

## Role of Liver Transplantation in Treatment of Colorectal Liver Metastases

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Surgical resection is that the only curative modality for colorectal liver metastases (CLM) and 5-year overall survival after resection is about 40%. Nonresectable CLM isn't curable and 5-year overall survival is currently about 10%. Before 1995, several liver transplantations for CLMs were performed, but outcome was poor (5-year survival rate: 18%). Liver transplantation for CLMs was abandoned and CLMs were even considered a contraindication to the procedure. Since then, the survival rate after liver transplantation generally has improved by almost 30%. During a prospective pilot study of liver transplantation for nonresectable CLM, a 5-year overall survival rate of 60% was demonstrated, however 19 of 21 patients experienced recurrence of disease. Here, current knowledge and ongoing research during this field is reviewed, and therefore the potential role for liver transplantation together of several treatment modalities for CLM discussed.

### Liver transplantation for nonresectable CLM in Norway – The SECA study

Due to traditionally low prevalence of hepatitis C and a fortunate donor situation, the typical waiting time for donor livers in Norway until recently has been but 1 month and few die on the roll. This made it possible to explore new indications for liver transplantation, including malignancies. Within the early a part of the millennium, CLM were considered a contraindication for liver transplantation. Data from the ecu Liver Transplant Registry (ELTR) showed 5-year survival of 18% after liver transplantation for CLM before 1995. However, survival after liver transplantation has improved with 20 to 30% since then, additionally, there are improvements in oncological treatment and imaging techniques, also because the introduction of the mammalian target of rapamycin (mTOR) inhibitors as immunosuppressive drugs with antioncogenic properties. Supported these factors, 5-year overall survival after liver transplantation for CLM of fifty was anticipated.

The SECA study was a pilot study for nonresectable CLM that was initiated at Oslo University Hospital in 2006. A complete of 21 patients underwent liver transplantation during this study. The 5-year overall survival was 60% (95% CI: 34–85%). Median follow-up was 27 months (range 8–60 months). Six of 21 patients died thanks to disseminated cancer after median 26 months (range 6–41 months) after liver transplantation. Disease-free survival was 35% at 1 year, and 19 of the 21 patients experienced recurrences, however, a big proportion of those were accessible for surgery and at follow up 33% of the patients had no evidence of disease.

The initial study protocol was quite strict regarding extent of disease and response to chemotherapy but after 11 months without included patients, a protocol amendment with wider inclusion criteria was approved. These consisted broadly of minimum six weeks of chemotherapy, good performance status and absence of extrahepatic disease. So, principally nonresectability was the sole criterion for patient selection. Accordingly, the study population ended up heterogeneous regarding T and N stage, previous exposure and response to oncological treatment. At time of liver transplantation, 16 patients had progressed

on first or later lines of chemotherapy, six patients had progressed on all standard lines of chemotherapy, and 38% of the patients had received second-line chemotherapy. The hepatic tumor load was extensive; median number of metastatic lesions was eight (range 4–40 metastases), and median diameter of the most important lesion was 4.5 cm (range 2.8–13.0 cm).

Since the survival enjoy hepatic resection for CLM is extensively documented, the prognostic factors and therefore the corresponding clinical scoring systems aren't utilized in the decision-making on whether to perform hepatic resection or not. However, regarding liver transplantation for CLM the choice of patients is vital due to the scarcity of donor livers. Outcome for a replacement indication must convince be comparable or better than outcome for established indications for liver transplantation. The heterogeneity of the SECA population made it likely that there have been differences in prognostic profiles of the patients. In both the patients with shortest survival, breaching of the liver capsule and cancer infiltration of diaphragm were found after vital structures were divided and transplantation unavoidable. Four factors were found to be significantly related to survival: maximal hepatic tumor diameter above 5.5 cm, time from primary cancer surgery but two years, carcinoembryonic antigen of quite 80 µg/l and progressive disease at time of liver transplantation. These are established clinical prognostic factors known from studies on liver resection. Five of the six deceased patients had all of those factors present. Very cautious interpretation on these findings is stressed due to the tiny study population, but the findings demonstrate a possible for choosing patients supported clinical parameters. Since the first report the SECA data has matured with quite two years. At 65 months (range 19–85 months) post liver transplantation, the four prognostic factors were still significantly related to survival, and if excluding the five patients with all four factors present, the survival at 6 and seven years was 60%.

All patients within the SECA study that was observed for quite 11 months experienced recurrence of disease. The median time to recurrence was 6 months (range 2–24 months), 17 patients experienced lung metastases and seven patients received metastases to their new liver. At end of follow up, seven patients were alive with no evidence of disease, eight patients were alive with recurrence and 6 patients were deceased. The initial recurrence pattern was: 68% lung metastases, 11% liver and lung metastases, 11% lymph gland metastases, 5% liver and ovarian metastasis and 5% experienced local recurrence of rectal tumor as first recurrence. No patient had metastases to the new liver only as first site, and liver metastases developed exclusively as a part of disseminated disease. At end of follow-up, six of the seven patients

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that developed liver metastases were dead. Median time from diagnosis of liver metastases to death was 14 months (range 4-21 months). In contrast, all the 12 patients with recurrences that didn't include the liver were alive at end of follow up, and patients with pulmonary first site recurrence had a 5-year overall survival of 72%.

Because the pulmonary metastases were slow growing, reassessment of CT scans by one experienced radiologist was performed. Tracing back from evident metastases altogether the 17 patients with pulmonary manifestations, revealed that seven of them had pulmonary metastases appearing as small nodules at time of liver transplantation. Four of them had pulmonary deposits on earlier CT scans also (2, 2, 3 and 12 months before liver transplantation, respectively). The survival analysis showed that the presence of those metastases at the time of liver transplantation didn't have negative impact on survival.

The SECA study was an uncontrolled pilot study. So as to match survival after liver transplantation with outcome from a contemporary chemotherapy study, data from an identical cohort of patients included within the NORDIC-VII study were obtained. The NORDIC-VII study was a three-arm, multicenter phase III clinical trial on Nordic FLOX and two different regimens containing cetuximab and FLOX as first-line treatment of metastatic CRC. Patients that had nonresectable CLM, no

extrahepatic disease, no BRAF mutation and similar age were extracted from the NORDIC-VII database. The study population characteristics ended up like the SECA population; however 5-year overall survival was 9% after start of first-line chemotherapy (n=47), significantly shorter than the 5-year overall survival within the SECA study. Six of the patients within the SECA study had progressive disease on all standard lines of chemotherapy, three after three lines of chemotherapy and three with mutation of Kras after second line of chemotherapy. For these patients, the median overall survival was 41 months and 5-year overall survival was 41% within the Nordic-VII study, the median overall survival for an identical cohort was significantly shorter, 5.6 months, and every one patients were dead before 2 years.

## Conclusion

Liver transplantation has the potential to be a neighborhood of the armamentarium of treatment modalities for CLM, but to what extent is yet to be established. The foremost obvious group that probably would enjoy the procedure is CLM patients with favorable prognostics and nonresectable disease despite modern surgical or oncosurgical approaches. Only a fraction of this group would be transplantable due to adulthood and comorbidity.