Medical complications following liver transplantation for non-resectable liver metastases from colorectal cancer

A prospective study

Åslaug Dahl and Birgitte Nordal

Project thesis

Supervised by Pål-Dag Line, MD, PhD

University of Oslo

Faculty of medicine

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Table of contents

Abbreviations

AKI: acute kidney injury
AWD: alive with disease
BP: blood pressure
CKD: chronic kidney disease
CNI: calcineurin inhibitor
CRLM: colorectal liver metastases
D: dead
DFS: disease-free survival
DM: diabetes mellitus
ECD: extended criteria donors
EVR: everolimus
FCRS: Fong clinical risk score
HCC: hepatocellular carcinoma
HT: hypertension
IGT: impaired glucose tolerance
ILTS: International Liver Transplantation Society
IS: immunosuppressant
LDLT: living-donor liver transplantation
LT: liver transplantation
mTORi: mammalian target of rapamycin-inhibitors
MTV: metabolic tumor volume
NED: no evidence of disease
NODAT: new-onset diabetes after transplantation
OS: overall survival
PFS: progression-free survival
SCC: squamous cell carcinoma
SLT: split liver transplantation
SRL: sirolimus
TAC: tacrolimus

1. Abstract

Background: Non-resectable CRLM is a common and severe manifestation of colorectal cancer associated low survival. The SECA studies on liver transplantation in unresectable disease have reported promising results with regard to survival compared to standard of care chemotherapy as well as other indications for LT. Considering the scarcity of available organs it is important to assess morbidity and mortality when introducing this treatment option into a wider clinical practice.

Methods: The charts of 58 patients who received LT from 2006 to 2020 for non-resectable CRLM, as part of the prospective studies; SECA and RAPID, were reviewed for postoperative and medical complications, with emphasis on infection, graft rejection, recurrence, de novo cancer, NODAT, HT, renal dysfunction and dyslipidemia. The patients were followed from transplant until death or end of follow-up 01.10.20.

Results: Median OS was 43,8 months (1,4-168,2). Twenty-one patients had NED at end of follow-up of which 9 were successfully treated for recurrence with curative intent. Twenty patients experienced acute rejection which did not significantly impact OS. 77,6% had recurrence and 7 patients developed de novo cancer. Single-site recurrence in lung or liver was associated with superior survival (p=0,023) compared to other sites or multisite recurrence. The 5-year cumulative incidence of HT, DM and hypercholesterolemia was 72,4%, 14,8% and 22,8% respectively. HT, DM and hypercholesterolemia at 1 year had no significant effect on OS, DM and hypercholesterolemia at 3 years were associated with inferior survival (p=0,002, p=0,020) while HT at 5 years was associated with increased survival (p=0,003). Timing of chemotherapy before LT did not significantly impact postoperative complications, infection or rejection.

Conclusion: When analyzing postoperative and medical complications there are no obvious concerns related to safety or increased morbidity when utilizing LT as treatment in selected patients with CRLM. The incidences of postoperative and medical complications are similar to other conventional indications for LT on standard IS regimen. For the most part we did not find a link between medical complications and survival, but this could become more apparent in a long-term perspective trial, containing a larger study sample. Thus, further research within this field is needed .

2. Introduction

2.1 Liver transplantation

Liver transplantation (LT) is the only curative treatment for acute and chronic terminal liver failure i.e. cirrhosis, primary sclerosing cholangitis and hepatocellular carcinoma (HCC). In Norway over 1600 people have undergone LT and 1 and 10 year survival after LT are 93 and 70% (1). The outcome after LT depends on multiple factors including age of recipient, underlying liver disease, age of donor, preoperative condition of the recipient and surgical complications (2).

2.1.1 History

The first LT was performed by Starzl et al. (USA) in 1963 on a 3-year-old patient. Five patients underwent LT by this group in 1963, but no one survived beyond 23 days (3).
A team in Norway started developing a surgical technique for LT in 1968, transplanting animals weekly. The first LT on a human was performed in 1969, but the patient died the following morning. The second LT was a woman in her forties. She was transplanted because of liver metastases from carcinoma in the colon. The primary tumor had been resected and she had no other evidence of metastases outside the liver. She was operated on several times and died of sepsis 24 days after LT. In 1972, they performed their third LT. The recipient was successfully treated for rejection but died after 53 days from a duodenal ulcer resulting in a fatal bleed. Norway was the first country in Scandinavia that legalized the concept of "brain death" by introducing a Transplantation Act in 1973. Allograft rejection was still a major concern and the immunosuppressive strategies with large doses of corticosteroids led to high morbidity and complication rates (4).
Roy Calne in Cambridge UK is given the main credit for the discovery and clinical introduction of cyclosporine, a drug that had a fundamental transformative impact on organ transplantation. This immunosuppressant (IS) is a calcineurin inhibitor (CNI) and was first registered in 1982. This allowed to a large extent the medical professionals to avoid rejection in the early postoperative period without relying on high dose steroids or body irradiation, thus making graft longevity a clinical reality (4). Together with improvement of surgical technique, this led to LT being recognized as a treatment for end-stage liver disease in 1983 at the National Institutes of Health Consensus Conference (5).
Development in transplantation surgery, such as split liver transplantation (SLT) and living-donor liver transplantation (LDLT) and extended criteria donors (ECDs), has been important

to combat longer waiting lists due to the scarcity of available organs, combined with more patients suffering from diseases requiring LT.

2.1.2 Split liver transplantation

To meet the need of smaller liver grafts in pediatric patients, Bismuth and Hussein described in 1984 a technique for reduced-size liver transplantation (6). Further development led to SLT allowing one donor organ to be divided for utilization in two recipients (7, 8). A child will usually receive segments 2 and 3, while the adult will receive segment 1, 4, and 5-8. If the two recipients are both adults, the liver is split in a left (30-40% of the liver volume) and right (60-70% of the liver volume) part. The split can be done in-situ or ex-situ (9). SLT requires a high-quality liver graft. The donor criteria in Scandiatransplant are age < 51, BMI < 26 kg/m2, ALAT/ASAT < 3x normal and ICU-stay < 4d. The graft-to-recipient weight ratio also plays a crucial role in SLT, it should not be less than 0,8-1,0% to minimize the risk of liver failure due to an insufficient liver functional mass (10).

To secure the access to suitable liver grafts for pediatric patients, the members of Scandiatransplant have since 2015 been required to split grafts fitting the aforementioned criteria, if there is a pediatric patient on the common waiting list (9).

2.1.3 Living-donor liver transplantation

The first reported LDLT was carried out in 1988 , but both recipients died (11). The first successful LDLT was performed in 1989 in Australia. The patient was a 17-month-old boy who received a left liver graft from his mother (12).

Further advancements were made with the first successful adult-adult LDLT with a left graft and an adult-child right liver graft (13, 14).

The access to deceased donor livers is fortunate in Norway compared to most countries, making LDLT unnecessary for adult patients. On the other hand, the procedure has been performed for children, because of difficulty procuring a graft with appropriate size in acceptable time. In 2015, three children were transplanted at Rikshospitalet, using a left graft from a parent, with favorable outcome for both donor and recipient (9).

2.1.4 Extended criteria donors

ECDs do not meet the conventional criteria for organ donation, thus carrying an elevated risk of recipient morbidity and mortality. There isn’t a clear definition of what constitutes an ECD

for liver grafts, but often cited criteria are advanced age, steatosis >30%, donation after circulatory death, organ dysfunction at the time of donation, risk of disease transmission (HBV, HCV, HIV, cancer) and cold ischemia time > 12 hours (15).

2.2 Complications due to liver transplantation and immunosuppression

2.2.1 Rejection

A study on 20-year survival after LT found that when comparing those who were still alive with those deceased, those who survived were less likely to have had multiple acute rejection episodes or progression from acute to chronic rejection. They also had a longer interval between LT and first rejection episode. Of the 293 patients, 30% experienced acute or chronic biopsy verified rejection. Sixty-three patients (22%) experienced only acute rejection, while 18 (6%) patients progressed to chronic rejection (16). In patients using tacrolimus, acute rejection occurs in 15-25% of recipients and it can normally be treated with steroids (17). A study found no significant increase in acute rejection in patients treated with mammalian target of rapamycin-inhibitors (mTORi) after LT due to HCC, compared to CNI (18). Chronic rejection is rarer, occurring in 2-17% of recipients (higher in pediatric patients than in adults) but is often more difficult to treat. It can ultimately require retransplantation or lead to death (17).

2.2.2 Arterial hypertension

Cardiovascular events were noted as the cause of death in 11% of liver recipients and hypertension (HT) is a known risk factor for such events (19). HT is a frequent condition in patients who have received a liver graft. The prevalence varies between studies, but two reviews state a prevalence between 30-70% and 45-75% (20, 21). Different characteristics in the population pre- and post-LT will influence the prevalence of HT. Two studies have found that use of mTORi was related to HT, while tacrolimus (TAC) was not (22, 23). Other randomized studies describe no significant difference in blood pressure (BP) on mTORi compared to TAC (24, 25). In a review of multiple transplantation studies the incidence of HT on sirolimus (SRL) was found to be 21-38% and 17-30% on everolimus (EVR) (26).
The International Liver Transplantation society (ILTS) recommendation for treating HT in liver recipients is lifestyle modification and minimization of IS. Calcium channel blockers (amlodipine, nifedipine) are the first choice for pharmacologic management. In patients with

concurrent chronic kidney disease (CKD) or diabetes mellitus (DM), ACEs, ARBs or direct renin inhibitors are recommended. The BP goal post-LT is < 130/80 (not adjusted for age) (27).

2.2.3 Diabetes mellitus

The prevalence of DM in liver recipients ranges from 13-28% in the first three years after LT, and one study noted that the prevalence increased steadily up to 7 years after transplantation. DM is associated with elevated mortality. One study also found that each additional year of DM increases mortality (19, 20, 28). DM is also linked to increased risk of graft rejection, reduced graft survival time and initial poor graft function, as well as infection, acute kidney injury (AKI) and biliary complications (29, 30). There are numerous risk factors for new-onset diabetes after transplantation (NODAT) including hepatitis C, male sex, ethnicity, family history, CMV-infection and IS (20).

SRL is independently linked to increased risk of NODAT according to studies based on the United States Renal Data system (n=20,124) (31). Two single-center experiences found no significant difference in prevalence of NODAT in patients treated with SRL or TAC (32, 33). According to the ILTS, conversion from TAC to cyclosporine can be beneficial for improving glucose control. As corticosteroids are highly diabetogenic, they also advise reducing their administration to a minimum. Lifestyle modification and medical treatment according to guidelines is also a strong recommendation. The HbA1c in these patients should ideally be < 42 mmol/mol (27).

2.2.4 Dyslipidemia

Reports of post-LT hyperlipidemia vary from 45% to 71% of patients. A major reason for the deviating findings is differing criteria used to diagnose hyperlipidemia in various studies. IS and renal dysfunction post-LT is associated with development of dyslipidemia (20, 27). Patients treated with SRL have a reported prevalence of hyperlipidemia, hypertriglyceridemia and hypercholesterolemia at 30-64%, 21-57% and 20-46% respectively (26). Patients receiving SRL or EVR after LT have a significant increase in cholesterol and triglycerides compared to patients receiving TAC (24, 32, 33).

ILTS recommends lifestyle modification for patients with dyslipidemia after LT. If not sufficient, medical therapy in the form of statins should be initiated. Pravastatin or fluvastatin are the recommended medications of choice, since these have the least interaction with CNIs.

Target LDL-C is <100 mg/dL (2,586 mmol/L) and TGA levels should be <250 mg/dL (2,82 mmol/L) (20, 27).

2.2.5 Renal failure

Avoiding impaired renal function is important, since renal failure is a major source of morbidity and mortality. A study on quality of life 30 years after LT found that renal dysfunction had a negative impact on the patients perception of good health and decreased quality of life (34). Renal insufficiency was also found to be a risk factor for death >1 year post-LT (19). The post-LT incidence of AKI ranges from 17% to 94%. AKI is associated with excess mortality and may often be caused by perioperative events. The cumulative incidence of CKD ≥ stage 3 and ≥ stage 4 is 36-57% and 5-25%, respectively. CNIs are nephrotoxic and development of CKD is highly associated with their use, leading to decreasing renal function in 13-33% of cases (27). A multicenter, randomized, open-label phase 3 trial found that mTORi in LT was associated with increased incidence of proteinuria, but not renal failure compared to mTORi-free regiments (35). In a single-center, randomized controlled trial on late conversion to SRL after LT in patients with impaired renal function (n=39) a significant increase in GFR was seen at 3 months in the SRL group compared to the TAC-group, but not at 12 months (25). Modifying the initial IS regime to include mycophenolate mofetil (MMF), induction therapy and lower dose or delayed introduction of TAC has been associated with a similar rejection rate and superior renal function at 6-12 months, compared to higher dosage of TAC. This is recommended by the ILTS, as well as avoiding mTORi in the first postoperative months. In the early postoperative period, it has proven beneficial to use EVR in combination with low dose-TAC, especially for patients with eGFR < 60 (27).

2.2.6 Malignancy

Malignancy is an important complication to organ transplantation and LT is no exception. The risk for cancer both related and unrelated to infections are increased. Nonmelanoma skin cancer and recurrent HCC are the most common cancers in liver recipients (36). CNI promotes malignancy (37, 38). In a study on patients surviving ≥ 5 years post-LT 14% developed de novo malignancy, most commonly post-transplant lymphoproliferative disease, squamous cell carcinoma (SCC) and prostate cancer (39).

SRL has been shown to have antiproliferative effects on a subset of cell lines in HCC and colorectal cancer in vitro (40, 41). A systematic review with meta-analysis of mTORi-based

IS after LT due to HCC showed that DFS was significantly improved at 1 year and 3 years compared to patients receiving CNI. Recurrence-rate was significantly lower in patients who got mTORi and OS was improved at 1, 3 and 5 years (18). A multicenter, open-label phase 3 trial found that patients receiving SRL and TAC from 4-6 weeks after LT for HCC had improved recurrence-free and OS the first 3 to 5 years after LT compared to patients on a CNI-based IS regime. In the subgroup receiving SRL monotherapy (19,2% of patients receiving SRL) recurrence-free survival and OS was higher than in the combination therapy group (35).

2.2.7 Postoperative complications

Immediate use of mTORi after transplantation leads to higher incidence of wound complications than CNI, probably due to the antiproliferative properties of mTORi causing delayed wound healing (42). Data collected in a retrospective single-center review, where 263 renal transplant recipients were treated de novo with SRL, showed an incidence of wound complications of 36% (43). The prevalence of wound complications was 12.4% in SRL-treated patients compared with 13.9% in historic controls (p = not significant) (44).
In a randomized multicenter open-label phase 3 trial on SRL use in LT due to HCC (n=525), where SRL was started 4 to 6 weeks post-LT the incidence of wound complications was 11,8% in the group receiving SRL (monotherapy or in combination with non-mTORi-drugs) compared to 6,2% in the TAC-group (35).
A ‘ black box’ warning due to data signaling increased risk of hepatic artery thrombosis (HAT) with decreased graft survival and patient death has led to a less common use of mTORi in LT (45). Other studies have showed low rates of HAT due to SRL after LT (46-48).

2.3 Liver transplantation in patients with liver metastases from colorectal cancer

LT for malignant liver tumors has been established as standard of care for over 20 years for HCC. A study by Mazzaferro et al from 1996 demonstrated that LT was an acceptable therapeutic strategy for HCC when appropriate patient selection criteria was applied. After 4 years, the overall OS and recurrence-free survival was 75% and 83% respectively. When applying the Milan criteria (one nodule ≤ 5 cm or ≤ 3 lesions, none > 3 cm and absence of

gross vascular invasion, metastases or lymph nodes involvement), the rates were even more promising: 4-year OS of 85% and recurrence-free survival of 92%. Among the patients who did not meet these criteria, the rates were 50% and 59%, respectively (49).

Colorectal cancer is the third most common cancer in the western world (50). Approximately half of the patients develop metastatic disease, either present at the time of diagnosis or later on. The liver is the most frequent metastatic site. The only potential curative treatment option for patients with liver metastases from colorectal cancer (CRLM) is liver resection. Unfortunately, only about 20-25% of patients with CRLM have resectable tumors, and for the remainder the only alternative treatment is palliative chemotherapy (51).

During the early era of LT, several centers attempted to transplant patients with non-resectable CRLM, but this practice was abandoned due to dismal survival outcomes (52). On this background CRLM was for many years considered a contraindication to LT.

2.3.1 The SECA-studies

The fortunate liver graft situation and short waiting-lists in Norway has allowed for a reexamination of liver transplantation as a treatment option for selected patients with non-resectable CRLM (2, 53).

2.3.2 Pilot "proof of concept study": SECA-I

There were 21 patients in the published paper from the SECA-I study. The research group found four prognostic factors for survival: tumor diameter < 5,5 cm, pre-LT CEA-level < 80 ug/L, time from resection of primary tumor to LT > 2 years and response to chemotherapy. By assigning a value of 1 for each of these four factors, the patients could be assigned an prognostic score termed the Oslo score, ranging from 0-4. Patients with an Oslo score of 0-1 or 2-3 had a significantly superior survival compared to the patients who had an Oslo score of 4. The study reported 5-year OS of 58% (54).

By reassessing the preoperative PET/CT scans performed on the patients in SECA-I, it was found that the PET enhancement data from these examinations could also be utilized as a tool in selecting patients for LT. Total metabolic tumor volume (MTV) and total lesion glycolysis under the determined cut-off values proved to be predictive for 3 and 5-year OS and DFS. The researcher also noted a trend towards inferior OS in patients with standardized uptake values (SUV) and tumor to background-ratio over the cut-off values, although these findings were not significant (55).

When comparing the OS of the patients in SECA-I who were low risk (Oslo score 0-3) and patients who underwent LT for HCC within the Milan criteria, the two groups had a 5-year OS rate of 75% and 76%, respectively. The DFS was shorter in both high (Oslo score 4) and low risk groups of CRLM patients, than in patients with HCC (56).

Also when comparing LT to standard of care chemotherapy in patients with CRLM, results were in favor of transplantation. DFS and OS of patients in SECA-I were compared with progression-free survival (PFS) and OS of patients receiving first-line treatment in the NORDIC-VII trial that had liver-only disease and fulfilled the selection criteria for the SECA-I study. The 5-year OS rate in the two groups were significantly different: 56% for the transplant group and 9% for those who received chemotherapy, despite PFS/DFS being 8-10 months in both groups. The researchers attributed this to differences in metastatic pattern at relapse/progression. Among the patients who underwent LT, relapse was often in the form of slowly growing lung metastases, while the chemotherapy group developed unresectable liver metastases or multisite disease (51).

The patients who participated in SECA-I, filled out European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire version 3.0, before and up to 3 years post LT. Three months after LT the patients had a significantly lower global health score, physical function score and role function score. There was no significant decrease in function or symptom scale 3 years after LT. Patients who died within 3 years had significantly higher reported scores for fatigue, pain and appetite loss at baseline. Patients with reported appetite loss or a fatigue score of at least 30 had significantly lower 3-year survival. Patients with general symptoms related to malignant disease may thus have reduced OS after LT, most likely due to progressive disease that is not readily detected by the other diagnostic procedures in the workup for transplant. On this background, one could consider quality of life to be incorporated into the selection process for LT in patients with CRLM (57).

Table 1: SECA-I study protocol

Main inclusion criteria
Unresectable CRLM without evidence of extrahepatic disease, assessed by:
CT of chest, abdomen and pelvic, whole body PET/CT scan and bone scan
Repeat CT scan of the chest at admission for LT
Frozen section of lymph nodes in the hepatic ligament and adjacent tissue perioperative
Completed radical excision of primary tumor
ECOG score 0-1
Minimum 6 weeks of chemotherapy

Main exclusion criteria
Weight loss > 10%
Standard contraindications for LT
Other malignancies

Immunosuppression protocol
Sirolimus, introduced first postoperative day, aim:
5-10 ng/mL first 4 weeks
10-20 ng/mL thereafter
Mycophenolate mofetil
Corticosteroids
Tapered to 0 or 5 mg/day at 1 month post-LT
Induction with basiliximab
2x20 mg IV bolus intraoperatively + 4th day post-LT (?)

Follow-up
Outpatient regime
Year 1: monthly
Year 2: every 3 months
Year 3 and onwards: every 6 months
CT scan of chest, abdomen and pelvis
Year 1: every 3 months
Year 2 and onwards: every 6 months
After recurrence: follow-up and treatment by responsible physician
(54)

2.3.3 The effect of stringent selection criteria: SECA-II

In a sequel study (SECA-II) the effect of more stringent selection criteria for LT was explored by utilizing the knowledge of negative predictive factors from the SECA-I study. The results from the first 15 patients were promising: a 5-year OS rate of 83% and 11 patients demonstrated no evidence of disease (NED) at the end of follow-up, including 4 patients who had no relapse more than 30 months post-LT. The 5-year DFS was 35%, but relapse was mostly in the form of slow-growing, resectable lung metastases. This is reflected in the 4-year OS after recurrence being 73%. None of these patients had an Oslo score above 1 or pre-LT CEA-level > 80 ug/L. The number of lesions, size of largest lesion and Fong clinical risk score (FCRS) were significantly lower in these patients than those in SECA-I.
The IS and follow-up regimen were modified after SECA-I. In SECA-II, the participants received TAC the first 4-6 weeks post-LT before conversion to SRL and the steroids were tapered to 0 in the course of the first 3-6 months post-transplant (58).
The study group reviewed the data from SECA-I and SECA-II to further evaluate the ability of different scoring systems pre-LT. They found that a FCRS of 0-2, MTV <70 cm^3 and an Oslo score of 0-2 all meant a significantly longer DFS, OS and OS after recurrence. Low

FCRS (0-2) gave the best OS, with all patients alive after 5 years, but this would also mean only 30% of the population would meet the inclusion criteria. The 5-year OS of patients with MTV <70 cm^3 or Oslo score of 0-2 were 78% and 70%, respectively. Inferior survival was observed for patients with right-sided (ascending colon) primary tumor compared to left-sided (transverse, left colon, sigmoid, rectum) (59). Poorer outcome in this patient group is also seen in liver resection and palliative chemotherapy (60, 61).
They found no significant difference in OS between patients with KRAS wild type and mutant status or patients with normal or elevated CEA-levels alone (note that CEA-level is taken into account in calculating the Oslo score).
The DFS does not have a close correlation with OS in these studies as is usually seen in cancer trials. Consequently DFS alone does not seem to be an appropriate measure of outcome (59).

2.3.4 Addressing the imbalance between organ supply and medical need: RAPID study

Simultaneously with the SECA-II study, the researchers also launched a study exploring the possibility of using a partial liver graft in patients with non-resectable CRLM - the RAPID (Resection and partial liver segment 2+3 transplantation with delayed total hepatectomy) study. The patients included would undergo a left hepatectomy and receive a graft of segment 2 and 3, and then undergo hepatectomy of the remaining right liver when the transplanted graft had reached a sufficient volume (62).
If the RAPID study can demonstrate favorable outcomes regarding survival and complications, it is possible this procedure can be applied in patients with CRLM at a larger scale by utilizing segment 2+3 as a surplus graft, thus contributing to the problem of organ shortage. It could also open the possibility of LDLT, as the donation of segment 2+3 is a safer procedure for the donor compared to donation of the full right or left liver lobe (63).

2.3.5 SECA-III

The SECA-III study is a randomized study between LT with ECD grafts against best available oncological treatment (64). Since the recipients of an LT on the basis of CRLM don't have reduced liver function, the recipients are expected to tolerate inferior graft quality better than those receiving LT because of diseases leading to chronic liver failure (65). This means the possible negative impact on the waiting list of introducing LT as a treatment option for

selected CRLM patients to an extent could be mitigated by the utilization of ECD donors, thus avoiding unacceptable long waiting lists.

2.4 Aim of the study

Given the contemporary results with liver transplantation in selected patients with CRLM the outcomes could possibly justify introduction of this treatment option into a wider clinical practice. Since the studies so far have been focusing on OS, detailed knowledge of overall morbidity and complications following treatment is lacking in the literature. Little is known about how prolonged chemotherapy treatment before transplantation may influence postoperative morbidity. Furthermore, since these patients are on an alternative IS regimen, a particular focus on possible long-term consequences related to mTORi is also pertinent. The aim of this study was therefore to assess the morbidity and complication frequency in patients that has been liver transplanted for CRLM, with particular emphasis on: Infection, graft rejection, recurrence, de-novo cancer, NODAT, renal dysfunction, HT and dyslipidemia.

3. Material and methods

From November 2006 to September 2020, a total of 58 patients received a full sized or partial graft LT due to CRLM as part of the SECA and RAPID studies. The patient population includes 23 patients in SECA-I, 1, 19 and 10 patients in SECA-II arm A, C and D, respectively, 2 patients in SECA-III and 3 patients in RAPID. The baseline characteristics are listed in table 2. The patients were followed from transplant until death or end of follow-up 01.10.20. The data were collected from the prospectively registered study databases as well as from the clinical patient records at Oslo University Hospital, OUS. Information on HLA from recipients and donors were retrieved from the Scandiatransplant database (YASWA). The variables collected are listed in table 3. Median follow-up in the whole sample was 43,8 months (range 1,4 - 168,1)

Each patient was assigned a status at 01.10.20, dead (D), alive with disease (AWD) or NED. Those with NED were both patients who didn't experience recurrence or those successfully treated for recurrence.

Table 2: Baseline characteristics	
Age at LT, median (range), years	57 (32-71)
Sex n, (%)	
Men	33 (56,9)
Women	25 (43,1)
Chemo, n (%)	
> 3w	33 (56,9)
< 3w	18 (31)

Table 3: Variables collected	
Transplantation date	Abdominal surgery during follow-up
Age at LT	De novo cancer
Sex	Lab at LT, 1y, 3y, 5y, rejection and metastases
Last follow-up	Hb, leuk, lymf, neut, trc, CRP, creatinine, eGFR,
Status per 01.10.20	tot chol, HDL, LDL, albumin, bilirubin
Last chemotherapy	ALP, LD, ASAT, ALAT, INR, HbA1c
Infection	Medication at LT, 1y, 3y, 5y
Rejection	Antidiabetics, antihypertensives, statins,
Date, RAI, steroid dosage, ATG	opioids (incl. at discharge)
Metastases	Permanent change of immunosuppressives
Date, localization, treatment	Donor information
Clavien-Dindo	Age, sex, HLA-mismatches
Previous abdominal surgery	

3.1 Lab

Laboratory values were registered when the patient arrived for LT, after 1, 3, and 5 years, and at time of rejection and recurrence. If a full set of tests had not been performed at the time of LT, tests obtained within two weeks pre-LT were used. Where values were given <X, the value was given as X. Renal function, expressed as eGFR was categorized in four groups; <20, 21- 40, 41- 60 and >60.

3.2 Chemotherapy

The patients were categorized by whether or not they received chemotherapy less than three weeks before LT or not. In some patients it was not possible to determine when last chemotherapy was given, thus resulting in missing data.

3.3 Infection

Postoperative infections were defined as infections in need of intravenous antibiotics and were registered for the first 90 days after LT. Infections treated with oral antibiotics and use of prophylactic intravenous antibiotics were excluded.

3.4 Surgical complications

Postoperative complications within 90 days of LT were classified by the Clavien-Dindo score (66). Only severe complications, defined as grade IIIa or higher were included. In patients with more than one postoperative adverse event, the highest scoring complication was registered.

3.5 Rejection

Rejections were graded by rejection activity index (RAI) (67). Only patients with biopsy-proven rejections grade RAI ≥ 3 who received pharmacological treatment was included. Patients with biopsy-verified rejection that was not treated and patients who received treatment on clinical suspicion were excluded. The total steroid dose used to treat rejection was collected from the patient records. Where steroid dose was not given or noted as "RH protokoll" (standard rejection protocol at Rikshospitalet), the value was set to 2500 mg.

3.6 Recurrence

Time of recurrence was noted as the date where a lesion was described as "metastasis" or "suspect of metastasis" by radiologist. In cases where a re-examination of CT-imaging revealed that the lesion was present at an earlier time, the date where it was first described was kept. When categorizing the localization(s) of recurrence, the first localization(s) described was used. The patients have usually undergone CT-imaging of the thorax and abdomen at the same time, but in some cases the examinations were performed at different timepoints. In this case, the date of recurrence was set to the date of the first examination, while the result of both scans was used when deciding localization.

The treatment of recurrence was categorized as potentially curative (surgical resection or radiofrequency ablation alone or in combination with radiation) or palliative (chemotherapy alone or in combination with radiation). If a patient had undergone surgical resection of one

lesion, but had other metastases that were unresectable, this was assessed as palliative treatment.

3.7 Hypertension

BP and the number of antihypertensive drugs were registered for patients before LT, at 1, 3 and 5 years after LT.

Hypertension grade was given based on classification in the 2018 ESC/ES Guidelines (68). The patients were divided into one of four groups based on their BP; Normal (≤ 139 mmHg systolic and/or ≤ 89 mmHg diastolic), grade 1 HT (140-159 mmHg systolic and/or 90-99 diastolic, including isolated systolic HT), grade 2 HT (160-179 mmHg systolic and/or 100-109 diastolic, including isolated systolic HT) and grade 3 HT (≥180 mmHg systolic and/or ≥ 110 mmHg diastolic, including isolated systolic HT).

In survival analysis patients with any grade of HT or using antihypertensive drugs were interpreted as having clinical/pharmacological HT. In a second survival analysis only patients with HT according to BP, regardless of medication status, were interpreted to have clinical-only HT.

3.8 Diabetes

HbA1c and use of antidiabetic drugs were registered from before LT and at 1, 3 and 5 years after LT. Patients were divided into 3 groups based on the national professional guidelines from the Norwegian Directorate of Health. Normal HbA1c < 42 mmol/mol, impaired glucose tolerance (IGT) 42-47 mmol/mol, DM ≥ 48 mmol/mol (69).

In survival analysis patients with DM according to aforementioned values or using antidiabetic drugs were interpreted to have clinical/pharmacological DM. In a second survival analysis only patients with DM according to HbA1c, regardless of medication status, were interpreted to have clinical-only DM.

3.9 Hyperlipidemia

Total-, HDL- and LDL-cholesterol and use of cholesterol lowering drugs were registered before LT, at 1, 3 and 5 years after LT. Triglycerides were not taken in the standard lab and are therefore omitted. Hypercholesterolemia were defined as total cholesterol > 7,0 mmol/L and/or LDL-cholesterol > 5,0 mmol/L based on recommendations for treatment with statins from The Norwegian Directorate of Health (70).

In survival analysis patients with hypercholesterolemia according to the aforementioned criteria or using cholesterol-lowering drugs were interpreted to have clinical/pharmacological hypercholesterolemia. In a second survival analysis only patients with hypercholesterolemia according to lab values, regardless of medication status, were interpreted to have clinical-only hypercholesterolemia.

3.10 Statistics

Numerical variables are given as median with min and max values, unless else stated. Categorical variables are given as number of events/patients and percentage of total events/patients. Calculations were performed in Microsoft Excel or Wizard. Survival analyses were calculated by the Kaplan-Meier method in SPSS (version 27). Differences between categorical groups were analyzed using the Fisher exact test or the Chi-Square test. Probability levels less than 0,05 were considered statistically significant.

3.11 Ethics

All patients were included in clinical studies approved by Regional Committees for Medical and Health Research Ethics, and gave their informed, written consent to participation. This study is a part of the total study portfolio, thus no further ethical approval was required for this sub-project.

4. Results

4.1 Survival

Median OS was 43,8 months ranging from 1,4 to 168,2 months. At the end of follow-up 30 (51,7%) patients had died, 7 (12,1%) patients were AWD and 21 (36,2%) of the patients had NED. Median follow-up time in patients with NED were 76,6 months ranging from 4,9 to 160,5 months. Twelve of the patients with NED (57,1%) did not recur during the follow-up period, while 9 (42,9%) patients were successfully treated with curative intent for recurrence.

Table 4: Disease-free and overall survival	
DFS, median (range), months	11,9 (0-91,4)
OS, median (range), months	43,8 (1,4-168,19)
Status, n (%)	
D	30 (51,7)
AWD	7 (12,1)
NED	21 (36,2)

Median DFS was 11,9 months ranging from 0 to 91,4 months. Thirteen patients (22,4%) did not develop metastasis during follow-up or the first 5 years post-transplant. One patient was discovered to have metastatic disease at the time of LT.

The timing of the last chemotherapy dose in relation to the time of LT did not significantly impact OS (p=0,494) or DFS (p=0,904).

4.2 Surgical complications

Twenty-four (41,4%) patients had no or light (grade I or II) complications, whereas 12, 15, 5, 1 and 1 patients had respectively Clavien-Dindo grade IIIa, IIIb, IVa, IVb and V. The different complications are listed in table 5. Three patients (5,2%) required a retransplantation, but none required a third graft. There was no significant difference in OS based on whether the patient had a Clavien-Dindo score or not (p = 0,884). Whether the patients received chemotherapy less than 3 weeks prior to LT, had no significant impact on postoperative complications (p = 0,806).

Table 5: Postoperative complications classified by Clavien-Dindo-score*		
Grade IIIa	12 (35,3%)	3 drainage fluid locus 2 pleural drainage 2 ERCP 2 chest tube insertions (pneumothorax) 1 ascitic drainage 1 balloon dilation + stenting liver vein 1 chest tube + stenting liver vein
Grade IIIb	15 (44,1%)	6 wound dehiscence 1 reduced circulation in a. hepatica 3 evacuation hematoma 2 intraabdominal hemorrhage 1 thrombectomy liver vein 2 thrombectomy liver artery
Grade IVa	5 (14,7%)	2 retransplantation 2 kidney failure 1 re-intubation
Grade IVb	1 (2,9%)	1 retransplantation + kidney failure
Grade V	1 (2,9%)	1 sepsis and organ failure

4.3 Infections

Sixteen patients (27,6%) had an infection requiring IV antibiotics within three months post-transplantation. There was no significant (p=0,298) relationship between infection and whether the patient received chemotherapy within three weeks before LT or not. No significant relationship between the occurrence of rejection and infection was observed (p=0,194). Infection had no significant impact on OS (p = 0,148)

Table 6: Postoperative infections	
Pneumonia	6
Bowel perforation	2
Spontaneous bacterial peritonitis	2*
UTI + pathogens in drainage fluid	1
Pathogens in drainage fluid	1
Diverticulitis	1
Unknown focus	3
* 1 patient had bacterial pathogens in ascitic fluid	

4.4 Rejection

Twenty patients were diagnosed with acute rejection. Eighteen of these had only one episode, while two patients experienced two episodes. Eighteen (90%) patients had steroid sensitive rejection, while two patients required additional treatment with anti-thymocyte globulin (ATG). Table 7 shows the distribution of RAI score in the population.

Table 7: Occurrence of rejections	
Patients experiencing rejection, n (%)	20 (34,5%)
Single rejection, n (%)	18 (90%)
Two episodes of rejection, n (%)	2 (10%)
Time from LT to rejection, median (range), days	26,5 (4 - 2157)
RAI score (n=22)	
RAI 3, n (%)	4 (18,2%)
RAI 4, n (%)	7 (31,8%)
RAI 5, n (%)	9 (40,9%)
RAI 6, n (%)	2 (9,1%)
Treatment	
Steroids only, n (%)	20 (90,9%)
ATG, n (%)	2 (9,1%)

There was no difference in rejection frequency based on when the patients received the last dose of chemotherapy before the transplant (p=0,972) and rejection did not impact OS (p=0,566)

4.5 Recurrence and de novo cancer

Recurrence occurred in 45 (77,6%) of the patients. Median time to recurrence was 9,8 months. The most common type of recurrence was lung metastases. Twentynine patients had recurrence in lung only and 4 patients had liver + lung. Other sites of recurrence were liver and lymph nodes. Three patients had metastasis at multiple sites on discovery. One patient had recurrence in the rectum and another in ovaries.

Potential curative treatment for recurrence were given in 24 patients (53,3%) Twenty-one (46,7%) patients received palliative treatment. Seven (12,1%) patients developed de novo cancer in the course of the study and a detailed list is provided in table 8.

Table 8: Recurrent disease	
Time to recurrence, median (range), months	9,8 (0-47,1)
Survival after recurrence, median (range), months	37,6 (3,5-157,8)
Metastasis, no of patients (%)	45 (77,6)
Lung	29 (64,4)
Liver	2 (4,4)
Liver + lung	4 (8,9)
Lymph node	5 (11,1)
Multi-site	3 (6,7)
Other	2 (4,4)
Treatment** n, (%)	
Palliative	21 (46,7)
Curative	24 (53,3)
De novo cancer, n	7
BCC	1
BCC + SCC	1
Lung	1
Adenocarcinoma coecum	1
Prostate	1
MDS	1
Tonsil	1

Whether the patient received last dose chemotherapy within 3 weeks before LT had no significant effect on recurrence (p=0,304 - Fisher exact test)

There was no significant difference in DFS, SAR or OS, based on recurrence site between patients with lung metastasis only compared to other sites (p=0,689, 0,129, 0,242 respectively), but when comparing patients with single-site recurrence in lung or liver with patients with recurrence in other sites SAR (p=0,014) and OS (p=0,023) was significantly improved, but DFS was not (p=0,461).

Figure 1: Overall survival according to site of recurrence

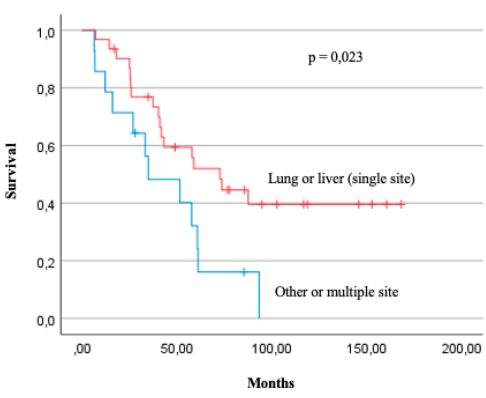
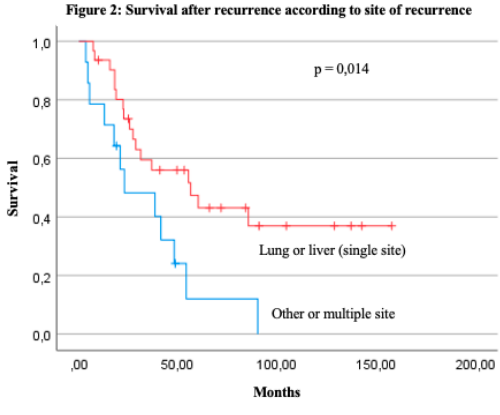


Figure 2: Survival after recurrence according to site of recurrence



4.6 Hypertension, diabetes and hyperlipidemia requiring treatment

Table 9: Occurrence of medical complications

	Prevalence pre-LT, n (%)	*Cum incidence 1 year, %*	*Cum incidence 3 years, %*	*Cum incidence 5 years, %*
HT	36 (62,1)	70,7	72,4	72,4
DM	3 (7,5)	11,1	13,0	14,8
Hypercholesterolemia	5 (8,8)	17,5	21,1	22,8
eGFR < 60	0 (0)	5,2	8,6	12,1

4.6.1 Prescribed treatment

The most common type of drug prescription prior to LT was antihypertensive drugs, used by 17,2%. The usage of antihypertensive and cholesterol lowering drugs both increased in the 5-year period after LT. For further details, consult table 10 and 11.

Pre-LT, five patients used only one antihypertensive drug, four used two and one patient three. One year after LT, 10 patients used only one antihypertensive drug, two patients used two drugs. Three years after LT, 9 patients used only one antihypertensive drug, three persons used two drugs. Five years after LT, 7 patients used only one antihypertensive drug, two persons used two drugs.

Both the prevalence at each point in time and the cumulative incidence rose steadily through follow-up, with the only exception being the use of antidiabetics at 5 years.

Table 10: Prevalence pre-LT and cumulative incidence of medications

	Prevalence pre-LT, n (%)	*Cum incidence 1 year, %*	*Cum incidence 3 years, %*	*Cum incidence 5 years, %*
Antihypertensive	10 (17,2)	22,4	29,3	31,0
Antidiabetic	1 (1,7)	3,5	3,5	1,7
Cholesterol-lowering	2 (3,4)	13,8	15,5	15,5

Table 11: Use of medication	
Antihypertensive drugs, no of patients (%)	
Pre-LT	10 (17,2)
1 year	12 (24)
3 year	12 (36,4)
5 year	9 (40,9)
Antidiabetic drugs, no of patients (%)	
Pre-LT	1 (1,7)
1 year	3 (6,0)
3 year	3 (9,1)
5 year	0 (0)
Cholesterol lowering drugs, no of patients (%)	
Pre- LT	2 (3,4)
I year	8 (16)
3 year	7 (21,2)
5 year	5 (22,7)

4.6.2 Hypertension

There was no significant difference in OS between normotensive patients and patients with clinical/pharmacological HT at 1 and 3 years post-LT. The OS was significantly improved (p=0,003) in patients with clinical/pharmacological HT compared to normotensive patients at 5 years. This was also true in the group of patients with clinical-only HT, compared to normotensive patients (p = 0,014)

Table 12: Occurrence of hypertension		
Pre-LT (n=58), n (%)	*Clinical-only*	*Clinical/pharmacological*
Normal	23 (39,7)	22 (37,9)
Hypertension	35 (60,3)	36 (62,1)
1 year (n= 46), n (%)		
Normotensive	17 (37,0)	13 (28,3)
Hypertension	29 (63,0)	33 (71,7)
3 years (n=31), n (%)		
Normal	10 (32,3)	6 (19,4)
Hypertension	21 (67,7)	25 (80,6)
5 years (n=22), n(%)		
Normal	7 (31,8)	6 (27,3)
Hypertension	15 (68,2)	16 (72,7)

4.6.3 Diabetes mellitus

Patients with normal or IGT had no significant increase in OS compared to patients with clinical/pharmacological or clinical-only DM pre-LT at 1 and 5 years, but there was a significant improved OS at 3 years (p=0,002).

Table 13: Occurrence of diabetes mellitus

Pre-LT, n (%)	*Clinical-only*	*Clinical/pharmacological*
Normal or IGT	37 (92,5)	37 (92,5)
DM	3 (7,5)	3 (7,5)
1 year, n (%)		
Normal or IGT	32 (91,4)	32 (86,5)
DM	3 (8,6)	5 (13,5)
3 years, n (%)		
Normal	20 (76,9)	20 (76,9)
DM	6 (23,1)	6 (23,1)
5 years, n(%)		
Normal	14 (87,5)	14 (87,5)
DM	2 (12,5)	2 (12,5)

4.6.4 Hypercholesterolemia

Patients with normal cholesterol levels pre-LT had a nearing-significantly improved OS (p=0,050) compared to patients with clinical only-hypercholesterolemia.

Patients with normal cholesterol levels at 3 years had significantly increased OS (p=0,02) compared to patients with clinical-only hypercholesterolemia, but not at 1 and 5 years. There was no significant difference in OS between patients with normal cholesterol levels and those with clinical/pharmacological hypercholesterolemia at any point in time.

Table 14: Occurrence of hypercholesterolemia		
Pre-LT, n (%)	*Clinical-only*	*Clinical/pharmacological*
Normal	54 (94,7)	52 (91,2)
Hypercholesterolemia	3 (5,3)	5 (8,8)
1 year, n (%)		
Normal	34 (89,5)	30 (75,0)
Hypercholesterolemia	4 (10,5)	10 (25,0)
3 year, n (%)		
Normal	28 (93,3)	21 (70,0)
Hypercholesterolemia	2 (6,7)	9 (30,0)
5 year, n (%)		
Normal	18 (90,0)	13 (65,0)
Hypercholesterolemia	2 (10,0)	7 (35,0)

4.6.5 Renal dysfunction

Before LT, all 58 patients had an eGFR >60. 3, 4 and 6 patients had eGFR 41-60 at 1, 3 and 5 years, respectively. 1 patient had eGFR 21-40 at 3 years and 5 years.

4.7 Opioid usage

23 patients (39,7%) used opioids at any point during the course of the study, 22 (95,7%) patients only used opioids either at discharge or after recurrence. Only 1 (4,3%) patient used opioids continuously from before LT to the end of follow-up. There was no use of opioids at other times than discharge in the subgroup of patients that did not experience recurrence.

Table 15: Use of opioids	
	n (%)
Pre-LT, n = 58	4 (6,9)
Discharge, n = 57	18 (31,6
1 year, n = 49	6 (12,2)
3 year, n = 33	4 (12,1)
5 year, n = 22	4 (18,2)

5. Discussion

Median OS was 43,8 months and median DFS was 11,9 months ranging from 1,4 to 168,2 months and 0 to 91,4 months respectively. Twenty-one (36,2%) patients had NED at end of follow-up with a median follow-up time of 76,6 months, thus suggesting that LT as treatment for CRLM is a superior alternative to liver resection and palliative chemotherapy in selected patients provided an acceptable rate/level of morbidity and complications (60, 61).

Sixteen (27,6%) patients experienced infection during the first 90 days post-LT. The most common type of infection was pneumonia which occurred in 6 patients (10,3%). This is comparable to the rate of pneumonia after LT for other indications (71). Postoperative infection had no significant impact on survival.

Thirty-four patients (58,6%) had a postoperative complication corresponding to Clavien-Dindo score III or higher. Grade IIIb was the most frequent score and three patients required a retransplantation. This is comparable with the rate of retransplantation after LT for other indications (72). There was no difference in OS based on whether the patient had a Clavien-Dindo score or not. This can most likely be explained by the fact that most complications that arose were treated correctly, thus avoiding a negative long-term survival impact. Although grade IVa and IVb complications are serious they are, as in the setting of postoperative renal failure or respiratory decompensation or graft failure, manageable, with dialysis, re-intubation and retransplantation.

All patients received chemotherapy before LT. There was no significant relationship between whether the patient received the last dose of chemotherapy within three weeks of LT and rate of infection, rejection or recurrence. Last chemotherapy did not significantly change OS. This suggests that timing of chemotherapy does not impact morbidity or mortality in this group adversely.

Twenty (34,5%) patients experienced rejection, which is comparable to incidence of rejection reported in other LT-studies (17). Only two patients had more than one rejection, and 90,9% of the rejections were steroid-sensitive. Median time to rejection was 26,5 days and RAI 4 and 5 were the most common scores. Rejection did not significantly impact the OS and this might be due to a relative low median time from LT to rejection, enabling prompt treatment.

Few patients experienced more than one rejection, and no one progressed to chronic rejection (17).

Recurrence occurred in 45 (77,6%) of the patients, with a median time to recurrence of 9,8 months. 64,4% had recurrence in the lung only, which was the most common site of metastasis. Patients with single-site recurrence in lung or liver had significantly better SAR and OS, this may be explained by the lung metastases being small and slow-growing and liver and lung metastases more often being resectable with the patients receiving potentially curative treatment. Seven (12,1%) patients developed de novo cancer during the course of the study. The patients were all on an alternative IS regimen with SRL. Little is known about SRL after LT in patients with CRLM, but mTORi have been found to reduce recurrence-rate and increase DFS in patients after LT due to HCC. This could possibly suggest that the incidence of malignancy could have been higher with a standard CNI-based IS regimen.

Hypertension is a common complication after LT and the patients in this population are no exception. The majority of the patients (62,5%) already had clinical/pharmacological hypertension before LT and the cumulative incidence rose to 72,4% within 5 years. This is comparable to other patient populations who have received LT (20, 21). In this population, there was no significant association between either form of HT and inferior OS. We found a superior survival in patients with HT at 5 years post-LT, which is somewhat counter-intuitive but at this point there are only 22 patients analyzed and the prevalence of clinical/pharmacological HT is 72,7%. Thus, the most likely interpretation of this outcome is that this is a coincidence, without probable causative effect. It is important to note that when interpreting patients as hypertensive in this study, only one BP was used and several of the patients self-reported a lower BP when measured at home or by their primary care physician. This can probably in part explain the disparity between the cumulative incidence of HT and the number of patients using antihypertensive drugs (31,0%).

The prevalence of clinical/pharmacological DM pre-LT was 7,5% and the cumulative incidence rose steadily in the 5 years after LT, to 14,8%. The prevalence of DM rose from pre-LT to 3 years, before a decline at 5 years. At 5 years, the DM status could only be determined for 16 patients. For four patients there were no records of HbA1c, so these were excluded when calculating the cumulative incidence. The only significant association between DM and OS was at 3 years, where DM was associated with inferior survival compared with

those who had a normal or impaired glucose tolerance. Also in DM, a discrepancy between the incidence of disease and use of antidiabetic drugs was observed (14,8% vs 1,7% at 5 years, respectively).

The incidence of hypercholesterolemia increased in the years following LT to 22,8% at 5 years, which is comparable to other studies (26). This was also the only medical complication where there was only a significant inferior OS associated with clinical-only hypercholesterolemia, but not with clinical/pharmacological hypercholesterolemia. The association between clinical-only hypercholesterolemia and inferior OS was approaching significance pre-LT ($p = 0,050$) and was significant at 3 years ($p = 0,020$). This means that only untreated hypercholesterolemia did impact survival negatively, but the cholesterol-status at 3 years could only be determined for 30 patients. This is nearly half of all the patients in an already small patient population, thus these results should be interpreted with caution and needs verification in larger trials.

Twenty-three (39,7%) of the patients used opioids at some point during the study, 95,7% of these only used opioids at discharge or after recurrence. Considering that LT is a major intervention and opioids are often included in palliative care, these numbers are not alarming. There was no use of opioids at other times than discharge in the subgroup of patients that did not experience recurrence, suggesting successful tapering of the medication and low risk for substance abuse.

This is part of a prospective study, where most of the information is gathered from patient records. These records are written by different physicians over several years and at times didn't contain the information needed for this study. A strength of the study was the thorough follow-up, but the population studied has decreased over the years due to death of patients, thus limiting the statistical power. The marked difference in follow-up time from less than 1 year to 14 years is a natural part of prospective studies, but also complicates the analysis. The limited number of patients is an obvious limitation, making the analysis prone to incomplete data, particularly when analyzing the incidence of medical complications beyond the immediate postoperative period. Several of the patients lacked BP, cholesterol or HbA1c levels at one or more points during follow-up. We presumed the lists of medications used are up to date and correctly charted, but this contains some level of uncertainty, since much of this information was not part of the postoperative visits in the protocol. Several of the patients

who experienced recurrence were followed mainly by their local oncologist, resulting in a less thorough information flow in the study records. When considering medical complications, a longer follow-up of the patients would be beneficial to establish to what extent these events contribute to increased morbidity and mortality as this link is well established and could become apparent only several years after LT.

6. Conclusion

Non-resectable CRLM is a severe manifestation of disseminated colorectal cancer that is associated with low survival. The SECA studies demonstrate promising results with regards to survival compared to standard of care chemotherapy and is in well selected cases comparable to standard indications for LT. The rate of medical and surgical complications after LT for CRLM seem to be in line with that reported in conventional indications for LT. Prolonged chemotherapy before transplantation does not influence the rate of complications or survival. We found comparable incidences of HT, DM and hypercholesterolemia in our patient group using mTORi as those previously reported in patients on a CNI-based regimen, thus supporting the use of this this alternative IS regimen due to its antiproliferative properties. For the most part we did not find a link between medical complications and survival, except DM and hypercholesterolemia at certain timepoints, but the restricted number of patients and the relative high mortality necessitates further research when taking the lifetime risk associated with these complications and the relative short follow-up of this study into account.

7. References

1. Scandiatransplant. Annual report 2019 [Internet]. Aarhus: Scandiatransplant office; 2019 [cited 2021 January 20]. Available from: http://www.scandiatransplant.org/resources/AnnualScandiatransplantdatareport2019.pdf.
2. Fosby B, Melum E, Bjøro K, Bennet W, Rasmussen A, Andersen IM, et al. Liver transplantation in the Nordic countries - An intention to treat and post-transplant analysis from The Nordic Liver Transplant Registry 1982-2013. Scand J Gastroenterol. 2015;50(6):797-808.
3. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. HOMOTRANSPLANTATION OF THE LIVER IN HUMANS. Surg Gynecol Obstet. 1963;117:659-76.
4. Lie M. The three first liver transplantations in Norway, and the road leading to them. Tidsskr Nor Laegeforen. 2015;135(23-24):2188-91.
5. Hibi T, Eguchi S, Egawa H. Evolution of living donor liver transplantation: a global perspective. J Hepatobiliary Pancreat Sci. 2018;25(8):388-9.
6. Bismuth H, Houssin D. Reduced-sized orthotopic liver graft in hepatic transplantation in children. Surgery. 1984;95(3):367-70.
7. Pichlmayr R, Ringe B, Gubernatis G, Hauss J, Bunzendahl H. [Transplantation of a donor liver to 2 recipients (splitting transplantation)--a new method in the further development of segmental liver transplantation]. Langenbecks Arch Chir. 1988;373(2):127-30.
8. Azoulay D, Castaing D, Adam R, Savier E, Delvart V, Karam V, et al. Split-liver transplantation for two adult recipients: feasibility and long-term outcomes. Ann Surg. 2001;233(4):565-74.
9. Guvåg S, Thorsen T, Aandahl EM, Hagness M. Levertransplantasjon - Indikasjoner, kirurgisk teknikk og resultater [Internet]. Oslo: Norsk kirurgisk forening; 2017 [updated July 11, 2017; cited 2021 January 15]. Available from: https://kirurgen.no/fagstoff/levertransplantasjon-indikasjoner-kirurgisk-teknikk-og-resultater/.
10. Hackl C, Schmidt KM, Süsal C, Döhler B, Zidek M, Schlitt HJ. Split liver transplantation: Current developments. World J Gastroenterol. 2018;24(47):5312-21.
11. Raia S, Nery JR, Mies S. Liver transplantation from live donors. Lancet. 1989;2(8661):497.
12. Strong RW, Lynch SV, Ong TH, Matsunami H, Koido Y, Balderson GA. Successful liver transplantation from a living donor to her son. N Engl J Med. 1990;322(21):1505-7.
13. Hashikura Y, Makuuchi M, Kawasaki S, Matsunami H, Ikegami T, Nakazawa Y, et al. Successful living-related partial liver transplantation to an adult patient. Lancet. 1994;343(8907):1233-4.
14. Yamaoka Y, Washida M, Honda K, Tanaka K, Mori K, Shimahara Y, et al. Liver transplantation using a right lobe graft from a living related donor. Transplantation. 1994;57(7):1127-30.
15. Vodkin I, Kuo A. Extended Criteria Donors in Liver Transplantation. Clin Liver Dis. 2017;21(2):289-301.
16. Duffy JP, Kao K, Ko CY, Farmer DG, McDiarmid SV, Hong JC, et al. Long-term patient outcome and quality of life after liver transplantation: analysis of 20-year survivors. Ann Surg. 2010;252(4):652-61.
17. Choudhary NS, Saigal S, Bansal RK, Saraf N, Gautam D, Soin AS. Acute and Chronic Rejection After Liver Transplantation: What A Clinician Needs to Know. J Clin Exp Hepatol. 2017;7(4):358-66.

18. Grigg SE, Sarri GL, Gow PJ, Yeomans ND. Systematic review with meta-analysis: sirolimus- or everolimus-based immunosuppression following liver transplantation for hepatocellular carcinoma. Aliment Pharmacol Ther. 2019;49(10):1260-73.
19. Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. Am J Transplant. 2010;10(6):1420-7.
20. Becchetti C, Dirchwolf M, Banz V, Dufour JF. Medical management of metabolic and cardiovascular complications after liver transplantation. World J Gastroenterol. 2020;26(18):2138-54.
21. Barnard A, Konyn P, Saab S. Medical Management of Metabolic Complications of Liver Transplant Recipients. Gastroenterol Hepatol (N Y). 2016;12(10):601-8.
22. Di Stefano C, Vanni E, Mirabella S, Younes R, Boano V, Mosso E, et al. Risk factors for arterial hypertension after liver transplantation. J Am Soc Hypertens. 2018;12(3):220-9.
23. Tong MS, Chai HT, Liu WH, Chen CL, Fu M, Lin YH, et al. Prevalence of hypertension after living-donor liver transplantation: a prospective study. Transplant Proc. 2015;47(2):445-50.
24. Charlton M, Rinella M, Patel D, McCague K, Heimbach J, Watt K. Everolimus Is Associated With Less Weight Gain Than Tacrolimus 2 Years After Liver Transplantation: Results of a Randomized Multicenter Study. Transplantation. 2017;101(12):2873-82.
25. Watson CJ, Gimson AE, Alexander GJ, Allison ME, Gibbs P, Smith JC, et al. A randomized controlled trial of late conversion from calcineurin inhibitor (CNI)-based to sirolimus-based immunosuppression in liver transplant recipients with impaired renal function. Liver Transpl. 2007;13(12):1694-702.
26. Kaplan B, Qazi Y, Wellen JR. Strategies for the management of adverse events associated with mTOR inhibitors. Transplant Rev (Orlando). 2014;28(3):126-33.
27. Charlton M, Levitsky J, Aqel B, O'Grady J, Hemibach J, Rinella M, et al. International Liver Transplantation Society Consensus Statement on Immunosuppression in Liver Transplant Recipients. Transplantation. 2018;102(5):727-43.
28. Parekh J, Corley DA, Feng S. Diabetes, hypertension and hyperlipidemia: prevalence over time and impact on long-term survival after liver transplantation. Am J Transplant. 2012;12(8):2181-7.
29. Ramos-Prol A, Hervás-Marín D, García-Castell A, Merino-Torres JF. Outcomes in patients with diabetes 10 years after liver transplantation. J Diabetes. 2017;9(11):1033-9.
30. Ling Q, Xu X, Xie H, Wang K, Xiang P, Zhuang R, et al. New-onset diabetes after liver transplantation: a national report from China Liver Transplant Registry. Liver Int. 2016;36(5):705-12.
31. Johnston O, Rose CL, Webster AC, Gill JS. Sirolimus is associated with new-onset diabetes in kidney transplant recipients. J Am Soc Nephrol. 2008;19(7):1411-8.
32. Vivarelli M, Dazzi A, Cucchetti A, Gasbarrini A, Zanello M, Di Gioia P, et al. Sirolimus in liver transplant recipients: a large single-center experience. Transplant Proc. 2010;42(7):2579-84.
33. Zimmermann A, Zobeley C, Weber MM, Lang H, Galle PR, Zimmermann T. Changes in lipid and carbohydrate metabolism under mTOR- and calcineurin-based immunosuppressive regimen in adult patients after liver transplantation. Eur J Intern Med. 2016;29:104-9.
34. Desai R, Jamieson NV, Gimson AE, Watson CJ, Gibbs P, Bradley JA, et al. Quality of life up to 30 years following liver transplantation. Liver Transpl. 2008;14(10):1473-9.
35. Geissler EK, Schnitzbauer AA, Zülke C, Lamby PE, Proneth A, Duvoux C, et al. Sirolimus Use in Liver Transplant Recipients With Hepatocellular Carcinoma: A Randomized, Multicenter, Open-Label Phase 3 Trial. Transplantation. 2016;100(1):116-25.

36. Engels EA, Pfeiffer RM, Fraumeni JF, Jr., Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. Jama. 2011;306(17):1891-901.
37. Yokoyama I, Carr B, Saitsu H, Iwatsuki S, Starzl TE. Accelerated growth rates of recurrent hepatocellular carcinoma after liver transplantation. Cancer. 1991;68(10):2095-100.
38. Hojo M, Morimoto T, Maluccio M, Asano T, Morimoto K, Lagman M, et al. Cyclosporine induces cancer progression by a cell-autonomous mechanism. Nature. 1999;397(6719):530-4.
39. Sheiner PA, Magliocca JF, Bodian CA, Kim-Schluger L, Altaca G, Guarrera JV, et al. Long-term medical complications in patients surviving > or = 5 years after liver transplant. Transplantation. 2000;69(5):781-9.
40. Sahin F, Kannangai R, Adegbola O, Wang J, Su G, Torbenson M. mTOR and P70 S6 kinase expression in primary liver neoplasms. Clin Cancer Res. 2004;10(24):8421-5.
41. Nozawa H, Watanabe T, Nagawa H. Phosphorylation of ribosomal p70 S6 kinase and rapamycin sensitivity in human colorectal cancer. Cancer Lett. 2007;251(1):105-13.
42. Pengel LH, Liu LQ, Morris PJ. Do wound complications or lymphoceles occur more often in solid organ transplant recipients on mTOR inhibitors? A systematic review of randomized controlled trials. Transpl Int. 2011;24(12):1216-30.
43. Knight RJ, Villa M, Laskey R, Benavides C, Schoenberg L, Welsh M, et al. Risk factors for impaired wound healing in sirolimus-treated renal transplant recipients. Clin Transplant. 2007;21(4):460-5.
44. Dunkelberg JC, Trotter JF, Wachs M, Bak T, Kugelmas M, Steinberg T, et al. Sirolimus as primary immunosuppression in liver transplantation is not associated with hepatic artery or wound complications. Liver Transpl. 2003;9(5):463-8.
45. Massoud O, Wiesner RH. The use of sirolimus should be restricted in liver transplantation. J Hepatol. 2012;56(1):288-90.
46. Harper SJ, Gelson W, Harper IG, Alexander GJ, Gibbs P. Switching to sirolimus-based immune suppression after liver transplantation is safe and effective: a single-center experience. Transplantation. 2011;91(1):128-32.
47. Montalbano M, Neff GW, Yamashiki N, Meyer D, Bettiol M, Slapak-Green G, et al. A retrospective review of liver transplant patients treated with sirolimus from a single center: an analysis of sirolimus-related complications. Transplantation. 2004;78(2):264-8.
48. Molinari M, Berman K, Meeberg G, Shapiro JA, Bigam D, Trotter JF, et al. Multicentric outcome analysis of sirolimus-based immunosuppression in 252 liver transplant recipients. Transpl Int. 2010;23(2):155-68.
49. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334(11):693-9.
50. Stein DE, Poggio JL, Rubin J. Colorectal Cancer [Internett]. London: BMJ Publishing Group; 2020 [updated March 11, 2020; cited 2020 November 17]. Available from: https://bestpractice.bmj.com/topics/en-gb/258.
51. Dueland S, Guren TK, Hagness M, Glimelius B, Line PD, Pfeiffer P, et al. Chemotherapy or liver transplantation for nonresectable liver metastases from colorectal cancer? Ann Surg. 2015;261(5):956-60.
52. Mühlbacher F, Huk I, Steininger R, Gnant M, Götzinger P, Wamser P, et al. Is orthotopic liver transplantation a feasible treatment for secondary cancer of the liver? Transplant Proc. 1991;23(1 Pt 2):1567-8.
53. Grunnet N, Bödvarsson M, Jakobsen A, Kyllönen L, Olausson M, Pfeffer P, et al. Scandiatransplant report 2009. Transplant Proc. 2010;42(10):4429-31.

54. Hagness M, Foss A, Line PD, Scholz T, Jørgensen PF, Fosby B, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg. 2013;257(5):800-6.
55. Grut H, Dueland S, Line PD, Revheim ME. The prognostic value of (18)F-FDG PET/CT prior to liver transplantation for nonresectable colorectal liver metastases. Eur J Nucl Med Mol Imaging. 2018;45(2):218-25.
56. Dueland S, Foss A, Solheim JM, Hagness M, Line PD. Survival following liver transplantation for liver-only colorectal metastases compared with hepatocellular carcinoma. Br J Surg. 2018;105(6):736-42.
57. Dueland S, Line PD, Hagness M, Foss A, Andersen MH. Long-term quality of life after liver transplantation for non-resectable colorectal metastases confined to the liver. BJS Open. 2019;3(2):180-5.
58. Dueland S, Syversveen T, Solheim JM, Solberg S, Grut H, Bjørnbeth BA, et al. Survival Following Liver Transplantation for Patients With Nonresectable Liver-only Colorectal Metastases. Ann Surg. 2020;271(2):212-8.
59. Dueland S, Grut H, Syversveen T, Hagness M, Line PD. Selection criteria related to long-term survival following liver transplantation for colorectal liver metastasis. Am J Transplant. 2020;20(2):530-7.
60. Wang K, Xu D, Yan XL, Poston G, Xing BC. The impact of primary tumour location in patients undergoing hepatic resection for colorectal liver metastasis. Eur J Surg Oncol. 2018;44(6):771-7.
61. Cremolini C, Antoniotti C, Lonardi S, Bergamo F, Cortesi E, Tomasello G, et al. Primary tumor sidedness and benefit from FOLFOXIRI plus bevacizumab as initial therapy for metastatic colorectal cancer. Retrospective analysis of the TRIBE trial by GONO. Ann Oncol. 2018;29(7):1528-34.
62. Line PD, Hagness M, Berstad AE, Foss A, Dueland S. A Novel Concept for Partial Liver Transplantation in Nonresectable Colorectal Liver Metastases: The RAPID Concept. Ann Surg. 2015;262(1):e5-9.
63. Clavien PA, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. N Engl J Med. 2007;356(15):1545-59.
64. Dueland S. Liver Transplantation Compared to Chemotherapy in Patients With ColoRectal Cancer (SECAIII) [Internet]. Oslo: U.S. National Library of Medicine; 2018 [updated September 16, 2020; cited 2021 January 14]. Available from: https://clinicaltrials.gov/ct2/show/NCT03494946?cond=liver+transplantation+colorectal&cntry=NO&city=OSLO&draw=2&rank=2.
65. Line PD, Dueland S. Liver transplantation for secondary liver tumours: The difficult balance between survival and recurrence. J Hepatol. 2020;73(6):1557-62.
66. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.
67. Banff schema for grading liver allograft rejection: an international consensus document. Hepatology. 1997;25(3):658-63.
68. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018;36(10):1953-2041.
69. Helsedirektoratet. Diagnostikk av diabetes, risikovurdering og oppfølging av personer med høy risiko for å utvikle diabetes [Internet]. Oslo: Helsedirektoratet; 2016 [updated April

15 2020; cited 2021 January 11]. Available from: https://www.helsedirektoratet.no/retningslinjer/diabetes/diagnostikk-av-diabetes-risikovurdering-og-oppfolging-av-personer-med-hoy-risiko-for-a-utvikle-diabetes#risikovurdering-og-pavisning-av-diabetes-praktisk.
70. Helsedirektoratet. Bruk av statiner og andre lipidsenkende legemidler ved primærforebygging av hjerte- og karsykdom [Internet]. Oslo: Helsedirektoratet; 2017 [updated March 5 2018; cited 2021 January 11]. Available from: https://www.helsedirektoratet.no/retningslinjer/forebygging-av-hjerte-og-karsykdom/legemidler-ved-primaerforebygging-av-hjerte-og-karsykdom/bruk-av-statiner-og-andre-lipidsenkende-legemidler-ved-primaerforebygging-av-hjerte-og-karsykdom#null-praktisk.
71. Angarita SAK, Russell TA, Kaldas FM. Pneumonia after liver transplantation. Curr Opin Organ Transplant. 2017;22(4):328-35.
72. Marudanayagam R, Shanmugam V, Sandhu B, Gunson BK, Mirza DF, Mayer D, et al. Liver retransplantation in adults: a single-centre, 25-year experience. HPB (Oxford). 2010;12(3):217-24.