

# Chemotherapy or Liver Transplantation for Nonresectable Liver Metastases From Colorectal Cancer?

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**Objective:** The primary objective was to compare overall survival (OS) in patients with colorectal cancer (CRC) with nonresectable liver-only metastases treated by liver transplantation or chemotherapy.

**Background:** CRC is the third most common cancer worldwide. About 50% of patients will develop metastatic disease primarily to the liver and the lung. The majority of patients with liver metastases receive palliative chemotherapy, with a median OS of trial patients of about 2 years, and less than 10% are alive at 5 years.

**Methods:** Patients with nonresectable liver-only CRC metastases underwent liver transplantation in the SECA study (n = 21). Disease-free survival (DFS) and OS of patients included in the SECA study were compared with progression-free survival (PFS) and OS in a similar cohort of CRC patients with liver-only disease included in a first-line chemotherapy study, the NORDIC VII study (n = 47). PFS/DFS and OS were estimated by the Kaplan-Meier method.

**Results:** DFS/PFS in both groups were 8 to 10 months. However, a dramatic difference in OS was observed. The 5-year OS rate was 56% in patients undergoing liver transplantation compared with 9% in patients starting first-line chemotherapy. The reason for the large difference in OS despite similar DFS/PFS is likely different metastatic patterns at relapse/progression. Relapse in the liver transplantation group was often detected as small, slowly growing lung metastases, whereas progression of nonresectable liver metastases was observed in the chemotherapy group.

**Conclusions:** Compared with chemotherapy, liver transplantation resulted in a marked increased OS in CRC patients with nonresectable liver-only metastases.

**Keywords:** chemotherapy, colorectal cancer, liver metastases, liver transplantation, overall survival

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Colorectal carcinoma (CRC) is one of the most frequent cancers worldwide, and about half of the patients develop metastases, primarily to the liver or lung. Surgical treatment of metastases is the only treatment option with curative potential; however, only about 10% to 20% of the patients seen at major hospitals are candidates

for surgical resection. Furthermore, the majority of patients undergoing liver resection develop relapse of the disease and 5-year survival is about 30% to 40% in most reported studies.<sup>1</sup> Most patients with colorectal liver metastases have nonresectable disease; these patients have poor prognosis and only about 10% survive up to 5 years.<sup>2,3</sup> Standard treatment option for patients with nonresectable liver-only metastases is palliative chemotherapy. Modern chemotherapy including the use of bevacizumab/EGFR antibodies has increased median survival of patients with metastatic CRC (mCRC) included in clinical trials from about 6 months to 2 years.<sup>4–6</sup>

Liver transplantation has been successfully developed as a treatment option for primary liver malignancy such as hepatocellular carcinoma with a 5-year overall survival (OS) after liver transplantation of about 70% to 80%.<sup>7,8</sup> Before 1995, several liver transplants for colorectal liver metastases were performed and results were reported to the European Liver Transplant Registry. The 1- and 5-year survival rates were 62% and 18%, respectively.<sup>7</sup> During this time period, the perioperative mortality after liver transplantation was high compared with the results obtained after 2005 and up to 30% of the patients treated before 1995 died from surgical or perioperative complications.<sup>9</sup> On the background of improvements in outcome after liver transplantation for nonmalignant diseases and development of immunosuppressants with antimalignant properties, we initiated a study reexamining liver transplantation as a treatment option in mCRC patients with nonresectable liver-only disease in 2006 (SECA study). Of patients included in first-line chemotherapy studies, about 20% have liver-only disease and we considered liver transplantation to be a treatment option for a selected subgroup of these patients.

We have recently reported a 5-year OS rate of 60% in 21 patients in the SECA study.<sup>10</sup> Without liver transplantation, the patients in the SECA study would have been offered palliative chemotherapy. The aim of this article is to compare our results with liver transplantation of mCRC patients with the best available nonsurgical treatment. Thus, in this report, we have compared disease-free survival (DFS)/progression-free survival (PFS) and OS in mCRC patients with nonresectable liver-only disease, treated with liver transplantation (SECA study),<sup>10</sup> and in the first-line chemotherapy study with Nordic FLOX with or without cetuximab (NORDIC VII).<sup>11</sup>

## METHODS

### Study Design and Procedures

The SECA study was an open, prospective pilot study with liver transplantation in patients with nonresectable CRC liver-only metastases.<sup>10</sup> All patients (n = 21) who underwent liver transplantation are included in the present analysis. No patients in the SECA study turned out to have a *BRAF* mutated tumor, and they were 65 years or younger at the time of liver transplantation.

The NORDIC VII study was a randomized, multicenter, 3-arm phase III trial in which patients were randomized 1:1:1 to Nordic FLOX (arm A), FLOX + cetuximab (arm B), and FLOX intermittently + cetuximab continuously (arm C). There were no significant differences between the treatment arms in terms of response rates,

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