

**Liver transplantation for colo-rectal liver metastasis:
survival without recurrence can be achieved**

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Footnote page

Alphabetical list of all abbreviations: ALPPS: associating liver partition and portal vein ligation for staged hepatectomy, CEA: carcinoembryonic antigen, mTOR: mammalian

Target-of-Rapamycin, RFA: radio-frequency ablation,

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To the Editor,

The management of patients with colo-rectal liver metastases has improved significantly over the recent years. However, most patients still cannot undergo complete resection, generally because the location of the metastases within the liver prevents any radical management, and explaining the interest for transplantation. The first attempts were performed in the eighties with poor outcomes, in part due to a high proportion of death not related to the neoplastic disease (1). More recently, the group of Oslo has shown a 60% five-year survival, in 21 patients with colo-rectal metastases (2). Such a survival was better than the one expected on chemotherapy alone (2-4). However, 95% (20/21) of patients had cancer recurrence, most within the first 18 months after transplantation. At present, liver transplantation for colo-rectal metastases remains highly controversial. The potential for long-term disease-free survival needs to be explored, which is the aim of this multi-centric collaborative retrospective study.

A total of 12 patients (6 females/6 males) underwent liver transplantation for colo-rectal liver metastasis, at centers affiliated to the “Compagnons Hépatobiliaires”, an association of hepato-pancreato-biliary and transplant surgeons, most trained at the Paul Brousse Hospital, Paris, France under the guidance of Professor H. Bismuth. Median age at transplant was 56 years (Table 1). Patients were managed in Lisbon (n=8), Coimbra (n=2), Paris (n=1), and Geneva (n=1) between October 1995 and October 2015 (date of transplant), and no other patient underwent transplantation for this indication at these respective transplant centers. Data collection was conducted according the relevant ethical standards at each institution. The location of the primary adenocarcinoma was the colon in 11 patients, and the rectum in one. Most primary cancers were T3 on pathology,

and many presented between 1 and 3 involved –N1– lymph nodes (two patients were N2 with more than 3 nodes involved, Table 1).

For most patients, liver metastases (9/12) were diagnosed within 12 months after the diagnosis of the primary cancer, and were considered as synchronous. When not diagnosed at the same time as the primary, liver metastases were discovered 4, 7, 19, 24 and 29 months after the primary. At the time of transplantation, patients presented a median of 9 liver metastases. Two had lesions >5 cm, of 5.5 and 8 cm. Median CEA level was 16.9 µg/l, and one patients had CEA >200 µg/l, of 314 µg/l.

Most (11/12) patients received chemotherapy prior to transplantation. Chemotherapy included irinotecan and oxaliplatin in 9 (82%) patients, and a biological agent in 6 (cetuximab in 2, bevacizumab in 3, and both agents in 1). Another patient was treated by intra-hepatic chemotherapy prior to transplantation. All patients responded to chemotherapy, and none was in progression at the time of the transplantation. The decision to conduct a post-transplant adjuvant chemotherapy was based, at least in the recent years, on the aim to obtain a minimum of four months of peri-transplant oxaliplatin and/or irinotecan-including chemotherapy. It was used in four patients.

Overall, most patients underwent complex, long-term chemotherapy treatment, with a median of two lines (1 in 1 patient, 2 in 6 patients, 3 in 2 patients, and 4 in 1 patient).

In addition to chemotherapy, 10 patients underwent liver metastasis resection, in one (n=5), two (n=3), or three (n=2) procedures, one of which was a two-stage resection. One patient underwent radio-frequency ablation (RFA) as part of the treatment. At the time of transplantation, any treatment by resection or RFA was not possible anymore.

Transplantations were performed 41 (12-97) months after the resection of the primary.

Liver grafts were from 6 non-marginal donors after brain-death, 5 domino donors with familial amyloid polyneuropathy, and one living-related donor. Transplantation was part of a planned treatment strategy following previous liver resection in 6 patients. In 2 patients, transplantation was performed upfront without previous resection, considered impossible because of diffuse liver disease. In three patients, transplantations were performed as salvage procedures: after massive bleeding (and packing) following liver resection, for a failed associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure, and for post-resection liver failure. Finally, one patient was transplanted with inferior vena cava replacement due to tumor invasion. Overall, 6 patients could be categorized as having planned transplantations, and 6 patients could be retrospectively considered as having received “compassioned” transplantations.

The median length of hospital stay for transplantation was 16 days. Seven patients had complications, including 3 patients with grade 2 complications according to Clavien-Dindo (pneumonia and fever of unknown origin treated by antibiotics, and rejection treated by steroids), 1 patients with grade 3b complication (biliary leak requiring endoscopic stenting), 2 patients with grade 4a complication (kidney failure requiring dialysis, prolonged ventilation requiring a tracheostomy), and 1 patient with grade 5 complication (death following severe bleeding and shock). Eight patients received mTOR inhibitors as part of their maintenance immunosuppression.

Overall patient survivals were 83 ± 11 %, 62 ± 15 %, and 50 ± 16 % at 1, 3 and 5 years, after a median follow-up of 26 (0-108) months (Figure 1). Six patients had a recurrence, affecting the lungs (n=5), the liver (n=3), and the peritoneum (n=1). Disease-free

survivals were 56 ± 14 %, 38 ± 15 %, and 38 ± 15 % at 1, 3 and 5 years. Treatment of recurrence included palliative chemotherapy in five patients and radiotherapy in one. Five patients were alive and free of cancer 7, 43, 47, 48, and 108 months after transplantation (Table 1).

Patients undergoing transplantation for compassionate indications (upfront, salvage, and vena cava involvement) had significantly worse disease-free survivals than patients with planned indications ($p=0.02$). Looking at the Oslo criteria (2), the last pre-transplant CEA level (≥ 80 vs. <80 $\mu\text{g/l}$, $p=0.09$) and the time between resection of the primary cancer and transplantation (≥ 24 vs. <24 months, $p=0.01$) also tended to predict disease-free survival.

The size of the largest metastasis at transplant (≥ 5.5 vs. <5.5 cm) failed to predict survival ($p=0.47$).

As a whole, the present investigation goes one step further compared to the Norwegian experience, as it demonstrates that disease-free survival can be achieved. However, such an outcome was only seen in patients after transplantation performed as deliberate procedures in a long-term treatment ($n=6$). These patients had previously undergone a combined oncological/surgical management with multiple courses of chemotherapy, and often multiple liver resections. None had a progressive disease at the time of transplantation. Conversely, the six patients with upfront, emergency, and extrahepatic disease transplantations (“compassionate” indications) did significantly worse, and most had a recurrence within 18 months, suggesting that transplantation in these situations must be avoided.

In addition, the present cohort shows that the time between colo-rectal surgery and transplantation (with a cut-off at 24 months) and the last CEA level (80 $\mu\text{g/l}$) tend to

predict disease-free survival, while tumor diameter (<5.5 cm) and cancer progression (no patient in progression) could not be identified. These factors as a whole should be used and refined for selecting patients for prospective trials (short time between primary and transplant, low CEA, small lesion, without progression)(2).

Of note, the Norwegian experience (21 published patients) has been possible thanks to the unique high organ donor availability in this country, where the recipient needs are covered within a short waiting time. In all other countries, the lack of donors represent a major challenge to transplantation for colo-rectal liver metastasis. Outcomes still need to be improved and validated before potentially justifying a systematic use of liver grafts for this indication on a common waiting list with patients with end-stage liver failure and hepatocellular carcinoma. In the meantime, domino, and living-donor liver grafts should be favored, and the RAPID concept further explored (5). In addition, current transplantation for non-resectable colo-rectal metastasis should be conducted within prospective trials with strict inclusion and exclusion criteria.

The present study should be seen as a proof-of-feasibility, demonstrating the potential of achieving disease-free survival after transplantation colo-rectal metastases in a meaningful proportion of patients. It should encourage turning away from more emotional indications, in favor of prospective studies with strict selection criteria to explore the potential of this modality.

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“Compagnons Hépatobilio-pancréatiques” group

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Table 1: characteristics of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Status	Alive without cancer	Alive without cancer	Alive without cancer	Alive without cancer	Alive without cancer	Dead with cancer	Dead with cancer	Dead with cancer	Dead with cancer	Alive with cancer	Dead with cancer	Dead without cancer
Time since transplantation (months)*	7	43	47	48	108	7	20	8	14	32	41	0
Time from transplant to recurrence (months)	NA	NA	NA	NA	NA	3	7	8	10	12	31	NA
Age at transplant (years)	65	56	73	54	54	58	38	38	56	56	61	59
Gender	F	M	M	M	F	F	F	F	M	F	M	M
Location of primary cancer	Colon	Rectum	Colon	Colon	Colon	Colon	Colon	Colon	Colon	Colon	Colon	Colon
TNM of primary	T4N1M1	T4N1M1	T3N1M1	T3N0M0	T2N0M0	T0N0M1	T3N0M1	T3N2M0	T3N2M1	T3N0M1	T3N1M1	T3N1M0
Time from primary to metastases (months)	0	0	0	7	29	0	0	24	0	0	29	4
Time from primary to transplant (months)	92	39	80	73	97	43	14	32	12	86	29	16
Largest metastasis at transplantation (cm)	3	2	2	1	8	40	55	15	40	15	20	60
Number of metastases at transplant	2	9	10	1	2	>15	>15	1	multiple	>15	1	3
CEA at transplantation (µg/l)	2	59	8	1	26	174	5	4	NA	314	NA	NA
Chemotherapy base prior to transplant	O/I	O/I	O/I	O/I	O/I	O/I	O/I	O/I	noO noI	O/I	no chemo	noO noI
Chemotherapy biological agent prior to transplant	beva	none	cetux	cetux	beva	beva + cetux	none	none	none	beva	no chemo	none
Number of resections prior to transplant	1	3	1	2	3	2	0	1	0	2	1	1

Grey background shows patients with ongoing disease-free survival, White background shows patients with recurrence and/or death

* until last follow-up (for the patients 1 to 5, and 10) or death

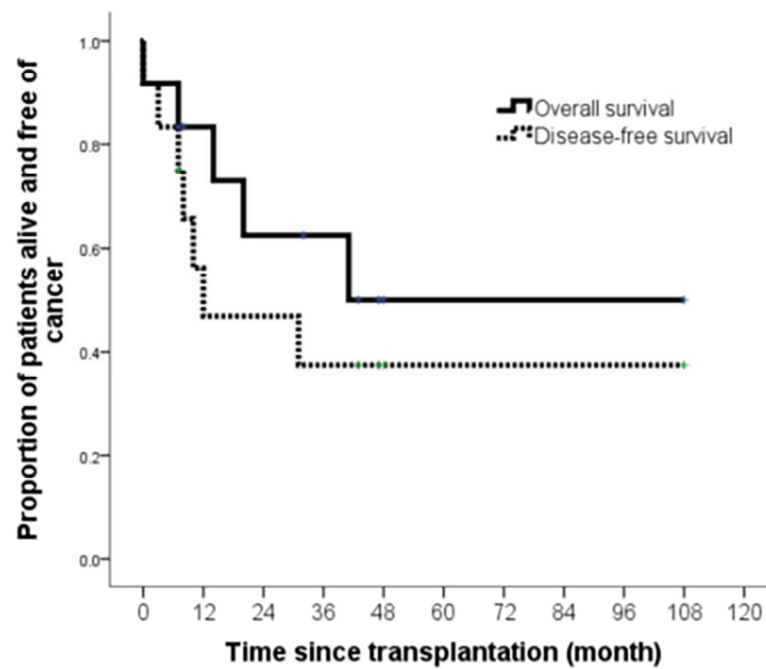
CEA: carcinoembryonic antigen, O/I: oxaliplatin/irinotecan, NA: not available or not applicable

Beva: bevacizumab, Cetux: cetuximab

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Figure legends

Figure 1: Overall (full line) and disease-free (dashed line) survivals



Overall survival	12	8	6	5	2	1
DFS	12	6	5	4	2	1

114x92mm (300 x 300 DPI)