Original article

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Liver transplantation for unresectable colorectal liver metastases in patients and donors with extended criteria (SECA-II arm D study)

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Background: **Patients with metastatic colorectal cancer receiving palliative chemotherapy have a 5-year survival rate of approximately 10 per cent. Liver transplantation using strict selection criteria in patients with colorectal cancer and unresectable liver-only disease will result in a 5-year survival rate of 56–83 per cent. The aim of this study was to evaluate survival of patients with colorectal liver metastases (CRLM) after liver transplantation using extended criteria for both patients and donors.**

Methods: **This was a prospective single-arm study. Patients with synchronous unresectable CRLM who were not suitable for arms A, B or C of the SEcondary CAncer (SECA) II study who had undergone radical resection of the primary tumour and received chemotherapy were included; they underwent liver transplantation with extended criteria donor grafts. Patients who had resectable pulmonary metastases were eligible for inclusion. The main exclusion criteria were BMI above 30 kg/m^2 and liver metastases larger than 10 cm. Survival was estimated using Kaplan–Meier analysis.**

Results: **Ten patients (median age 54 years; 3 women) were included. They had an extensive liver tumour load with a median of 20 (range 1–45) lesions; the median size of the largest lesion was 59 (range 15–94) mm. Eight patients had (y)pN2 disease, six had poorly differentiated or signet ring cell-differentiated primary tumours, and five had primary tumour in the ascending colon. The median Fong clinical risk score was 3 (range 2–5) and the median Oslo score was 1 (range 1–4). The median plasma carcinoembryonic antigen level was 4·3 (range 2–4346) μg/l. Median disease-free and overall survival was 4 and 18 months respectively.**

Conclusion: **Patients with unresectable liver-only CRLM undergoing liver transplantation with extended patient and donor criteria have relatively short overall survival.**

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Introduction

Colorectal cancer is one of the most common malignancies worldwide and a leading cause of cancer-related death in Western countries[1]. About 25 per cent of patients present with synchronous metastases, and overall about 50 per cent develop liver metastases. Liver resection is currently considered the only curative option for patients with colorectal liver metastases (CRLM), with 5-year survival rates ranging from 25 to 50 per cent after complete resection[2,3]. However, only about 20 per cent of patients are candidates for curatively intended liver resection, and the majority develop further recurrence[3–5]. The standard treatment for patients with unresectable CRLM is palliative chemotherapy. The expected median overall survival (OS) from the start of first-line chemotherapy is about 2 years, and the 5-year OS rate is approximately 10 per cent[6].

The indication for liver transplantation (LT) has broadened in recent years, and LT is now considered the standard of care for patients with end-stage liver disease, as

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Patients with unresectable liver metastases from colorectal cancer	Weight loss > 10 per cent in the last 6 months
Previous resected primary tumour with histological evidence of adenocarcinoma	Patient BMI > 30 kg/m^2
No signs of extrahepatic metastatic disease or local recurrence according to PET/CT	Other malignancy not treated curatively
No signs of extrahepatic metastatic disease or local recurrence according to CT or MRI (thorax/abdomen/pelvis) within 4 weeks before the faculty meeting at the transplant unit	Known hypersensitivity to rapamycin
If previous local relapse or extrahepatic lymph node metastases, these lesions should have been treated curatively more than 1 year before inclusion in the study	Largest liver metastasis > 10 cm
No signs of local recurrence as judged by colonoscopy/CT colography within 12 months before the faculty meeting at the transplant unit	Palliative resection of primary colorectal cancer
Patients at least 18 years of age	Pregnant or breastfeeding women
Good performance status, ECOG grade 0 or 1	Any reason why, in the opinion of the investigator, the patient should not participate
Satisfactory blood test results: Hb > 10 g/dl; neutrophils > $1{\cdot}0 \times 10^9$/l (after any G-CSF); TRC > 75×10^9/l bilirubin < two times upper limit of normal; ASAT and ALAT < five times upper limit of normal; creatinine < 1·25 times upper limit of normal; albumin > lower normal level	
Standard surgical procedure with adequate resection margins including CRM of at least ≥ 2 mm for patients with rectal cancer	
No extrahepatic disease at time of liver transplantation, except patients may have resectable pulmonary lesions (< 15 mm) at time of inclusion in the study	
The patient may be included without further chemotherapy treatment. If treated by chemotherapy, the patient should have response or stable disease according to RECIST 1.1	
Signed informed consent and expected cooperation of the patient for the treatment and follow-up must be obtained and documented according to good clinical practice and national/local regulations	

ECOG, Eastern Cooperative Oncology Group; Hb, haemoglobin; G-CSF, granulocyte–macrophage colony-stimulating factor; TRC, thrombocytes; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; CRM, circumferential resection margin; RECIST, Response Evaluation Criteria In Solid Tumors.

well as for selected patients with malignant liver tumours such as hepatocellular carcinoma and liver metastases from low-grade neuroendocrine cancer[7,8]. Some transplant centres also accept patients with hilar cholangiocarcinoma[9]. LT for malignancy has increased over time, and LT for malignant tumours comprises 16·5 per cent of all LTs in the European Liver Transplant Registry (www.eltr.org).

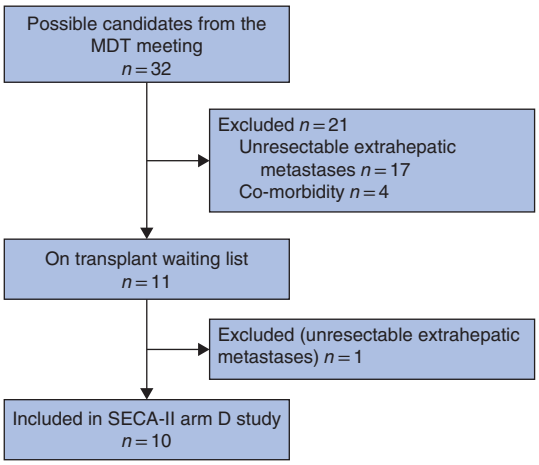
The present authors have reported previously on the outcome of the SECA-I study, in which 21 patients with unresectable CRLM underwent LT, with a 5-year OS rate of 60 per cent[10]. The recently published SECA-II study[11], which had more strict selection criteria than SECA-I, included 15 patients, and the 5-year Kaplan–Meier-estimated OS rate was 83 per cent at a median follow-up of 36 months. Furthermore, Toso and colleagues[12] reported a 5-year OS rate of 50 per cent in 12 patients with colorectal cancer who had LT in 1995–2015 outside study protocols.

The scarcity of donor organs for LT in most countries is a major challenge. In the USA, the waiting list mortality rate of approximately 20 per cent is driven primarily by low organ availability relative to demand[13]. Hence, it is a challenging process to implement LT as a treatment option for selected patients with unresectable CRLM, even when it seems likely that they might obtain similar, or even better, 5-year survival than patients undergoing retransplant for non-malignant end-stage liver disease, which today is considered an established indication[14].

Based on the SECA-I study, negative predictive factors for short OS appear to be a maximum tumour size above 5·5 cm, progressive disease on chemotherapy, interval from resection of the primary tumour to transplant less than 24 months, and pretransplant carcinoembryonic antigen (CEA) level greater than 80 μg/ml. A score assigning one point to each of these factors has been termed the Oslo score. The criteria of the Oslo score are probably good surrogate markers of favourable tumour biology. Although the scoring might be useful for selecting patients, it does not consider various other clinicopathological features of the disease that are relevant for prognosis in a non-transplant setting, such as location of the primary (right-sided *versus* left-sided and rectal), *BRAF* mutation status, histological differentiation, and node status of the primary.

This article presents the findings in ten patients with unresectable CRLM who, for different reasons, did not

Fig. 1 Flow diagram of patients included in the SECA-II arm D study



MDT, multidisciplinary team.

meet the strict inclusion criteria for the arms A, B and C of the SECA-II study[11]; hence this study is named the SECA-II arm D study. These patients were included in a study protocol with less strict inclusion criteria using an extended criteria donor (ECD) graft that did not meet the criteria for routine use in patients on the regular waiting list, thereby not impacting on the waiting list negatively. The majority of the patients (9 of 10) were transplanted with an ECD graft.

The aim of the present study was to investigate the effect of wider selection criteria for both recipients and donors than those used in the SECA-II study on OS after liver transplantation in patients with unresectable CRLM.

Methods

The SECA-II arm D study (NCT01479608) was a prospective study including patients with unresectable CRLM. It received approval from the regional ethics committee and institutional review board. All patients gave signed informed consent before inclusion. Inclusion and exclusion criteria are shown in *Table 1*. In contrast to the SECA-I study (NCT01311453) and previous SECA-II study (NCT01479608), patients who had resectable pulmonary metastases or who had previously undergone resection of pulmonary metastases were also eligible for inclusion. The patients should have received chemotherapy before inclusion, but there was no prerequisite regarding the

Table 2 Patient and donor characteristics

Patient no.	Reason for exclusion from arm C of SECA-II study	Other	ECD organ	Donor sex and age (years)
1	Previous extrahepatic disease (resection of pulmonary metastases)	pT3 N0; maximum of 2 CRLM	Brain tumour (ependymoma)	F, 23
2	Less than 10 per cent response	pT3 N2, poorly differentiated; right side; maximum of 35 CRLM	Older age	F, 78
3	Less than 1 year from primary diagnosis; possible pulmonary metastases	T3 N2, signet ring cell; right side; maximum of 40 CRLM	Hepatitis B (HBsAg+, HBcAg+); DCD donor	F, 52
4	Progressive disease (on third line)	ypT2 N2, moderately differentiated; right side; maximum of 40 CRLM	Graft 1: > 80% steatosis	Graft 1: M, 69
			Graft 2: Urinary bladder cancer	Graft 2: M, 66
5	Less than 10% response	pT3 N2, poorly differentiated; *BRAF* mutation; maximum of 50 CRLM	Normal liver	F, 49
6	Less than 1 year from primary diagnosis; less than 10% response	pT3 N2, poorly differentiated, *BRAF* mutated; right side; maximum of 45 CRLM	Hepatitis B (HBsAg+); split liver (segments I + IV–VIII)	F, 29
7	Relapse/new primary; less than 10% response	ypT2 N0, well differentiated; maximum of 15 CRLM	Lymphogranulomatosis in 1975 (chemotherapy)	M, 55
8	Less than 10% response	pT4 N2, moderately/poorly differentiated; maximum of 20 CRLM	Hepatitis B (HBsAg+, HBcAg+)	F, 71
9	Less than 10% response; other malignancy (papillary thyroid carcinoma)	ypT3 N2, poorly differentiated; maximum of 30 CRLM	Hepatitis B (HBsAg+)	M, 22
10	Surgical removal of ovarian metastases; progressive disease	pT3 N2, moderately differentiated; right side; maximum of 50 CRLM	Hypernatraemia, raised transaminases due to cardiac arrest	F, 47

ECD, extended criteria donor; CRLM, colorectal liver metastases; HBsAg, hepatitis B surface antigen; HBcAg, hepatitis B core antigen; DCD, donation after circulatory death.

Table 3 Baseline characteristics and previous treatments

	No. of patients* (*n* = 10)
Age at LT (years)†	54 (30–70)
Sex ratio (F : M)	3 : 7
ECOG grade	
0	6
1	4
Treatment before resection of primary	
None	7
Chemotherapy	2
Chemoradiotherapy	1
Baseline characteristics of primary tumour	
pT1	0
ypT2	2
(y)pT3	7
pT4	1
(y)pN0	2
pN1	0
(y)pN2	8
Location of primary	
Right colon	5
Transverse colon	1
Left colon	0
Sigmoid colon	3
Rectum	1
No. of chemotherapy lines before LT	
1	10
2	10
3	3
Type of chemotherapy before LT	
5-Fluorouracil	10
Irinotecan	10
Oxaliplatin	9
EGFR antibody	5
Bevacizumab	6
Progressive disease at LT	2
***KRAS* status**	
Mutated	3
Wild-type	7
CEA (μg/l)†	
At LT	4 (2–4346)
Maximum level	31 (4–5087)
Other treatment before LT	2
Liver resection	2 (1 and 5 resections)
No. of resected metastases	1 and 9
Size of largest resected metastasis (mm)	50 (in both patients)
RFA/microwave ablation	2‡
Maximum no. of lesions on CT/MRI†	38 (2–50)
Fong clinical score†	
At diagnosis	3 (2–5)
At LT	3 (2–5)
CT findings at LT†	
Maximum no. of lesions	20 (1–45)
Maximum size of lesions (mm)	59 (15–94)
Histological findings at LT†	
Maximum no. of lesions	9 (1–21)
Maximum size of lesions (mm)	60 (19–100)
Time from primary surgery to LT (months)†	16·5 (4–173)

*Unless indicated otherwise; †values are median (range). ‡The same two patients who had liver resection (size of metastases ablated: 12 and 30 mm). LT, liver transplantation; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; CEA, carcinoembryonic antigen; RFA, radiofrequency ablation.

response to chemotherapy at time of being listed for LT, or time from primary diagnosis to LT.

The immunosuppression protocol consisted of induction with basiliximab, corticosteroids, mycophenolate and tacrolimus the first 4–6 weeks, then conversion from tacrolimus to the mammalian target of rapamycin (mTOR) inhibitor sirolimus, aiming for a level of 5–10 μg/ml in the first 4 weeks and 10–12 μg/ml thereafter. Corticosteroids were tapered to zero within the first 6 months after LT. No patient received adjuvant chemotherapy after LT. Patients had regular outpatient follow-up visits once a month in the first year, every 3 months in the second year, and every 6 months thereafter. Treatment at the time of relapse was at the discretion of the responsible physician. Patients starting palliative chemotherapy discontinued mycophenolate at the initiation of chemotherapy.

Data before LT were collected from medical records, and data following LT were registered prospectively in a case report form.

Disease-free survival (DFS) was defined as time from LT to suspected metastatic lesions or local relapse detected by CT, MRI or PET–CT. OS was calculated from the date of LT to end of follow-up (1 April 2019). Graft survival was calculated from time of LT to either graft failure/death or end of follow-up.

Risk stratification of patients was performed using both the Fong clinical risk score[15] and the Oslo score[10] (1 point for each of the following pretransplant characteristics: largest lesion greater than 5·5 cm, plasma CEA level above 80 μg/l, time from surgery of primary tumour to LT less than 24 months, and progressive disease on chemotherapy at time of LT).

PET–CT was performed in all patients before LT to measure and calculate the metabolic tumour volume (MTV) for all liver metastases[16].

Table 4 Treatment after recurrence

Patient no.	Time from LT to recurrence (months)	First site of relapse	Treatment modality	Target organ for RT	OS after relapse (months)
1	n.a.	n.a.	n.a.	n.a.	n.a.
2	3	Multiple pulmonary metastases	Palliative RT (4 Gy × 5); chemotherapy	L2 vertebrae	8
3	16	Multiple pulmonary metastases	Chemotherapy		7 (still alive)
4	1	Multiple pulmonary metastases	Palliative RT (4 Gy × 5)	Th11–L4 vertebrae	5
5	n.a.	n.a.	n.a.	n.a.	n.a.
6	3	Multiple pulmonary metastases, lymph nodes, liver metastases, peritoneal lesion	Chemotherapy		3
7	9	Pulmonary metastases	Potentially resectable		6 (still alive)
8	9	Rectum	n.a.	n.a.	Still alive
9	3	Lymph nodes	RT (2 Gy × 25); chemotherapy; SIRT	Liver hilum and medial to segment I	13
10	5	Multiple pulmonary metastases	Chemotherapy; palliative RT (3 Gy × 10)	Left part of pelvic bone	12

LT, liver transplantation; RT, radiotherapy; OS, overall survival; L, lumbar; Th, thoracic; n.a., not applicable; SIRT, selective internal radiotherapy.

Postoperative complications within 90 days of LT were scored according to the Clavien–Dindo classification system[17].

The study protocol is given in *Appendix S1* (supporting information). The study was registered in ClinicalTrials .gov (number NCT01479608).

Statistical analysis

Survival analyses were estimated with the Kaplan–Meier method, using the log rank test to compare outcomes between two groups. Differences between median values were compared with the Mann–Whitney *U* test. For comparison between two groups with categorical variables the two-sided Fisher's exact test was used. $P < 0{\cdot}050$ was considered statistically significant. Statistical analyses were performed using IBM SPSS® version 25.0 (IBM, Armonk, New York, USA).

Results

The cohort in this report consisted of ten patients (*Fig. 1*) who, for various reasons, were not eligible for inclusion in arm C of the SECA-II study[11] (*Table 2*). One patient received a split-liver graft (segments I + IV–VIII); the rest received a full donor graft. Nine of the ten patients received a donor organ that did not meet the standard criteria for donation, including donation after circulatory death (DCD), older age donors, liver steatosis (greater than 60 per cent), donors with previous hepatitis B infection, and some donors with a previous malignancy (*Table 2*). One patient received a normal donor liver as there were no other eligible candidates on the waiting list at the time of LT.

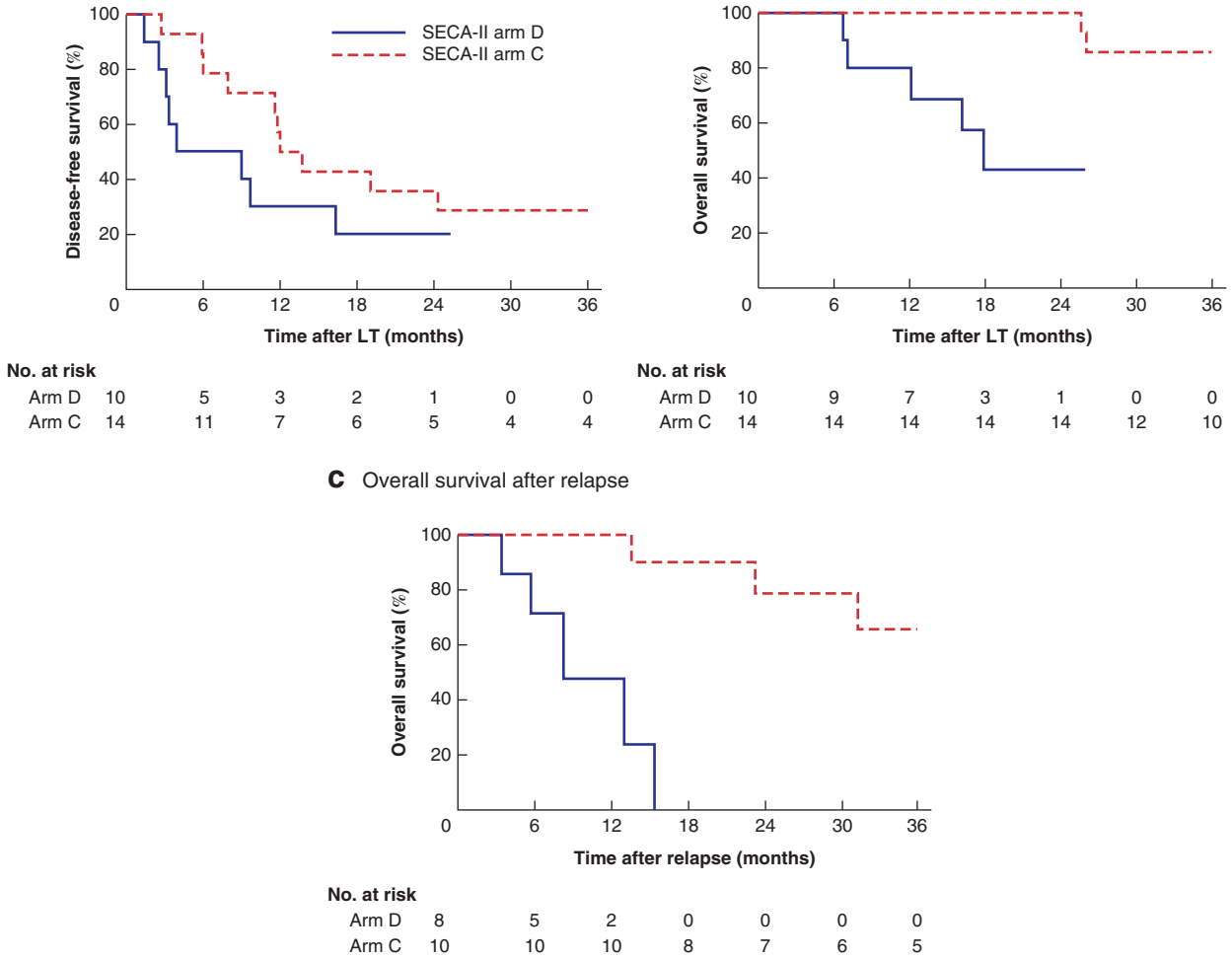
Baseline characteristics of the patients before LT are summarized in *Table 3*. Ten patients were transplanted between May 2014 and June 2018. All patients presented with synchronous CRLM, defined as liver metastases within 12 months of diagnosis of the primary colorectal tumour. The median time from primary diagnosis to LT was 17·5 (range 4–173) months.

The majority of patients had a (y)pT3 and a (y)pN2 primary tumour (7 of 10 and 8 of 10, respectively), and five patients had a right-sided primary tumour. Two patients had a *BRAF* mutation, and six had a poorly differentiated/signet ring cell-differentiated primary. All patients had received two or three lines of chemotherapy before LT, and two had progressive disease on the last line of chemotherapy at time of LT. Two patients had undergone liver resection and radiofrequency/microwave ablation treatment before LT; one of these patients had also had resection of a pulmonary metastatic lesion 8 years before LT. This patient had been diagnosed with well differentiated, lymph node-negative sigmoid cancer and synchronous liver metastases 14 years before LT. Another patient had a Krukenberg tumour removed surgically at the same time as the primary tumour 14 months before LT, and one patient was operated on for a papillary thyroid carcinoma shortly before LT.

Clinical outcome

The median follow-up of patients who were still alive was 23 months after LT. Eight of the ten patients had relapse of metastatic colorectal cancer after LT at the end of follow-up, with pulmonary metastasis being the first site of relapse in six patients. One of these six patients

Fig. 2 Kaplan–Meier analysis of disease-free and overall survival after liver transplantation, and overall survival after recurrence in SECA-II arms C and D



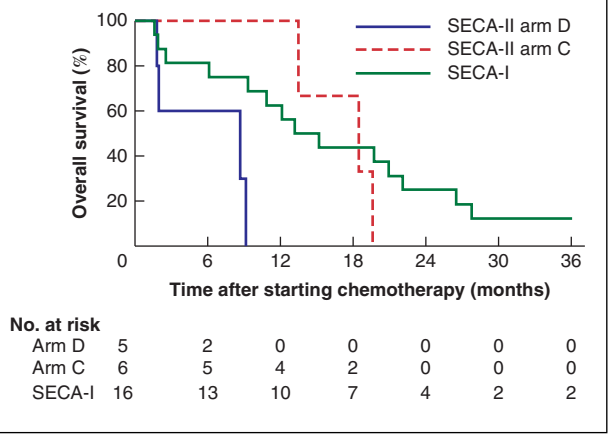
a Disease-free and **b** overall survival calculated from time of liver transplantation (LT); **c** overall survival calculated from time of relapse after LT. **a** $P = 0{\cdot}202$, **b** $P = 0{\cdot}002$, **c** $P < 0{\cdot}001$ (log rank test).

also had metastases in the donor liver graft, lymph nodes and peritoneum. The number of pulmonary metastases in the five patients with only lung metastases at time of relapse was 2–18 lesions. Six patients received palliative chemotherapy and/or palliative radiotherapy. Treatment after relapse is shown in *Table 4*. None of the patients with pulmonary metastases had resection of the pulmonary lesions due to multiplicity. One patient had local pelvic relapse 9 months after LT.

Of the ten patients included in the study, median DFS was 4 months and median OS was 18 months (*Fig. 2a,b*). Five patients were still alive at end of follow-up of 10–26 months, and two of these patients had no evidence of recurrence 23 and 26 months after LT.

Patients with right-sided primary tumour had a median DFS of 3 months and all relapsed within 16 months of LT, whereas median DFS in patients with a left-sided primary was 10 months and two patients had not relapsed 23 and 26 months after LT ($P = 0{\cdot}108$). Median OS in patients with a right-sided primary was 12 months with only one patient alive after 23 months, whereas median OS in patients with a left-sided primary was not reached ($P = 0{\cdot}104$). The one patient still alive with a right-sided primary had multiple lung metastases detected

Fig. 3 Kaplan–Meier analysis of overall survival from start of palliative chemotherapy after liver transplantation in SECA-II arms C and D, and SECA-I study



P = 0·003 (SECA-II arm C *versus* arm D), *P* = 0·018 (SECA-I *versus* SECA-II arm D), *P* = 0·918 (SECA-I *versus* SECA-II arm C) (log rank test).

at 16 months after LT, and received palliative chemotherapy. All patients with PET MTV liver values above 70 cm^3 had relapse within 10 months of LT and had died within 17 months of LT, except for one patient with two lung metastases 4 and 7 mm in size. One of the two patients with a *BRAF* mutation had OS of 6 months, and the other patient was still alive 26 months after LT with no evidence of relapse. In comparison, the eight patients with wild-type *BRAF* had a median OS of 18 months (*P* = 0·878).

Two patients had a Fong score of 2 at time of diagnosis of the primary (y)pN0 tumour; these patients were still alive at follow-up of 16 and 23 months after LT. One of these two patients was the only one with a Fong score of 2 at LT, and had no evidence of disease at the end of follow-up of 23 months.

Overall survival after relapse

Median OS after recurrence was 8 months; three of the eight patients with recurrence were still alive at end of follow-up, with OS from time of relapse of 0·6, 6·6 and 7·3 months (*Fig. 2c*). Five patients received palliative chemotherapy, one of whom was still alive 3 months after start of chemotherapy. The other four patients survived for 1–9 months after the start of palliative chemotherapy (*Fig. 3*).

SECA-II arm D *versus* SECA-II arm C and SECA-I studies

The patients included in the present study were compared with patients with synchronous liver metastases included in the SECA-I (19 patients) and SECA-II (14 patients) trials (*Table 5*). As only patients with synchronous disease were included in SECA-II arm D, only patients with synchronous disease from SECA-I and -II studies were compared. The authors have shown previously[18] that patients included in the SECA-I trial with metachronous disease had much better OS than those with synchronous liver metastases. Patients in the present study had significantly higher Fong and Oslo scores at the time of LT, and a significantly greater median number and size of largest liver metastases compared with those in the SECA-II trial (*Table 5*). There was no significant difference in plasma CEA level or pretransplant PET MTV values at the time of LT between patients in SECA-II arm D and those in arm C.

DFS in SECA-II arm D and the 14 patients with synchronous liver metastases in the SECA-II study was similar (*Fig. 2a*). However, there was a significant difference between these two transplanted groups in OS (*Fig. 2b*), and in OS after relapse (*Fig. 2c*). Kaplan–Meier analysis of OS at 2 years after LT was 100 per cent in SECA-II, 91 per cent in SECA-I and 43 per cent in SECA-II arm D. Five patients with relapse in the SECA-II arm D study died 3–13 months after the relapse.

In the SECA-II study, eight of ten patients with relapse underwent surgical treatment, whereas six of eight patients in SECA-II arm D with relapse received palliative chemotherapy and/or radiotherapy. Two patients in the arm D study may be candidates for resection of two pulmonary lesions and resection of pelvic relapse respectively. In patients starting palliative chemotherapy, median OS from the start of palliative chemotherapy was 13·1, 17·4 and 8·6 months for patients in SECA-I, SECA-II and SECA-II arm D studies respectively (*Fig. 3*).

Of patients with an Oslo score of 1–2, three of the eight patients in SECA-II arm D were alive at 2 years after LT compared with all 11 of those in SECA-I (*P* = 0·021) (*Fig. 4*).

Graft survival

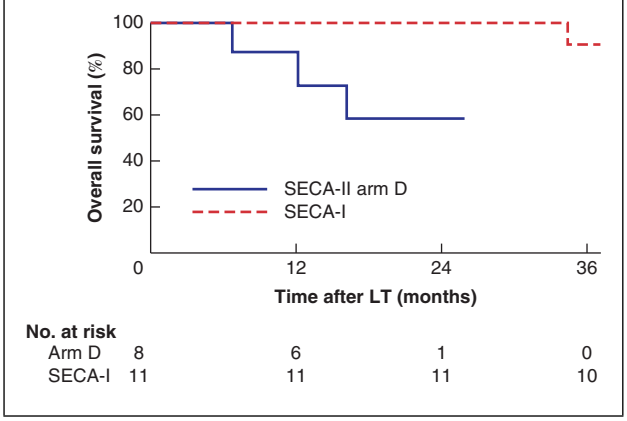
Details of donors and liver grafts are shown in *Table 2*. The median age of donors was 52 (range 22–78) years. Three patients received a graft from a donor with previous malignancy (ependymoma, urothelial carcinoma and lymphogranulomatosis). There was no evidence of transfer of any of these malignancies to the LT recipients. A total of ten ECD liver grafts were included in the analysis. The median survival of the ECD grafts was 16 months. Two donors were both hepatitis B core and surface antigen positive and the recipients were treated with entecavir after transplantation. No transfer of hepatitis B from the donors to the graft recipients was observed. One patient

Table 5 Differences in parameters between SECA-I, SECA-II and SECA-II arm D

	SECA-I ($n = 19$)	SECA-II ($n = 14$)	SECA-II arm D ($n = 10$)	P‡
Time from primary diagnosis to LT (months)	16·8 (5·7–35·9)	23·3 (13·3–78·3)	17·5 (5–173)	0·259
Age at LT (years)	53 (29–64)	59 (35–71)	54 (30–70)	0·172
Fong clinical score at LT	3 (2–5)	2 (1–3)	3 (2–5)	0·006
Oslo score at LT	2 (1–4)	1 (0–1)	1 (1–4)	0·022
Liver lesions at LT	8 (4–40)	5 (1–53)	20 (1–45)	0·016
Size of largest liver metastasis at LT (mm)	52 (28–130)	25 (3–47)	59 (15–94)	0·001
CEA at LT (μg/l)	15 (1–2002)	2·5 (1–30)	4·3 (2–4346)	0·138
MTV at LT (cm^3)	119 (0–874)	17 (0–140)	36 (0–201)	0·403
First site of relapse	Lung 10; multiple 4; liver 2, lymph node 2; pelvis 1	Lung 7; multiple 2; lymph node 1	Lung 5, multiple 1, lymph node 1; pelvis 1	
First treatment of relapse	Surgery: lung 9; multiple sites 2; liver 1; other 1	Surgery: lung 3; liver 2	Palliative RT: 3	
	RFA: lung 1	Chemotherapy: 2	Palliative chemotherapy: 3	
	Palliative chemotherapy: 4			
	Palliative RT: 1			
Time from relapse to start of treatment (months)	2·7 (0–17·1)	12·9 (0·2–32·4)	4·2 (1·5–6·3)	0·026
OS from start of chemotherapy (months)	13·1 (1·6–64·4)	18·4 (3·0–19·5)	8·6 (1·8–9·1)	0·003§
Histological differentiation of primary	Unknown	Poor 1; moderate 11; well 1; not classified 1	Poor 6; moderate 2; well 1; not classified 1	
Tumour of ascending colon†	4 (21)	1 (7)	5 (50)	0·050¶
pN2 status of primary†	7 (37)	1 (7)	8 (80)	0·001¶

Values are median (range) unless indicated otherwise; † values are number (percentage). LT, liver transplantation; CEA, carcinoembryonic antigen; MTV, metabolic tumour volume; RT, radiotherapy; RFA, radiofrequency ablation; OS, overall survival. ‡SECA-II *versus* SECA-III arm D (non-parametric Mann–Whitney *U* test); §log rank test (Kaplan–Meier analysis); ¶Fisher's exact test.

Fig. 4 Kaplan–Meier analysis of overall survival after liver transplantation in patients with an Oslo score of 1–2 in SECA-II arm D and SECA-I



LT, liver transplantation. $P = 0·021$ (log rank test).

who received a graft with more than 80 per cent steatosis had graft failure shortly after LT, and was retransplanted at day 43 with a liver graft from a donor with previous urinary bladder cancer. For nine of the ten grafts, the short graft survival was due to relapse of metastatic colorectal cancer. All patients who died from progressive colorectal disease had functioning grafts at the time of death; no death was related to a non-functioning graft.

Complications of the liver transplant procedure

Grade I and II complications were both observed in two patients each. Postoperative complications requiring interventions (grade IIIb–IVb) were registered in six of the ten patients: grade IIIb in three patients, grade IVa in two and grade IVb in one patient (retransplant) (*Table S1*, supporting information).

Discussion

The authors have reported previously[10,11] on the outcome of patients with colorectal cancer who underwent LT in the SECA-I and II studies. After a median follow-up of 27 and 36 months in SECA-I and -II, Kaplan–Meier estimates of 5-year OS were 60 and 83 per cent respectively. SECA-I was an exploratory pilot study, and the study population

was therefore heterogeneous regarding factors that may be prognostic of survival after LT, including: number and size of largest liver lesion, plasma CEA level, response to chemotherapy and time from colorectal cancer diagnosis to LT. Inclusion in the SECA-II study was more stringent, with the interval from diagnosis to LT of at least 1 year and a response rate to chemotherapy of at least 10 per cent, according to RECIST criteria[19], at the time of LT.

PET–CT is important for patient selection, enabling the detection of extrahepatic disease not seen on CT[20]. None of the patients included in the present trial had extrahepatic disease on PET–CT at time of LT. Furthermore, high liver uptake values based on PET examination (MTV value) are related to reduced OS after LT compared with that in patients with lower values[16]. Patients included in this study had moderate PET MTV liver values.

The majority of patients in SECA-II arm D, SECA-I and SECA-II studies had a relapse, with lung being the primary site. The pulmonary metastases in patients in the SECA-I and SECA-II studies were often single lesions[11], and in general these increase at a slow rate[21]. The majority of patients in SECA-I and -II studies with pulmonary metastases had resection, and obtained a status of no evidence of disease with long OS after relapse. In contrast, owing to the multiplicity of relapses for most patients in SECA-II arm D, palliative treatment was the only treatment that had been administered to date in all patients who relapsed. Furthermore, OS from the start of palliative chemotherapy was shorter in SECA-II arm D than in SECA-I and SECA-II, thus also contributing to reduced OS after relapse than in SECA-II.

Patients included in the present study were not eligible for the SECA-II study. The Kaplan–Meier analysis of OS after LT was less than 2 years, despite a low median Oslo score and relatively low Fong score and PET MTV value compared with those in the SECA-I study. In comparison, the 2-year OS rate in SECA-I and SECA-II was 90–100 per cent. The present patient cohort had a higher tumour load determined by size and number of metastatic liver lesions compared with that in SECA-I and -II. In general, the patients had several factors that were negative for survival following resection of the primary tumour and after liver resection. The majority of included patients had both a (y)pN2 primary tumour and a poorly differentiated primary tumour on histological examination. In comparison, seven of 21 patients (33 per cent) included in the SECA-I trial had a (y)pN2 primary, although histological differentiation of the primary tumour was unknown[10]. Furthermore, five of the ten patients included in the present study had a right-sided (ascending colon) primary tumour. Patients with right-sided primaries have a reduced OS after liver resection[22–24], as well as reduced OS from the start of first-line chemotherapy[25]. In the SECA-I study, none of the patients with right-sided tumours survived for 5 years after LT (unpublished results).

Patients in the present study had similar Fong scores to those in SECA-I, and patients with an Oslo score of 1–2 had significantly shorter OS than patients with a similar Oslo score in the SECA-I study, suggesting that additional factor(s) not included in the Oslo and Fong scores determine posttransplant survival in patients with colorectal cancer. The results reported for patients in SECA-II arm D suggest that, in addition to the Fong score, Oslo score and PET MTV liver uptake values, tumour location, histological differentiation and lymph node status of the primary should be taken into account when selecting patients with unresectable colorectal cancer for LT.

Only two of the ten patients were without recurrence 23 and 26 months after LT. One of these patients was transplanted more than 14 years after being diagnosed with synchronous disease and 8 years after resection of a colorectal pulmonary metastatic lesion. The patient had a left-sided (sigmoid) and lymph node-negative primary tumour, and had also undergone several liver resections and radiofrequency ablation treatments before receiving LT. Others[12] have shown that patients with colorectal cancer who have more than 3 years from diagnosis to LT have better OS than those with a shorter time between diagnosis and LT.

Two patients with a *BRAF* mutation were included in the present study. These are the only such patients known to the present authors to have undergone LT. Patients with a *BRAF* mutation have been excluded from other ongoing LT studies (ClinicalTrials.gov: NCT02864485, NCT03488953 and NCT02597348). Few patients with colorectal cancer and a *BRAF* mutation have received liver resection as, in general, these patients have reduced OS after liver resection[26]. Furthermore, patients with colorectal cancer plus metastatic disease and a *BRAF* mutation also have a reduced OS from the start of first-line palliative chemotherapy than those with the wild-type *BRAF* gene[27]. One of the two patients in the present study had a raised plasma carbohydrate antigen (CA) 19-9 level at the time of LT and relapsed shortly after surgery (at 3 months), surviving for only 6 months. The other patient with a *BRAF* mutation had a plasma CA19-9 level within the normal range at LT, and is alive and without apparent relapse after 26 months of observation. It has been shown previously[28] that patients with a *BRAF* mutation and increased plasma CA19-9 levels have very short OS when starting first-line chemotherapy. Both of the two present *BRAF*-mutated patients had (y)pN2 disease and a poorly differentiated primary tumour.

The use of ECD grafts, as performed in the present study, appears to be safe. No transfer of viral or malignant disease was observed; however, owing to the early relapse of malignant disease and short OS from time of relapse, survival of the donor grafts was short. Graft failure was observed in one patient who received a donor graft with more than 80 per cent steatosis, so caution is advisable when using severely steatotic grafts. ECD liver grafts may be used in patients with colorectal cancer as, in general, they do not have liver failure at the time of LT. By using such donor grafts, LT might be able to be offered to selected patients with colorectal cancer and expected long-term OS after LT[11,18].

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.