, giving 1 point for each of the following: synchronous metastatic disease (<12 months from diagnosis), lymph node–positive primary, >1 lesion, size >5 cm, and CEA > 200 μg/L.[2] The Oslo Score (0 to 4 points) was calculated by giving 1 point for each of the following pretransplant characteristics: largest lesion >5.5 cm, plasma CEA levels >80 μg/L, time from surgery of primary tumor to LT of <2 years, and progressive disease on chemotherapy at time of LT.[13]

2.1 | Statistical analyses

OS and DFS were estimated by using the KM method. Log-rank test was used to compare outcome between groups. Difference between

groups was compared by Mann-Whitney *U* test. A 2-tailed probability level <.05 was considered statistically significant. Analyses were performed with SPSS version 25 (IBM, Armonk, NY).

3 | RESULTS

The baseline characteristics of the 19 patients are given in Table 1. Three of the patients had metachronous liver metastases. Sixteen had (y)pT3 primary tumor, with (y)pN + in 10 patients. Ten patients had MTV < 70 cm^3. The median follow-up of patients alive at the cut-off date of this report is 85 months.

Patients with MTV < 70 cm^3 (low MTV) had significantly lower median number (*P* = .022) and size (*P* = .002) of liver metastases compared with patients with MTV > 70 cm^3 (high MTV, Table 2). Patients with low MTV also had significantly lower median CEA levels, FCRS, and Oslo Score compared with patients with high MTV, with *P* values of .001, .001, and .004, respectively. There was no significant difference between the MTV groups in sex, T stage, N stage, *KRAS* mutated patients, right- vs left-sided primary tumor, or time from primary surgery to LT (Table 2).

The 9 patients with MTV > 70 cm^3 were observed until death. They had a median OS of 27 months from transplant (range 6-86 months). Eight of the 10 patients with MTV < 70 cm^3 are alive 33 to 147 months after LT, and 7 have been observed for >5 years. Two patients died after 33 and 57 months, respectively. Patients with MTV < 70 cm^3 had significant longer DFS, OS, and OS from time of relapse compared with patients with MTV > 70 cm^3 (Figure 1A-C). Median DFS was 23.0 and 3.5 months in the low- and high-MTV groups, respectively (*P* < .001), and 5-year OS was 78% and 22%, respectively (*P* = .001). Five-year OS from time of relapse was 71% vs 11% in the low- and high-MTV groups, respectively (*P* = .014).

Six patients had an FCRS of 0 to 2, and 13 patients had an FCRS of 3 to 5. Patients with an FCRS of 0 to 2 had significantly longer DFS, OS, and OS after relapse compared with patients with a score of 3 to 5 (Figure 2A-C). Median DFS in patients with an FCRS of 0 to 2 and 3 to 5 was 23 and 6 months, respectively (*P* = .023). Two patients with FCRS of 0 to 2 have been observed for 55 and 71 months without signs of relapse. In contrast, all 13 patients with an FRCS of 3 to 5 had a relapse within 47 months. All 6 patients with FCRS of 0 to 2 were alive 33 to 147 months after LT, whereas 5-year OS in patients with an FRCS of 3 to 5 was 31% (*P* = .004), with 2 patients still alive after 65 and 98 months after LT (Figure 2B). No patient with an FRCS of 5 survived for 5 years. Four patients with an FRCS of 0 to 2 had recurrence. They are all alive 15 to 115 months after relapse, whereas 5-year OS from time of relapse in patients with an FRCS of 3 to 5 was 15% with 2 of the 13 patients alive 51 and 59 months after relapse (*P* = .010, Figure 2C).

Thirteen patients had an Oslo Score of 0 to 2 and 6 patients had an Oslo Score of 3 to 4. Patients with an Oslo Score of 0 to 2 had significantly longer DFS, OS, and OS after relapse compared with patients with score of 3 to 4, with *P* values of .004, .004, and .019, respectively (Figure 3A-C). Median DFS in patients with an Oslo Score of 0 to 2 was 19 months, compared with only 3 months in patients with an Oslo Score of 3 to 4. All patients with an Oslo Score of 3 to 4 had a relapse, whereas 2 patients with an Oslo Score of 0

TABLE 1 Baseline characteristics and previous treatments (N = 19)

Age at LT (median, range)	56.8 (28.7-71.1) y
Sex (female/male)	8/11
Treatment before resection of primary	
No treatment	12
Chemotherapy	3
Chemoradiation therapy	3
Chemotherapy + radiation therapy	1
Primary	
ypT0	2
(y)pT2	1
(y)pT3	16
(y)pN0	9
(y)pN1	4
ypN2	6
Location of primary	
Right colon	4
Colon transversum	1
Left colon	2
Sigmoid	4
Rectum	8
Chemotherapy before LT	
First line	7
Second line	9
Third line	3
Chemotherapy given before LT	
5-Fluorouracil	19
Irinotecan	16
Oxaliplatin	15
EGFR antibody	4
Bevacizumab	7
At time of LT	
KRAS mutation/wt/unknown	5/13/1
CEA at LT (μg/L, median and range)	5 (1-2002)
FCRS at LT (median and range)	3 (1-5)
Median number of lesions on CT scan at LT (range)	7 (1-53)
Median size of lesions on CT scan at LT (range)	45 mm (7-130 mm)
Time from diagnosis to LT (median and range)	24.0 mo (5.8-78.1 mo)
Time from primary surgery to LT (median and range)	22.3 mo (2.3-78.1 mo)

CEA, carcinoembryonic antigen; CT, computed tomography; EGFR, epidermal growth factor receptor; FCRS, Fong Clinical Risk Score; LT, liver transplant.

TABLE 2 Different parameters between MTV < 70 cm^3 and MTV > 70 cm^3 groups at time of transplant (median and range)

	MTV < 70 cm^3 (n = 10)	MTV > 70 cm^3 (n = 9)	*P* value[a]
Time from primary surgery to LT (mo)	14 (2-78)	23(6-36)	.905
Age, y	59 (53-71)	54 (29-60)	.028
Sex (female/male)	4/6	4/5	.905
FCRS at LT	2 (1-4)	4 (3-5)	.001
Oslo Score at LT	1 (0-2)	3 (0-4)	.004
No. of lesions	5 (1-36)	22 (4-53)	.022
Size of lesions (mm)	30 (7-52)	96 (26-130)	.002
CEA (μg/L)	2 (1-30)	274 (3-2002)	.001
KRAS (wt/mutant)	2/7	3/6	.730
(y)pT-stage	T2 = 1, T3 = 9	T0 = 2, T3 = 7	.604
(y)pN-stage	N0 = 7, N2 = 3	N0 = 2, N1 = 4, N2 = 3	.079
Right- vs left-sided	1/9	3/6	.400

CEA, carcinoembryonic antigen; FCRS, Fong Clinical Risk Score; LT, liver transplant; MTV; metabolic tumor volume.

[a]Nonparametric Mann-Whitney *U* test.

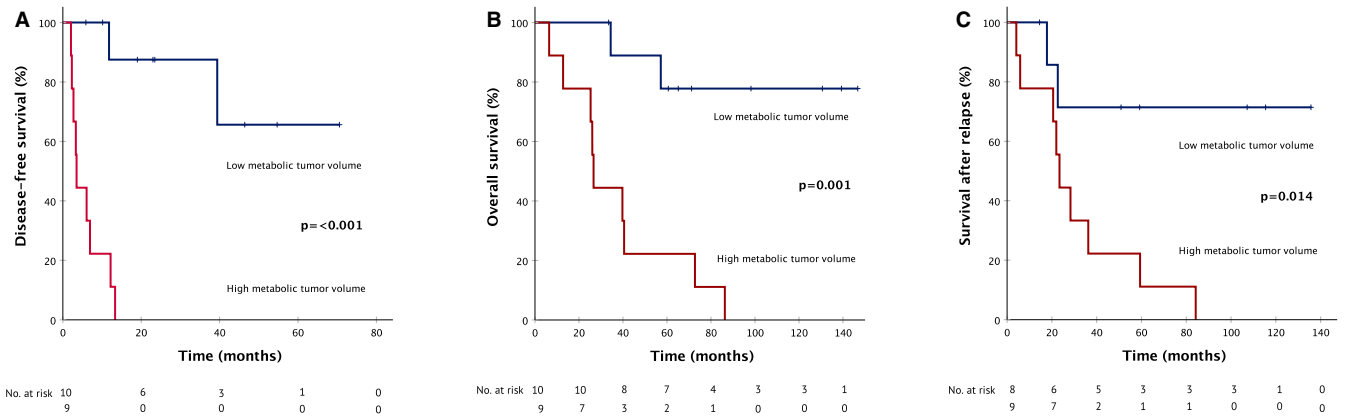

FIGURE 1 Disease-free survival (A), overall survival (B), and survival after relapse (C), from time of liver transplant in patients with colorectal cancer with nonresectable liver-only metastases receiving liver transplant. Metabolic tumor volume (MTV) in liver determined by PET scans. Blue line, MTV < 70 cm^3; red line, MTV > 70 cm^3 [Color figure can be viewed at wileyonlinelibrary.com]

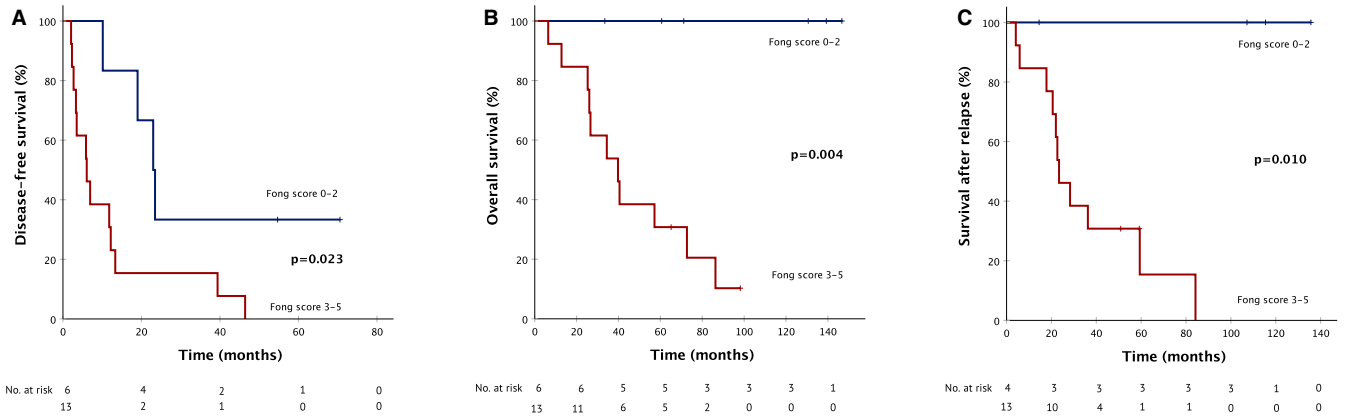

FIGURE 2 Disease-free survival (A), overall survival (B), and survival after relapse (C), from time of liver transplant in patients with colorectal cancer with nonresectable liver-only metastases receiving liver transplant. Blue line, Fong Clinical Risk Score 0 to 2; red line, Fong Clinical Risk Score 3 to 5 [Color figure can be viewed at wileyonlinelibrary.com]

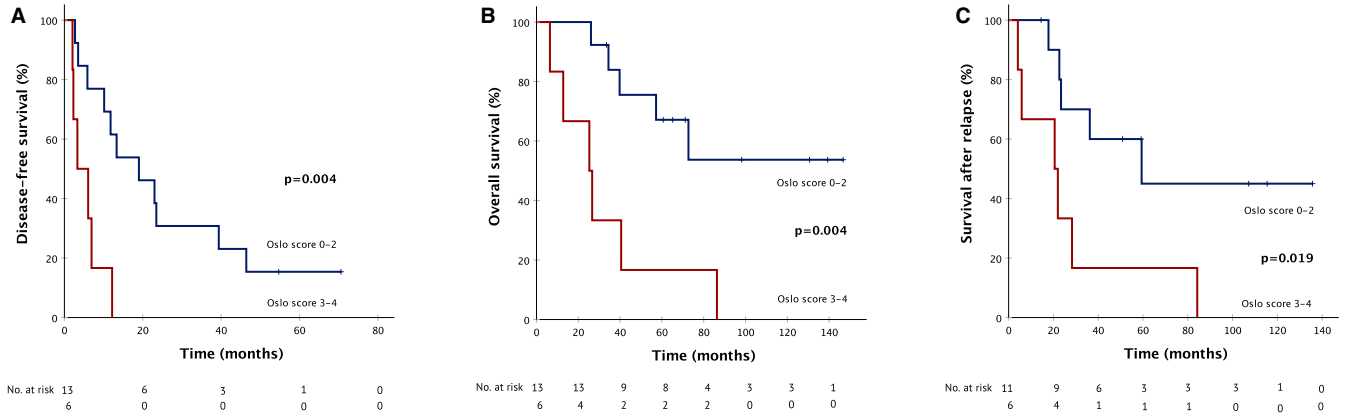

FIGURE 3 Disease-free survival (A), overall survival (B), and survival after relapse (C), from time of liver transplant in patients with colorectal cancer with nonresectable liver-only metastases receiving liver transplant. Blue line, Oslo Score 0 to 2; red line, Oslo Score 3 to 5 [Color figure can be viewed at wileyonlinelibrary.com]

to 2 have been observed for 55 and 71 months without a relapse. These are the same patients as the 2 patients with an FRCS of 0 to 2 without signs of recurrence. The 5-year OS in patients with an Oslo Score of 0 to 2 was 67% compared with 17% in patients with an Oslo Score of 3 to 4 (Figure 3B). The longest OS in patients with an Oslo Score of 3 to 4 was 86 months. In contrast, a patient is alive after 33 months, and 7 of 13 patients with an Oslo Score of 0 to 2 are alive >60 months after LT, with 1 patient observed for 147 months posttransplant. No patient with an Oslo score of 4 survived for 5 years. Patients with an Oslo Score of 0 to 2 had 5-year OS from time of relapse of 45% compared with 17% in patients with an Oslo Score of 3 to 4 (P = .019; Figure 3C). One patient with an Oslo Score of 0 to 2 is still alive 136 months after relapse.

Five patients had *KRAS* mutant and 13 had *KRAS* wild-type (wt) tumors, whereas *KRAS* mutation status could not be determined in 1 patient. There was no significant difference in OS between patients with *KRAS* wt and mutant status (median 73 months vs 40 months, P = .754).

Four patients had a primary tumor in the ascending colon (right-sided primary tumor) compared with 15 patients with their primary tumor in the transverse colon (n = 1), left colon (n = 2), sigmoid (n = 4), or rectum (n = 8) (left-sided primary tumors). Patients with right-sided primary tumor had significantly reduced DFS compared with patients with left-sided tumors, with a median DFS of 4 months and 13 months, respectively (P = .044; Figure 4A), and OS was 6 to 40 months in the right-sided group. In comparison, patients with left-sided primary had a median OS of 86 months and 5-year OS of 66% (P = .001; Figure 4B). Further, patients with right-sided tumors had shorter OS from time of relapse compared with left-sided tumors (P = .016), and all patients with right-sided primary tumors were dead at 37 months after the recurrence. In contrast, the median OS from time of relapse in patients with left-sided tumors was 59 months, with 3 patients alive 107 to 136 months after relapse (Figure 4C). There was no significant difference in age, sex, MTV, MTV < 70 cm^3, FCRS, Oslo Score, CEA level, largest liver lesion, and number of liver lesions between right-sided tumors and left-sided tumors. However, right-sided tumors had borderline more *KRAS* mutated tumors (P = .079) (Table 3).

Nine patients had elevated CEA plasma levels at time of LT. They all relapsed within 2 years from LT, whereas 2 patients with normal CEA levels were observed for 55 and 71 months without

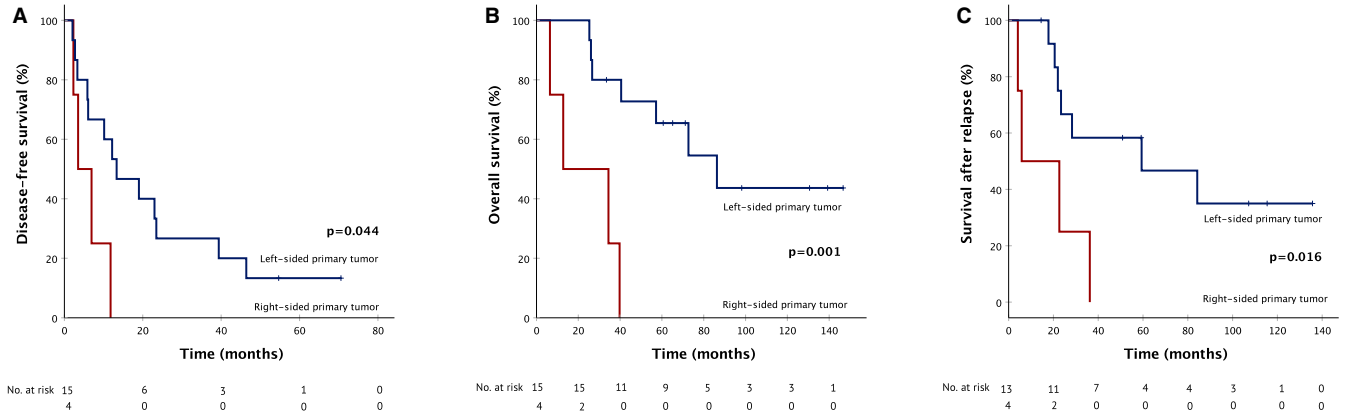

FIGURE 4 Disease-free survival (A), overall survival (B), and survival after relapse (C), from time of liver transplant in patients with colorectal cancer with nonresectable liver-only metastases receiving liver transplant. Red line, right-sided primary tumor; blue line, left-sided primary tumor [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Different baseline parameters between right- and left-sided primary tumors at time of transplant (median and range)

	Right-sided (n = 4)	Left-sided (n = 15)	*P* value[a]
Time from primary surgery to LT (mo)	9 (6-29)	23(2-78)	.124
Age, y	49 (29-61)	58 (45-71)	.152
Sex (female/male)	3/1	5/10	.221
FCRS at LT	3.5 (3-5)	3 (1-5)	.411
Oslo Score at LT	2.5 (2-4)	1 (0-4)	.185
No. of lesions	11 (5-35)	7 (1-53)	.665
Size of lesions (mm)	75 (30-119)	34 (7-130)	.357
CEA (μg/L)	140 (2-279)	4 (1-2002)	.530
KRAS (wt/mutant)	1/3	12/2	.079
(y)pT-stage	T0 = 1, T3 = 3	T0 = 1, T2 = 1, T3 = 13	.736
(y)pN-stage	N0 = 1, N1 = 1, N2 = 2	N0 = 8, N1 = 3, N2 = 4	.357
MTV (cm^3)	123 (0-874)	23 (0-397)	.530
MTV < 70 cm^3 vs > 70 cm^3	1/3	9/6	.307

CEA, carcinoembryonic antigen; FCRS, Fong Clinical Risk Score; LT, liver transplant; MTV; metabolic tumor volume.

[a]Nonparametric Mann-Whitney *U* test.

recurrence. Median DFS in patients with CEA levels within and beyond the normal range was 12 and 6 months, respectively (*P* = .055). The 5-year OS in patients with elevated CEA as opposed to within normal levels was 40% and 60%, respectively (*P* = .150). Patients with CEA values in the normal range at time of LT had 5-year OS after relapse of 50% compared with 13% in patients with elevated CEA values (*P* = .424).

KM-estimated OS and range of OS observed based on the 3 selection criteria (PET MTV values < 70 cm^3, FCRS of 0 to 2, and Oslo Score of 0 to 2) are given in Table 4. An FCRS of 0 to 2 gave the best OS, but a selection based on an FRCS of 0 to 2 would mean that fewer than half of the patients would have been offered a transplant compared with the Oslo criteria of 0 to 2. The 6 patients with an FRCS of 0 to 2 all had MTV < 70 cm^3 and an Oslo Score of 0 to 2, with 3 having an Oslo Score of 0 and 2 having a score of 1, and the last 1 having an Oslo Score of 2. The 3 patients with metachronous liver metastases and lymph node–negative primary tumor were in the FCRS 0-to-2 group. These 3 patients are all alive >10 years (131 to 147 months) after LT and 107 to 136 months after relapse.

4 | DISCUSSION

The 5-year OS in patients with a median of 1 resectable CRLM is about 50% both with and without neo-/adjuvant chemotherapy.[4] Patients with nonresectable CRLM have a median OS from the start of first-line chemotherapy of about 2 years and 5-year OS of about 10%.[6-9,16] Selective internal radiation therapy in addition to standard chemotherapy did not increase OS in a randomized trial.[17] Further, patients with intolerance or progressive disease on second or third lines of chemotherapy have a median OS of about 5 to 7 months. The new approved drugs in metastatic CRC—regorafenib and TAS-102—increased OS by 1.4 to 1.8 months compared with best supportive care.[18,19] In a similar cohort of patients, we have previously shown that LT results in a median OS of 41 months and a 5-year OS of 44%,[20] indicating the superiority of LT compared with oncological treatment. In the present report, a 5-year OS of up to 100% in highly selected cases was obtained (6/19 patients). The scarcity of organs mandates selection of the patients who benefit the most from LT. In this report, we present mature long-term data after LT. All the patients still alive were followed for >5 years, except 1 patient with a follow-up of 34 months.

The total number and size of the largest lesion are of prognostic importance for outcome in transplant for HCC. Patients within the Milan criteria have in general a 5-year OS of about 75%,[10] whereas increasing the number and size of largest lesion reduces the 5-year OS according to the "metro-ticket" concept.[21] Recently, biological markers have been added to the metro-ticket concept. Similarly, a scoring system based on morphology of liver lesions and factors like CEA may be used for selecting patients with CRLM for LT to obtain long OS.[13,15]

The majority of the patients experienced a relapse; however, in contrast to HCC with recurrence, the CRC cohort had a long OS from the time of relapse,[22] exceeding 5 years in many cases (Figures 1C, 2C and 3C). The long survival time after relapse might be explained by that the recurrences were mostly slow growing and often resectable pulmonary metastases, thus providing the patients a status of no evidence of disease.[23]

The current report shows that different scoring systems may select patients with CRLMs to obtain long-term OS (Figures 1B,

TABLE 4 Overall survival after liver transplant based on different selection criteria

Group	No. of patients	Overall survival (mo)	Kaplan-Meier 5-y overall survival (%)	No. of patients observed >5 y[a]	No. of patients who died before 5 y
MTV < 70 cm^3	10	33-147	78	7/9	2
FCRS 0-2	6	33-147	100	5/5	0
Oslo Score 0-2	13	22-147	67	8/12	3

FCRS, Fong Clinical Risk Score; MTV; metabolic tumor volume.

[a]One additional patient is alive 33 months after liver transplant.

2B, and 3B). The tradeoff in applying very stringent criteria is obviously that few patients will be eligible. Low FCRS (0 to 2) provided the highest 5-year OS but would limit the cohort to 30% of the patients. All of the 3 scoring systems separated patients with long vs short OS after relapse, but which selection criterion to use is dependent on what is considered an acceptable survival outcome balanced against waiting times and waitlist mortality in the region. Access to living donation might lead to different considerations. Because recurrence alone is not predictive of short survival, DFS is not an appropriate outcome parameter with which to assess the efficacy of LT in CRLM.[22]

Similar to the experience seen in liver resection[24-26] and palliative chemotherapy,[27] right-sided tumors were associated with an inferior outcome, with no patient surviving 5 years. Thus, caution is probably warranted in offering these patients LT (Figure 4B).

Metachronous disease was associated with long OS with 2 patients alive 10.9 to 12.3 years after LT; 1 additional patient died after 7.7 years of a sudden, unrelated cardiovascular event. These findings, although based on small numbers, suggest that patients with metachronous disease have a considerable benefit of LT compared with palliative chemotherapy.

The data presented are mature with median follow-up of 85 months. The majority of low-risk patients are alive, and median OS in these groups will increase even further. Using the presented scoring systems and considering clinical parameters like metachronous disease and location of the primary tumor, a selection ensuring an OS comparable to standard indications for LT is possible. Based on the 3 scoring systems, 0.24 to 0.51 patient per 1 million people per year would be eligible, representing 1% to 2% of yearly transplants in United States. A consequence of the present results suggests that highly selected patients with CRC may be considered for LT as part of prospective studies because the total world experience is still limited.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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DATA AVAILABILITY STATEMENT

This was a retrospective analysis of data from the prospective SECA-I[12] and SECA-II[13] studies.

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