Editorial

Liver transplantation for unresectable colorectal metastasis: a new hope

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Despite recent advances in medical and surgical treatments, surgical resection remains the only curative option for patients with colorectal liver metastasis (CRLM). Unfortunately, only a minority of patients with CRLM are candidates for liver resection. The 5-year survival of patients with liver-only disease and deemed unresectable is difficult to quantify but likely ranges around 5 to 10%. Since 2013, a few studies have shown that liver transplantation (LT) is feasible for selected patients with unresectable CRLM (1,2). Recently, the Oslo University Hospital LT group has published their latest results with modified selection criteria and should be congratulated for their efforts. Nevertheless, the evidence available is still developing. For example, currently, there is a lack of robust evidence supporting the widespread use of LT for CRLM outside Norway, a particular region in terms of graft scarcity.

In 2013, Hagness *et al.* published the first series of patients with unresectable CRLM who underwent LT (1). The SECA-I trial was a prospective pilot study to assess the safety and effectiveness of LT for patients with unresectable CRLM. Details of the SECA-I design are presented in *Table 1*, along with its main results. Briefly, 25 patients were listed for LT, and 21 (84%) underwent LT. After a median follow-up time of 27 months, none of the patients was disease-free. The disease-free survival (DFS) was 35% at 1-year and 0% at 2-year. Interestingly, the overall survival (OS) was 95%, 68%, and 60% at 1-, 3- and 5-year. This difference between DFS and OS led the authors to evaluate recurrence patterns more closely. They identified that after LT, recurrences occurred at sites amenable for further treatment. For example, 7/21 (33%) patients had lung-only recurrences and underwent ablation and/or surgical resection. In terms of safety, no patient died because of post-operative complications. Nonetheless, major complications (Clavien-Dindo IIIa) occurred in 10/21 (49%) of their patients. Of note, four patients developed hepatic artery thrombosis and, of them, two required re-transplantation. The SECA-I trial demonstrated that LT for patients with unresectable CRLM is safe and effective. However, the rate of recurrences was high, which was the focus of criticism concerning the utility of LT for CRLM patients.

In their most recent study, entitled SECA-II, Dueland *et al.* assessed the impact of more restrictive selection criteria (3). The study presents the results of 15 patients with unresectable CRLM who underwent LT. The smaller population size reflects, likely, the more stringent inclusion criteria which included, in addition to the same inclusion criteria in the SECA-I trial: unresectable liver-only colorectal metastases, at least 10% response to systemic therapy, and at least 1-year between the primary tumor diagnosis and the listing for LT (*Table 1*). In comparison with the SECA-I trial, patients in SECA-II had a lower tumoral burden and carcinoembryonic antigen levels (*Table 1*). After a median follow-up of 36 months, 8/15 (53%) patients developed disease recurrence. The DFS was 53%, 44%, and 35% at 1-, 2- and 3-year, respectively. The OS was 100%, 83%, and 83% at 1-, 3- and 5-year, respectively. Authors reported the survival after recurrence. They have shown a 72% survival after recurrence at 4-years. In terms of complications, the rate of major complications

Table 1 Details on design and main results from the SECA-I and SECA-II trials

Study design	SECA-I (2013)	SECA-II (2019)
Inclusion criteria	Unresectable CRLM	Same as SECA-I, plus: At least 10% of response to chemotherapy by the RECIST criteria
	Absence of extrahepatic disease	No lesion >10 cm before chemotherapy
	Complete resection of primary tumor	If more than 30 lesions, all must be <5 cm and patients must have at least 30% response to chemotherapy by the RECIST criteria
	ECOG status ≥1	Patients with less than 10% response to chemotherapy may be included proven then had 20% response after locoregional therapies (TACE and/or TARE/SIRT)
	Minimum 6 weeks of chemotherapy	At lease 1-year follow-up between the primary resection and listing for LT
Exclusion criteria	Weight loss >10%	Same as SECA-I, plus: BMI >30 kg/m^2
	Contraindication for LT	Prior extra-hepatic colorectal metastasis (even if completely resected)
	Presence of other malignancies	
Immunosuppression	Sirolimus, mycophenolate mofetil and corticosteroids and induction with basiliximab	Induction with basiliximab, corticosteroids and tacrolimus for 4–6 weeks
	Sirolimus on PO-1 aiming serum level of 5–10 ng/mL for the first 4 weeks and 10–20 ng/mL thereafter	Then, conversion to sirolimus
Adjuvant therapy	None	None
Outcomes	Overall survival	Overall survival
	Disease-free survival	Disease-free survival
Main results		
Population	25 patients listed	15 patients listed
	21 patients underwent LT	15 patients underwent LT
Primary tumor staging	16/21 15 patients had pT3	11/15 patients had (y)pT3
	7/21 patients had N0	8/15 patients had (y)pN0
	7/21 patients had N2	1/15 patient had (y)pN2
Number of lesions at LT, median [range]	8 [4–40]	5 [1–53]
Size biggest lesion at LT, cm, median [range]	4.5 [2.8–13.0]	2.4 [0.3–4.7]
CEA at LT, μg/L, median [range]	15 [1–2002]	2 [1–30]
Fong clinical risk score at LT	16/21 patients had ≥3	median [range], 2 [1–3]
Follow-up, median [range]	27 [8–60 months]	36 [5–60 months]

Table 1 (*continued*)

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Study design	SECA-I (2013)	SECA-II (2019)
Overall survival	95% 1-year	100% 1-year
	68% 3-year	83% 3-year
	60% 5-year	83% 5-year
Disease-free survival	35% 1-year	53% 1-year
	0% 2-year	44% 2-year
	–	35% 3-year
Main conclusion	LT is feasible for patients with unresectable CRLM	More restrictive selection criteria result in improved outcomes

BMI, body mass index; CEA, carcinoembryonic antigen; CRLM, colorectal liver metastasis; ECOG, Eastern Cooperative Oncology Group; LT, liver transplantation; PO, post-operative; SIRT, selective internal radiation therapy; TACE, transarterial chemotherapy; TARE, transarterial radioembolization.

was similar to the previous study: 47%. In contrast, no patient required re-transplantation. Therefore, the SECA-II trial, successfully showed that more restrict selection criteria improve the outcomes. The main criticism, however, should be the short follow-up time. Of the 11 patients who were alive at the end of follow-up, only one had reached the 5-year mark. This lack of longer follow-up, unfortunately, still prevents any strong conclusion from being drawn about the long-term benefit of LT for patients with CRLM.

The SECA-II trial sheds light on additional topics worthy of mention. The pre-LT examination with ^{18}F-FDG PET/CT has been shown as an option for patient selection. Assessing the ^{18}F-FDG PET/CT might identify tumors with less aggressive tumoral biology, as well as improve detection of extrahepatic disease (4). Negative nodal status on primary resection was associated with improved outcomes when compared to patients with N+ disease. As seen in the SECA-I trial, patients with higher Fong Clinical Risk Score also had the worst outcomes in the SECA-II trial. The time between the primary colorectal surgery and LT deserves further investigation. In the SECA-II trial, the authors applied a mandatory 1-year follow-up period before LT. Finally, in SECA-II, patients were required to have a minimal response to chemotherapy to get listed for LT. Likely, these criteria will be applied in the future to select those patients who will benefit the most from LT.

The lack of a control group is the primary limitation in both SECA studies. The group from Oslo tried to compare the LT cohort with different cohorts of patients treated with palliative chemotherapy (5). The validity of such comparisons remains unclear. A prospective trial specifically designed to compare patients with similar baseline characteristics treated with LT and palliative chemotherapy alone would be ideal for demonstrating the precise benefit of LT. In this regard, two prospective trials are currently recruiting patients to compare outcomes after LT versus chemotherapy alone: in France, the TRANSMET trial (NCT02597348) and, in Norway, the SECA-III trial (NCT03494946). The inclusion of patients with unresectable CRLM in the LT waiting list would increase the scarcity of deceased donor grafts. In this regard, strategies to increase the donor pool are needed. This is even more important to consider when we note that in the SECA-I trial, two patients required re-transplantation. To increase the pool of grafts, the use of marginal grafts could be explored. The group from Oslo University Hospital has developed the RAPID concept: left lateral hepatectomy with left lateral segment graft implantation followed by completion hepatectomy after adequate graft volume has been achieved. The use of grafts from live donors would not impact on graft scarcity. Our group is currently recruiting patients with unresectable CRLM for live donor LT in a prospective trial (NCT02864485).

In conclusion, LT is feasible for patients with unresectable CRLM. The evidence from the SECA-II trial shows that selection criteria are imperative; although, the best way to select these patients is still to be determined. The ideal criteria for patient selection would be a combination of tumoral biology (e.g., tumoral burden, serum CEA levels, ^{18}F-FDG PET/CT evaluation, etc.), response to previous treatments (either chemotherapy or locoregional) and time elapsed between the primary

colorectal resection and the LT. Furthermore, each LT jurisdiction will have to adjust these criteria to its organ availability to minimize adversely impacting waitlist outcomes for other patients. Finally, the group from Oslo University Hospital has made a remarkable contribution to the transplantation community, but much remains to be clarified before LT for CRLM can be widely accepted.

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