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ORIGINAL ARTICLE

Treatment of relapse and survival outcomes after liver transplantation in patients with colorectal liver metastases

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NCT01311453 (SECA-I study)
NCT01479608 (SECA-II study) and
NCT02215889 (Rapid study).

SUMMARY

Liver transplantation (LT) in selected colorectal cancer (CRC) patients with nonresectable liver-only metastases may result in 5-year overall survival of up to about 70–100%. However, the majority will have recurrent disease. All patients included in this report were included in prospective studies. Forty-four out of 56 patients had a relapse, and all 44 patients received treatment for recurrent disease. The organ of the first relapse was lung metastases in 23 of the 44 patients. The first treatment modality of the relapse was the treatment with curative intent in 55.8% of the patients, and chemotherapy was the first treatment administered to 25.6% of the patients. Patients receiving surgery of lung metastases had a 5-year overall survival of 66.5% from the time of metastasectomy. Patients receiving treatment with curative intent for metastases to other organs had a 5-year overall survival of 24.8%. Nine of the 44 patients had no evidence of disease (NED) at the end of the follow-up. Median time of NED in these patients was 54.3 months, and median overall survival from the time of LT was 8.4 years. Because of the high incidence of recurrent disease, these patients should have a systematic long-term follow-up since many of the relapses may be treated with curative intent.

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Key words
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Introduction

Colorectal cancer (CRC) is one of the most frequent malignancies worldwide and the second most common cause of cancer-related death in Western societies [1]. About half of the patients have metastatic disease at the time of diagnosis or will later develop such. Liver is the most frequent metastatic site [2]. Liver resection of colorectal liver metastases (CRLM) has been considered the most important curative treatment option with reported 5-year overall survival (OS) of 30–50% in most studies [3,4]. However, only a minority of patients with metastatic disease are candidates for liver resection [5]. The second most frequent site of metastasis is the lungs [6], and many centres will resect pulmonary metastases in selected patients, after observation over time with potential curative intent [7]. Even patients with both liver and pulmonary lesions may be eligible for curative surgical treatment, often following neoadjuvant chemotherapy.

The only realistic treatment option for the majority of CRC patients with metastases to liver, lung or other sites is, however, palliative chemotherapy with median OS of about 24–30 months from the start of the first-line treatment, reported in most studies [8–10]. Furthermore, median OS from the start of the second- and third-line chemotherapy is 10–12 months and about 7 months, respectively [11–13].

In 2006, a pilot study (SECA-I) re-examining LT for nonresectable CRLM was initiated at Oslo University Hospital. Despite the fact that almost all patients had relapse at the time of the first report, Kaplan–Meier-calculated 5-year OS was 60% [14]. By more strict selection criteria (SECA-II study), a 5-year OS of 83% has been reported [15]. Although the majority of CRC patients eventually will develop metastatic disease after LT, the implementation of strict selection criteria 5-year OS rates ranging from 70 to 100% may be obtained [16]. However, wider inclusion criteria will result in a considerable lower OS [17]. CRC patients developing relapse after LT may obtain long OS from the time of recurrent disease [16,18]. The present report describes the pattern and treatment of recurrence after LT for CRLM and how these factors influence OS from the time of relapse in these patients.

Materials and methods

LT in CRC patients was initiated as a pilot study in November 2006 at Oslo University Hospital. The concept of LT in CRC has been extended by several studies with different inclusion criteria [14,15,17]. All patients included in the different prospective LT studies had signed informed consent before LT, and all studies had been approved by the Regional Ethics Committee and Institutional Review Board. All the patients except one patient were considered to have nonresectable CRLM by the multidisciplinary liver team in our institution.

The different Clinicaltrail.gov registration numbers are as follows: NCT01311453 (SECA-I study), NCT01479608 (SECA-II, arm A, B, C and D) and NCT02215889 (RAPID study), respectively. The inclusion and exclusion criteria for the different LT studies, as well as immunosuppression used in the different studies, have previously been reported [14,15,17], and major criteria for the different studies are given in Table S1. There was no requirement for KRAS or BRAF wild type tumours in the different studies; however, it turned out that only two patients with BRAF mutation were included in SECA-II arm D and no patients with BRAF mutation in any of the other studies. Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography in combination with computed tomography (PET/CT) was performed on all patients prior to listing for LT to exclude patients with extrahepatic disease. Although, patients with 1–3 resectable pulmonary lesions might be included in SECA-II arm D and Rapid studies. Metabolic tumour volume (MTV) from the CRLM of each patient was obtained from the per-operative PET scans as previously described [19]. None of the patients received adjuvant chemotherapy after LT. The patients had regular out-patient follow-up once a month the first year, every three months the second year and every six months thereafter. CT scans were performed every 3 months during the first two years and then every 6 months in patients without a relapse. Treatment at the time of relapse was according to the protocols at the discretion of the physician responsible for the treatment of the patients. SD and PDL were responsible for treatment at the time of relapse. Patients that may be candidates for curative treatment of the recurrent disease were referred to HPB or Thoracic MDT meetings at Oslo University Hospital. Patients starting palliative chemotherapy or radiotherapy received treatments at their local hospitals.

Disease-free survival (DFS) was defined as the time from LT to suspected metastatic lesions or local relapse described by CT/MRI/PET-CT scans, diagnosis of another malignancy or death of any causes. OS was calculated from the date of LT to the end of follow-up (1 August 2020). Survival from the time of relapse was calculated as OS minus DFS in patients having relapse.

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Patients with small lung metastases where pulmonary resection was scheduled, in general, received pulmonary resection when the lesions reach about 10–15 mm in diameter to avoid 'missing lesions' at resection.

Risk stratification was performed using the Fong clinical risk score (FCRS) [20] as well as the Oslo Score (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 tumour to LT of less than 24 months, progressive disease on chemotherapy at the time of LT) [14] and PET-MTV-value <70 cm^3.

Statistical analyses

Survival analyses were performed using the Kaplan–Meier method. The Log-rank test was used to compare the outcome between groups. The difference between median values of groups was calculated by the nonparametric Mann–Whitney U-test. A p-value less than 0.05 was considered statistically significant. The analyses were performed by IBM SPSS version 25.0.

Results

A total of 56 CRLM patients were included in three prospective LT studies at Oslo University Hospital between November 2006 and June 2019. At the end of follow-up, 44 (79%) of these patients had a relapse after LT (23 patients in SECA-I, 19 patients in SECA-II (arm A, B, C and D) and 2 patients in the RAPID study). Baseline characteristics at the time of LT for the 44 patients with a relapse are given in Table 1. Eight patients of the total cohort of 56 patients have been observed for more than 24 months without a relapse and four of these patients have more than 60 months of follow-up. Pulmonary metastases were observed as the first recurrence of disease in 23 of 44 patients (52.3%). Other primary sites of the first relapse are given in Table 2. Median DFS was 9.0 months (range 1.3–46.4 months, Fig. 1), with 68% and 93% of the recurrences evident at 12 and 24 months, respectively. There was no difference in DFS between patients having a pulmonary relapse and other sites of the first relapse (median 10.2 months compared to 8.0 months, $P = 0.450$).

All patients with relapse have started treatment for tumour recurrence. Patients have received various treatment modalities for relapse, and some have had several separate treatments of recurrences (Figure S1).

The initial relapse treatment modality was surgery in 25 patients (56.8%), palliative chemotherapy in 11 patients

Table 1. Baseline characteristics and previous treatments (n = 44).

Age at LT (median, range)	56.7 (28.7–70.0) years
Sex (female/male)	18/26
Treatment before resection of primary	
No treatment	29
Chemotherapy	9
Chemo-radiation therapy	4
Chemotherapy + Radiation therapy	2
Primary	
(y)pT0	2
(y)pT1	1
(y)pT2	6
(y)pT3	32
(y)pT4	3
(y)pN0	15
(y)pN1	13
ypN2	16
Location of primary	
Right colon	10
Left colon	7
Sigmoideum	12
Rectum	15
Chemotherapy before LT	
1.line	15
2.line	22
3.line	7
Chemotherapy given before LT	
5-FU	44
Irinotecan	36
Oxaliplatin	37
EGFR-antibody	13
Bevacizumab	17
At time of LT	
KRAS mutation /wt/unknown	14/28/2
CEA at LT (µg/l, median and range)	7 (1–4346)
Fong Clinical Score at LT (median and range)	3 (1–5)
Oslo Score (median and range)	1 (0–4)
MTV (median and range)	32.5 cm^3 (0–874 cm^3)
Prior liver resection	36 no, 8 yes
RFA	40 no, 4 yes
Median number of lesions on CT scan at LT (range)	9 (1–53)
Median size of lesions on CT scan at LT (range)	37 mm n
Time from diagnosis to LT (median and range)	18.6 months (5.3–73.6 months)
Synchronous CRLM (≤ 12 months from diagnosis)	40 yes, 4 no

Table 2. Organ of the first relapse (n = 44).

Organ of relapse	Number of patients	Per cent of patients
Lung	23	52.3
Liver	5	11.4
Lymph node	5	11.4
Ovary	2	4.5
Local rectal	2	4.5
Adrenal	1	2.3
Multiple sites	6	13.6

(25.0%), palliative radiation therapy in 5 patients (11.4 %) radiofrequency ablation (RFA) in 3 patients (6.8%) and neoadjuvant chemo-radiation before surgery for rectal recurrence in one patient (2.3%). The various initial treatment modalities for the first site of relapse are given in Table 3, and the chemotherapy administered after LT is given in Table 4. Surgery, RFA and neoadjuvant chemo-radiation were all considered to be treatments with curative intent, whereas chemotherapy and palliative radiation therapy were considered to be palliative treatments. Median time from LT to the first treatment with curative or palliative intent was 24.0 months (95% CI 5.4–42.5 months) and 10.4 months (95% CI 5.5–15.3 months), respectively ($P < 0.001$), and five year OS from time of first treatment of relapse was 51.3% and 0%, respectively ($P < 0.001$, Fig. 2).

Furthermore, median time from relapse to start of curative treatment in patients with pulmonary metastases and other primary sites was 11.0 months (range 1.2–32.4 months) and 2.0 months (range 0–17.2 months), respectively ($P = 0.003$). One of the 16 patients treated by surgical resection of pulmonary lesions underwent in total 7 pulmonary resections from June 2008 to January 2014. The patient is still alive more than 13 years after LT. Four patients had two pulmonary resections, and 10 patients had one pulmonary resection each.

The resection of liver hilar lymph node metastases after LT was performed in four patients. These four patients also received postoperative radiation, 2 Gy × 25. Three patients underwent liver resection of metastases in donor grafts, and one patient had two liver resections post-LT. Ovarian metastases were resected in two patients, and one patient received neoadjuvant chemo-radiation and surgery for a local rectal recurrence. Furthermore, one patient was resected for adrenal metastasis, and a few days later, a single brain metastatic lesion.

Five-year OS from the start of curative intended treatment in patients with pulmonary lesions was 69.6% compared to 25.4% in patients with other sites of relapse, also receiving treatment with a curative intent (Fig. 3, $P = 0.020$).

Thirty-three out of the 44 patients with recurrence have started palliative chemotherapy. Median OS from the onset of palliative chemotherapy was 18.5 months (range 0.6–60.4 months). Palliative chemotherapy was the primary treatment modality in 11 patients, and another 22 patients had undergone surgical resection of metastases , RFA or radiotherapy prior to initiation of palliative chemotherapy.

We have previously shown that FCRS 0–2 vs 3–5, PET liver MTV values <70 cm^3 vs >70 cm^3 and Oslo Score 0–2 vs 3–4 may predict OS and OS from the time of relapse [16]. These factors were not significantly related to OS from the time of the start of palliative chemotherapy (FCRS $P = 0.283$, MTV $P = 0.200$ and Oslo Score $P = 0.123$). The 5-year OS after potential curative treatments of the recurrence was, however, 76.20% and 41.6% in patients with FCRS 0–2 vs FCRS

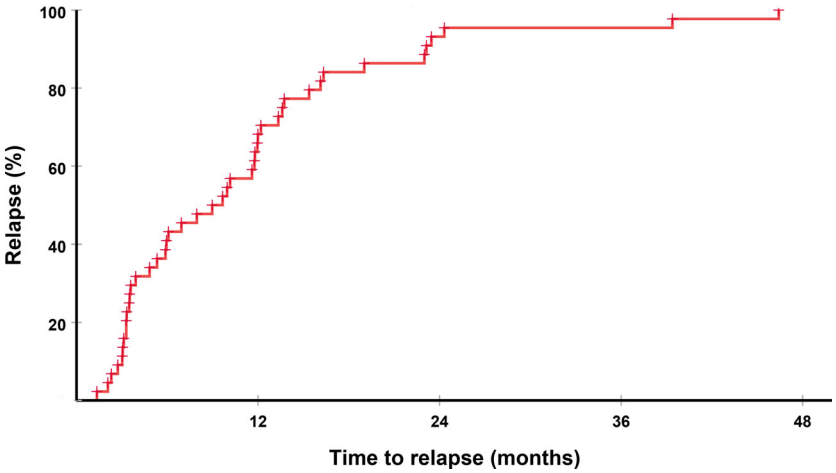

Figure 1 Time from liver transplantation to relapse in 44 patients with recurrent disease.

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Table 3. First treatment of relapse related to the first site of relapse (n = 44).

Organ of relapse	Surgery	Chemotherapy	Radiation therapy	RFA*
Lung	16	5	1	1
Liver	2	1	0	2
Lymph node	3	1	1	0
Other single site	2	0	0	0
Local rectal	0	0	1†	0
Multiple sites	2	4	2	0

*Radio frequency ablation.

†Neoadjuvant chemo-radiation (capecitabine + 2 Gy × 25).

Table 4. Chemotherapy administered after liver transplantation (n = 33).

Chemotherapy before LT	
1.line	16
2.line	9
3.line	4
4.line	3
5.line	1
Chemotherapy given after LT	
Capecitabine	12
5-FU	22
Irinotecan	23
Oxaliplatin	16
EGFR-antibody	14
Bevacizumab	6

3–5 (P = 0.217, Fig. 4a). Similarly, the 5-year OS after curative intended treatment of relapse was 67.0% and 26.7% in patients with MTV below and above 70 cm^3 (P = 0.017, Fig. 4b) and 61.0% and 16.7% in patients with Oslo Score of 0–2 vs 3–4 (P < 0.001, Fig. 4c).

Nine of the 44 patients with relapse after LT have no evidence of disease (NED) after receiving surgery or RFA of the metastatic site. Seven of these patients underwent the resection of pulmonary metastases, with two patients who were operated twice. Furthermore, two of the nine patients had RFA of small single liver metastases in the liver graft. Median time of NED status after curative treatment in these nine patients was 66.4 months, range 23.1–117.7 months with five patients having NED more than 5 years after treatment. These nine patients have a median OS from time of LT of 9.4 years (range 6.1–13.0 years), and median time from LT to last curative treatment of recurrence is 33.1 months (range 11.8–133.1 months). Three of these nine patients were diagnosed with a new primary malignancy; nonsmall cell lung cancer, prostate cancer and KRAS mutated ascending colon cancer (in a patient with KRAS wild type rectal primary), and all these tumours were treated with curative intent.

Discussion

In the pilot study (SECA-I study) revisiting LT in CRC patients initiated in 2006 including patients with nonresectable liver-only metastases, more than 50% of the patients had received two or more lines of chemotherapy, and some of the patients had progressive disease on the third-line chemotherapy at the time of LT [14]. LT resulted in longer OS compared with a similar group of CRC patients starting the first-line chemotherapy [21]. Furthermore, we have recently published that patients with extensive CRLM may benefit from LT compared with portal vein embolization and liver resection [22].

Robust clinical selection criteria utilizing FCRS, PET liver uptake MTV values and Oslo Score may separate CRLM patients with long and inferior OS after LT and 5-year OS of about 70–100% may be obtained [16]. Applying strict inclusion criteria to obtain such high 5-year OS will result in few CRC patients being candidates for LT. Furthermore, FCRS, PET liver uptake MTV values and Oslo Score also predict patients who will have long vs short OS from the time of relapse .

The majority of the patients had a relapse after LT. Despite the high recurrence rate, adjuvant chemotherapy was not included in the study protocols. The reason for not including adjuvant chemotherapy in the protocols was the following: No randomized studies have shown a significant improvement in OS in patients with CRLM having liver resections. Although less than 400 patients have been included, these adjuvant CRLM studies compared with more than 2000 patients in adjuvant colon cancer studies. The EORTC study with 364 CRLM patients with 1–4 CRLM with a median of one lesion and no patients having prior to inclusion been exposed to oxaliplatin, resulted in about 4% increased 5-year OS [23]. According to the EORTC-study protocol, these patients should receive 3 months of neoadjuvant and 3 months of adjuvant chemotherapy compared with no chemotherapy in the control arm of the study [23]. Furthermore, the chemotherapy treatment resulted in considerable toxicity with less than 50% of the included patients receiving the protocol specified chemotherapy treatment. According to standard practice adjuvant treatment in CRC, patients should be started within 8 weeks after surgery. Starting

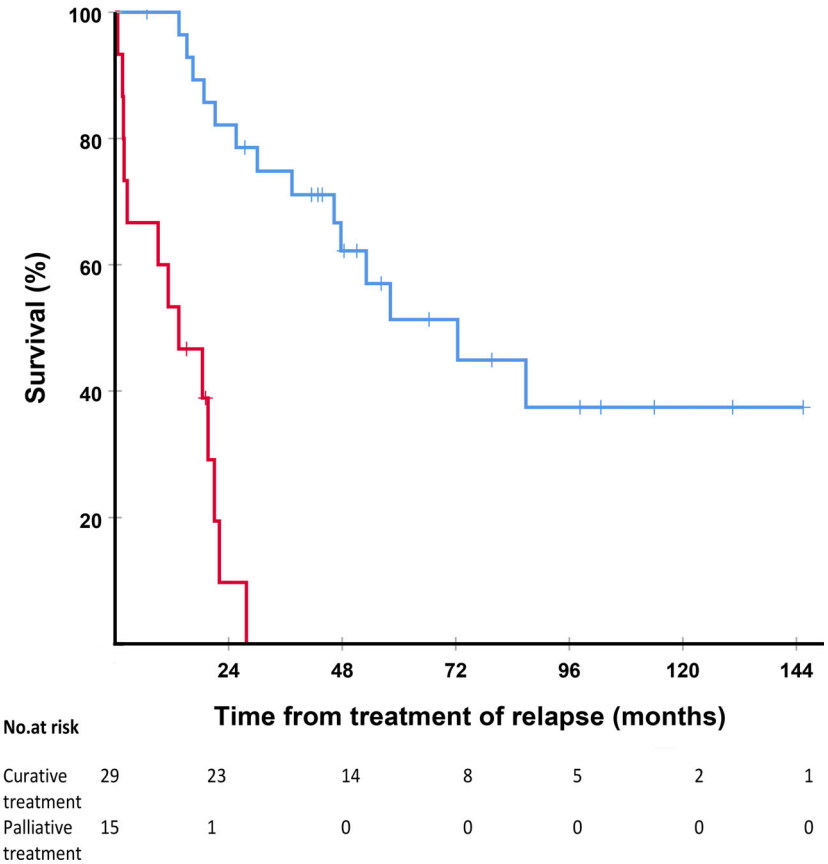

Figure 2 Overall survival from time of first treatment of recurrent disease in patients receiving treatment with curative intent (n = 29, blue line) or treatment with palliative intent (n = 15, red line). Difference between the two groups was $P < 0.001$.

adjuvant chemotherapy within 8 weeks of surgery may be more difficult to administer in patients having received LT compared with patients who have received surgery for CRLM or a primary colon cancer. All patients included in this report had received 5-FU prior to LT, and 37 of the 44 patients had also received oxaliplatin containing chemotherapy regimens prior to LT, and this might suggest that the benefit of adjuvant chemotherapy after LT would be even less than observed in the EORTC study. Adding irinotecan to 5-FU adjuvant treatments has shown no benefit after the resection of CRLM or a colon primary tumour.

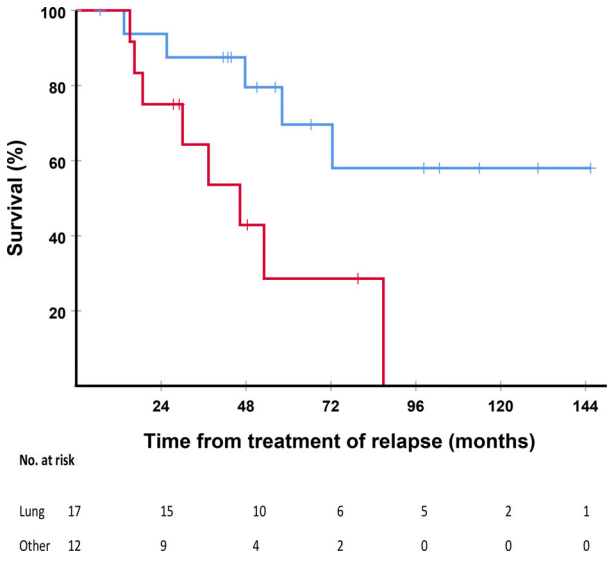

Figure 3 Overall survival from time of curative treatment in patients having pulmonary metastases (n = 17, blue line) and other organ metastases (n = 12, red line). Difference between the two groups was $P = 0.020$.

The impact of recurrence after LT for CRLM is vastly different from that seen in LT for HCC, which is associated with, in general, a dismal prognosis [18]. However, the minority of HCC patients having a recurrent disease that may be resected have better prognosis [24]. Compared with HCC patients, CRC patients had a short DFS, with the majority being treated for recurrence within two years post-transplant LT [14]. Despite the difference in DFS between liver transplanted HCC and CRC patients, OS after LT was similar in these two transplant indications [18]. The explanation is linked to the fact that the most common recurrence site in CRC patients was pulmonary metastases (Table 2), and as previously reported, pulmonary lesions increased in size at a slow rate despite immunosuppression treatment

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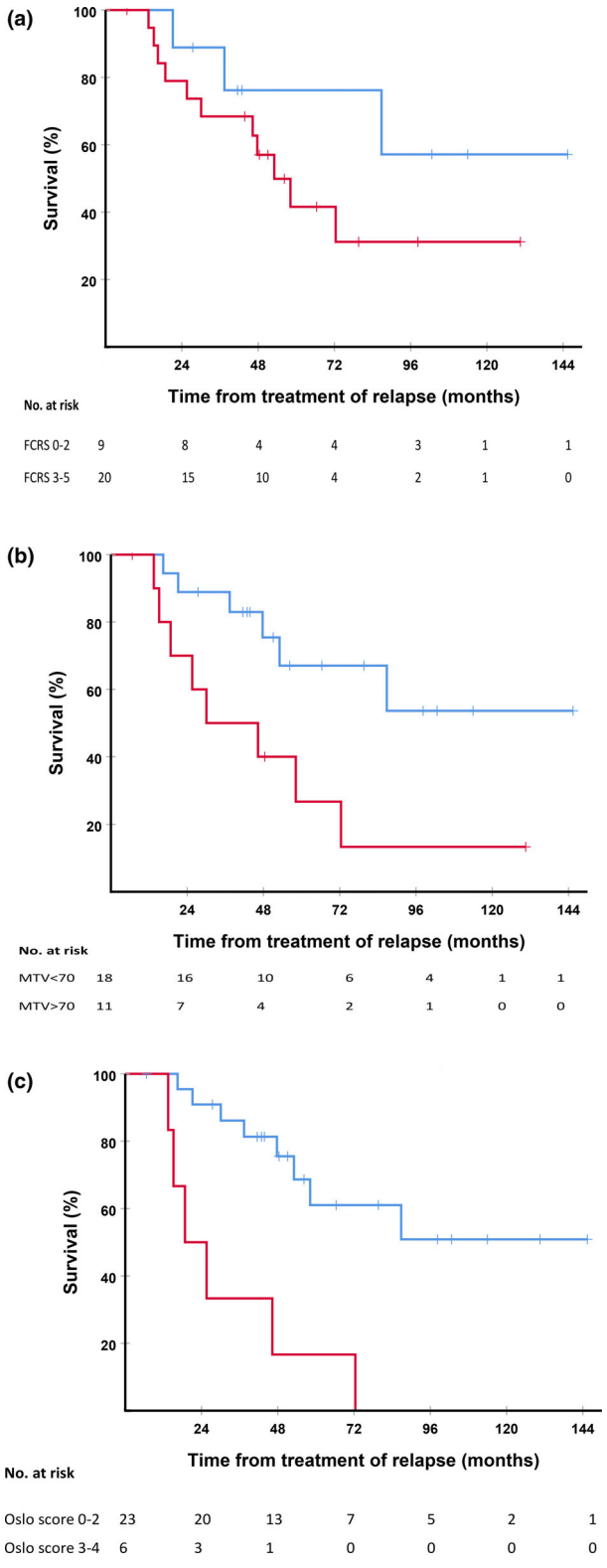

Figure 4 (a) Overall survival after curative intended treatment in patients with Fong clinical risk score 0–2 (n = 9, blue line) and Fong clinical risk score 3–5 (n = 20 red line). Difference between the two groups was P = 0.217. (b) Overall survival after curative intended treatment in patients with PET-MTV< 70 cm^3 (n = 18, blue line) and PET-MTV≥70 cm^3 (n = 11 red line). Difference between the two groups was P = 0.017. (c) Overall survival after curative intended treatment in patients with Oslo Score 0–2 (n = 23, blue line) and Oslo Score 3–4 (n = 6 red line). Difference between the two groups was P < 0.001.

post-LT [7]. Finally, many of the pulmonary lesions were resected (Table 3), and the patients obtained status of NED. The majority of the relapses were treated with a curative intent. As shown in Fig. 2, patients receiving curative treatment of the relapse had long overall survival from the time of relapse, especially patients receiving resection of pulmonary metastases (Fig. 3). DFS in CRC patients is not a useful measurement of treatment efficacy after LT in these patients, in contrast to what has been observed in HCC patients and other malignancies in surgical oncology. The assessment of whether LT should be offered as a treatment option in patients with CRLM, therefore, ought to be based on OS from time of LT and not DFS.

When considering implementation of LT for selected CRC patients, a close follow-up programme for these patients for monitoring signs of recurrent disease is a prerequisite, since a large proportion will develop relapse, similar to what is seen after liver resection, but with a distinctly different pattern in terms of site of recurrence. Treatment with curative intent of metastatic disease post-LT is possible in many of these patients, gaining about 50% or higher 5-year OS from the time of treatment of relapse (Figs 2 and 3). Some patients may even require several resections post-LT and, nevertheless, have a clear survival benefit, exemplified by one patient resected for pulmonary lesion about 10 years after LT. This further underlines that these patients should be offered a long-term follow-up programme after LT.

Donor liver grafts are a scarce source worldwide, and futile use of liver grafts should be avoided. It is, therefore, recommended to limit liver transplantation to patients with low FRCS, PET liver MTV values and Oslo Score, since these factors predict longer OS both after LT and from time of curative treatment of relapse [16]. Furthermore, we have previously shown that patients with the primary tumour in ascending colon has inferior OS after LT and LT should, therefore, be implemented with caution in these patients [16].

In the present report, it is shown that FRCS, PET liver MTV values and Oslo Score had no significant impact on survival from time of onset of palliative treatment, but demonstrated a prolongation of survival in patients receiving curative treatment for relapse (Fig. 4a,b,c). This observation is somewhat surprising

since all patients receiving curative treatment had low volume disease at the time of relapse.

The majority of the patients with recurrence have received palliative chemotherapy at some time point including many of the patients initially treated with a curative intent. It is previously shown that patients tolerated chemotherapy combined with immunosuppression treatment, although they may have increased diarrhoea, mucositis and skin toxicity, especially when receiving regimens containing irinotecan/EGFR antibodies [25]. The present experience suggests that these patients benefit from chemotherapy since OS from the start of chemotherapy was considerable longer than what has been reported in CRC patients receiving only best supportive care [12,13]. Median OS was also longer than reported in most studies in CRC patients receiving the second line of chemotherapy [11,26].

At the end of follow-up, nine of the 44 patients with recurrent disease have NED, and eight of these nine patients have been observed for more than two years after curative treatment of a recurrence. The median OS from the time of LT in these patients is more than nine years. These findings may suggest that many patients may be cured despite having a recurrent disease post-LT. Furthermore, this further underlines that DFS alone is not a useful measure to assess the efficacy of LT in CRLM patients.

In conclusion, the present report suggests that long-term survival, and for a proportion, even cure may be obtained in CRC patients receiving LT, despite the high incidence of recurrence after LT. The most frequent relapses are in the form of small pulmonary metastases that increase both in size and in numbers at a slow rate and may be resected with curative intent. Transplanted CRC patients need a close long-term follow-up schedule with an active and aggressive approach towards resectable recurrences.

Authorship

SD contributed to the idea. SD and TMS did the statistical analysis. All authors participated in writing the article. SD prepared the first draft. All the authors collected the data and reviewed the final article.

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Conflicts of interest

The authors have declared no conflicts of interest.

SUPPORTING INFORMATION

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

Figure S1. Flow-chart showing the different treatment modalities after relapse.

Table S1. Major inclusion/exclusion criteria in the different study protocols.

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