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# Secondary non-resectable liver tumors: A single-center living-donor and deceased-donor liver transplantation case series

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ABSTRACT

*Background:* During the last decades, deceased-donor liver transplantation (DDLT) has gained a place in the therapeutic algorithm of well-selected patients harbouring non-resectable secondary liver tumors. Living-donor LT (LDLT) might represent a valuable means to further expand this indication for LT.
*Methods:* Between 1985 and 2016, twenty-two adults were transplanted because of neuroendocrine ($n = 18$, 82%) and colorectal metastases ($n = 4$, 18%); 50% received DDLT and 50% LDLT. In LDLT, 4 (36%) right and 7 (64%) left grafts were used; the median graft-to-recipient-weight ratios (GRWR) were 1.03% (IQR 0.86%-1.30%) and 0.59% (IQR 0.51%-0.91%), respectively. Median post-LT follow-up was 64 months (IQR 17–107) in the DDLT group and 40 months (IQR 35–116) in the LDLT group. DDLT and LDLT recipients were compared in terms of overall survival, graft survival, postoperative complications and recurrence.
*Results:* The 1- and 5-year actuarial patient survivals were 82% and 55% after DDLT, 100% and 100% after LDLT, respectively ($P < 0.01$). One- and 5-year actuarial graft survivals were 73% and 36% after DDLT, 91% and 91% after LDLT ($P < 0.01$). The outcomes of right or left LDLT were comparable. Donor hepatectomy proved safe, and one donor experienced a Clavien IIIb complication. Bilirubin peak was significantly lower after left hepatectomy compared with that after right hepatectomy [1.3 (IQR 1.2–2.2) vs. 3.3 (IQR 2.3–5.2) mg/dL; $P = 0.02$].
*Conclusions:* The more recent LDLT series compared favorably to our DDLT series in the treatment of secondary liver malignancies. The absence of portal hypertension and the use of smaller left grafts make recipient and donor surgeries safe. The safety of the procedures and lack of interference with the scarce allograft pool are expected to lead to a more frequent use of LDLT in the field of transplant oncology.


## Introduction

Starzl introduced the concept of liver transplantation (LT) to treat unresectable liver tumors. Eight of the ten first LT were done because of liver malignancies: five for hepatocellular cancer (HCC), one for cholangiocellular cancer and two for colorectal cancer liver metastases (CR-LM) [1]. These indications are all hot topics in every contemporary meeting of hepatology, oncology and transplantation. The idea of total hepatectomy as the treatment for unresectable liver malignancies spread during the LT "adolescent" phase (1963–1983) [2]. Unfortunately, the enthusiasm of pioneering centers rapidly faded away. Improper selection, heavy immunosuppression and poorly developed chemotherapy resulted in prohibitively high recurrence rates. The introduction of the Milan criteria (MC) in 1996 changed the outlook, making LT the treatment of choice for HCC in cirrhotic patients [3]. The 5-year overall survival rate grew from 12%, before 1985, to 70%–80%, during the past decade. These stringent criteria revealed the potential of LT in the field of hepatobiliary oncology, renewing the interest for LT as a possible treatment for well-selected, unresectable, secondary liver tumors [4–6]. However, the implementation of this concept

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in clinical practice is hampered by ethical debates concerning the legitimate use of scarce organs for controversial indications. Living-donor LT (LDLT) might push these boundaries. In view of the increasingly crucial role of LDLT for hepatobiliary malignancies, we deemed appropriate to compare the UCLouvain experience of LDLT and DDLT in this revolutionary field of transplantation oncology, in order to draw clinically relevant conclusions.

## Methods

### *Transplant patients*

This single-center retrospective study evaluates the results of LT for unresectable liver-only metastases. The institutional review board approved the study, which complies with the *Declaration of Istanbul*. The study population consists of 22 adults (aged ≥16 years), 4 women (18%) and 18 men (82%), who received LT at the University Hospitals Saint-Luc, Brussels, for secondary malignancies (Tables 1 and 2). Eighteen patients suffered from neuroendocrine tumor liver metastases (NET-LM) and 4 from CR-LM. The 11 whole-liver DDLTs (50%) were performed during the period February 1985 - September 2016. The 11 LDLTs (50%) were performed during the period April 2003–September 2016, and consisted of 4 right (segments V–VIII) and 7 left grafts (segments I–IV), representing 15% of our whole LDLT activity. The characteristics of primary NET and CR are presented in Tables 3 and 4.

In living-donor recipients, the primary NET was located in pancreas ($n=5$) and small intestine ($n=4$). In one case, the 1 cm primary tumor in the ileum was found and resected 3 years after LT. In deceased-donor recipients, the primary NET was located in pancreas ($n=6$), small intestine ($n=1$) and biliary tract ($n=1$). In three cases, the primary tumor was not detected before LT, despite an extensive and repeated workup. Two of them underwent successful duodeno-pancreatectomy and distal spleno-pancreatectomy at 7 and 13 months after LT (Fig. 1). In one patient, which had undergone previous oesogastric surgery for unclear reason, no extra-hepatic primary lesion has been found (during follow-up of 188 months). Over time, the indications for LT in our center have been progressively adapted to the findings of the European

**Table 1**
Characteristics of neuroendocrine tumor metastases at liver transplantation.

| LT No. | Year of LT | Age at LT (yr) | Surgery-to-LT delay (mon) | Primary tumor location | No of liver lesions[a] | Max liver lesion diameter (mm) | Hepatic involvement | Pre-LT liver surgery | Lymph nodes involvement | CgA at LT (ng/mL) | Ki67 | Maintenance IS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Living-donor liver transplantation – neuroendocrine tumor liver metastases[a] | | | | | | | | | | | | |
| 1290 | 2003 | 55 | 126 | Small bowel | 2[b] | 20 | <25% | No | Neg. | 15.9 | 2% | TAC, MMF > SRL[c] |
| | 2009 | 55 | 55 | Pancreas tail | 3[e] | 20 | <25% | Yes | Neg. | 12.6 | 15% | TAC |
| 1695[d] | | | | | | | | | | | | |
| 1723 | 2009 | 52 | 0[f] | Small bowel | 84 | 17 | 25%–50% | No | Neg. | 1048.0 | 5% | TAC, SRL |
| 1732 | 2009 | 36 | 46 | Pancreas head | 17 | 12 | <25% | Yes | Hepatoduodenal node | 16.3 | >80% | TAC |
| 2028 | 2013 | 46 | 126 | Small bowel | 8 | 7 | <25% | No | Neg. | 88.1 | 2%–4% | TAC |
| 2197 | 2016 | 44 | 100 | Pancreas head | 5 | 15 | <25% | No | NA | 6.2 | 5–10 | TAC |
| 2200 | 2016 | 50 | 30 | Pancreas tail | 4 | 16 | 25%–50% | No | Neg. | 0 | 17% | SRL, MMF |
| 2225 | 2016 | 53 | 19 | Small bowel | 6 | 40 | 25%–50% | No | Neg. | 33.1 | 7% | TAC |
| 2246 | 2016 | 36 | 26 | Pancreas head | 17 | 15 | <25% | Yes | Neg. | 32.7 | 23% | TAC |
| Deceased-donor liver transplantation – neuroendocrine tumor liver metastases[a] | | | | | | | | | | | | |
| 84 | 1987 | 43 | 0[f] | Pancreas tail | 3 | 210 | >50% | No | NA | NA | NA | CyA, AZA, CS |
| 229 | 1988 | 59 | 18 | Pancreas tail | 2 | 100 | >50% | Yes | Neg. | NA | 30% | CyA, AZA, CS |
| 263 | 1989 | 45 | 2 | Pancreas tail | Innumerable | 130 | >50% | No | Neg. | NA | NA | TAC, CS |
| 1195 | 2001 | 55 | 40 | Small bowel | 8 | 50 | >50% | No | Neg. | 145.0 | <2% | TAC, MMF, CS > SRL[c] |
| 1224 | 2002 | 39 | 0[f] | Pancreas head | 12 | 30 | >50% | No | Neg. | 20.4 | 35% | TAC, MMF, CS > SRL[c] |
| 1311 | 2003 | 27 | 0[f] | Possibly gastric | Innumerable | 200 | >50% | No | NA | 1084.0 | <2% | TAC, CS IS withdrawal |
| 1942 | 2012 | 57 | 63 | Pancreas tail | Innumerable | 35 | <25% | No | Neg. | 16.3 | 5–10% | None |
| 2005 | 2013 | 51 | 0 | Biliary tract | 29 | 10 | <25% | No | Hepatoduodenal node | 154.0 | <2% | TAC |
| 2261 | 2016 | 58 | 24 | Pancreas head | 101 | 20 | 25%–50% | No | Neg. | 13.6 | 9% | TAC |

AZA: azathioprine; CgA: chromogranin A; CS: corticosteroids; CyA: cyclosporine; IS: immunosuppression; LT: liver transplantation; MMF: mycophenolate mofetil; SRL: sirolimus; TAC: tacrolimus: NA: not available; Neg: negative.
[a] All lesions were bilobar and unresectable.
[b] Not resectable after chemotherapy.
[c] Switch to sirolimus monotherapy after recurrence (LT 1195 and 1290) and after development of renal insufficiency (LT 1224).
[d] ABO incompatible LT.
[e] Recurrence after right lobectomy.
[f] Primary tumor found after LT.

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**Table 2**
Characteristics of colorectal cancer liver metastases at liver transplantation.

| LT No. | Year of LT | Age at LT (yr) | Surgery-to-LT delay(mon) | Primary tumor location | No of liver lesions[a] | Max liver lesion diameter (mm) | Hepatic involvement | Pre-LT liver surgery | Lymph nodes involvement | CEA at LT (μg/L) | KRAS/BRAF/MMR mutation | Maintenance IS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Living-donor liver transplantation – colorectal cancer liver metastases | | | | | | | | | | | | |
| 2230 | 2016 | 52 | 7 | Transverse colon | 6[b] | 16 | <25% | Yes | Liver hilum | 1.0 | Neg. | TAC |
| 2257 | 2016 | 53 | 21 | Sigma | 14 | 23 | <25% | Yes | Neg. | 94.9 | Neg. | TAC |
| Deceased-donor liver transplantation – colorectal cancer liver metastases | | | | | | | | | | | | |
| 11 | 1985 | 34 | 26 | Rectum | 10 | 60 | >50% | No | NA | 300.0 | NA | CyA, AZA, CS |
| 31 | 1986 | 63 | 49 | Left colon | Innumerable | 150 | 25–50% | No | NA | 61.0 | NA | CyA, AZA, CS |

AZA: azathioprine; CS: corticosteroids; CyA: cyclosporine; IS: immunosuppression; LT: liver transplantation; TAC: tacrolimus; NA: not available; Neg: negative.
[a] All lesions were bilobar and unresectable.
[b] 2 active and 4 missing lesions at LT.

**Table 3**
Characteristics of primary tumors (neuroendocrine tumor).

| LT No. | Year of LT | Primary tumor location | G | T | N | M | Pre-LT primary tumor surgery | Pre-LT CT | Pre-LT somatostatin analogues | Pre-LT sunitinib | Pre-LT LRT | Carcinoid syndrome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Living-donor liver transplantation – neuroendocrine tumor liver metastases | | | | | | | | | | | | |
| 1290 | 2003 | Small bowel | 1 | 3 | 2 | 0 | Small bowel resection | No | Yes | No | No | Yes |
| 1695 | 2009 | Pancreas | 2 | 3 | 1 | 1 | Distal spleno-pancreatectomy<br>Left colectomy<br>Left adrenectomy<br>Liver metastasectomy (twice) | No | No | No | Yes[a] | No |
| 1723 | 2009 | Small bowel | 2 | X[b] | X | 1 | Small bowel resection after LT | No | Yes | No | Yes[a,c] | Yes |
| 1732 | 2009 | Pancreas | 3 | 2 | 1 | 1 | Duodeno-pancreatectomy<br>Liver metastasectomy | No | No | Yes | No | No |
| 2028 | 2013 | Small bowel | 1 | 4 | 1 | 1 | Small bowel resection | No | Yes | No | No | No |
| 2197 | 2016 | Pancreas | 2 | 2 | 1 | 1 | Pancreatic enucleation (main lesion)<br>Partial duodenectomy (second lesion) | EVL | No | No | No | Yes |
| 2200 | 2016 | Pancreas | 2 | 4 | 0 | 0 | Distal spleno-pancreatectomy<br>Left colectomy | No | No | Yes | No | No |
| 2225 | 2016 | Small bowel | 1 | 1 | 1 | 1 | Small bowel resection. | No | No | No | Yes[c] | No |
| 2246 | 2016 | Pancreas | 2 | 3 | 0 | 1 | Duodeno-pancreatectomy<br>Liver metastasectomy | No | Yes | No | No | Yes |
| Deceased-donor liver transplantation – neuroendocrine tumor liver metastases | | | | | | | | | | | | |
| 84 | 1987 | Pancreas | 2 | X[b] | X | 1 | Distal spleno-pancreatectomy after LT | No | No | No | No | No |
| 229 | 1988 | Pancreas | 3 | 2 | 0 | 1 | Distal spleno-pancreatectomy<br>Liver metastasectomy. | DOX, CPT | No | No | Yes[a] | No |
| 263 | 1989 | Pancreas | 2 | 2 | NA | 1 | Spleno-pancreatectomy (MEN1) | No | No | No | No | Yes |
| 1195 | 2001 | Small bowel | 1 | 1 | 0 | 1 | Small bowel resection | No | No | No | No | No |
| 1224 | 2002 | Pancreas | 3 | X[b] | X | 1 | Duodeno-pancreatectomy after LT | ETP, CPT | No | No | No | No |
| 1311 | 2003 | Possibly gastric | 1 | X[d] | X | 1 | Oesogastric surgery | No | Yes | No | No | No |
| 1942 | 2012 | Pancreas | 2 | 3 | 1 | 1 | Distal spleno-pancreatectomy | No | No | Yes | Yes[a] | No |
| 2005 | 2013 | Biliary tract | 1 | 2 | 1 | 1 | No | No | Yes | No | No | Yes |
| 2261 | 2016 | Pancreas | 1 | 2 | 1 | 1 | Duodeno-pancreatectomy<br>Liver metastasectomy. | No | Yes | Yes | No | No |

CPT: cisplatin; CT: chemotherapy; DOX: doxorubicin; ETP: etoposide; EVL: everolimus; G: differentiation grade of neuroendocrine tumors (good = 1, moderate = 2, poor = 3) following ENETB classification [41]. LRT: locoregional treatment; LT: liver transplantation; MEN1: multiple endocrine neoplasia type 1; NA: not available.
[a] Liver transarterial chemoembolization.
[b] Primary tumor not found before liver transplantation.
[c] Liver radiofrequency ablation.
[d] Primary tumor never found.

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**Table 4**
Characteristics of primary tumors (colorectal cancer).

| LT No. | Year of LT | Primary tumor location | T | N | M | Pre-LT primary tumor surgery | Pre-LT CT | Pre-LT 5-fluorouracil | Pre-LT oxaliplatin | Pre-LT irinotecan | Pre-LT bevacizumab |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Living-donor liver transplantation – colorectal cancer liver metastases | | | | | | | | | | | |
| 2230 | 2016 | Transverse colon | 4 | 1b | 1a | Resection of the transverse colon | Yes | Yes | Yes | Yes | No |
| 2257 | 2016 | Sigma | 3 | 2a | 1a | Sigmoidectomy | Yes | Yes | Yes | No | Yes |
| Deceased-donor liver transplantation – colorectal cancer liver metastases | | | | | | | | | | | |
| 11 | 1985 | Rectum | 3 | 0 | 0 | Anterior resection of the rectum | Yes | Yes | No | No | No |
| 31 | 1986 | Left colon | NA | NA | 0 | Left hemicolectomy | Yes | Yes | No | No | No |

CT: chemotherapy; LT: liver transplantation; NA: not available.

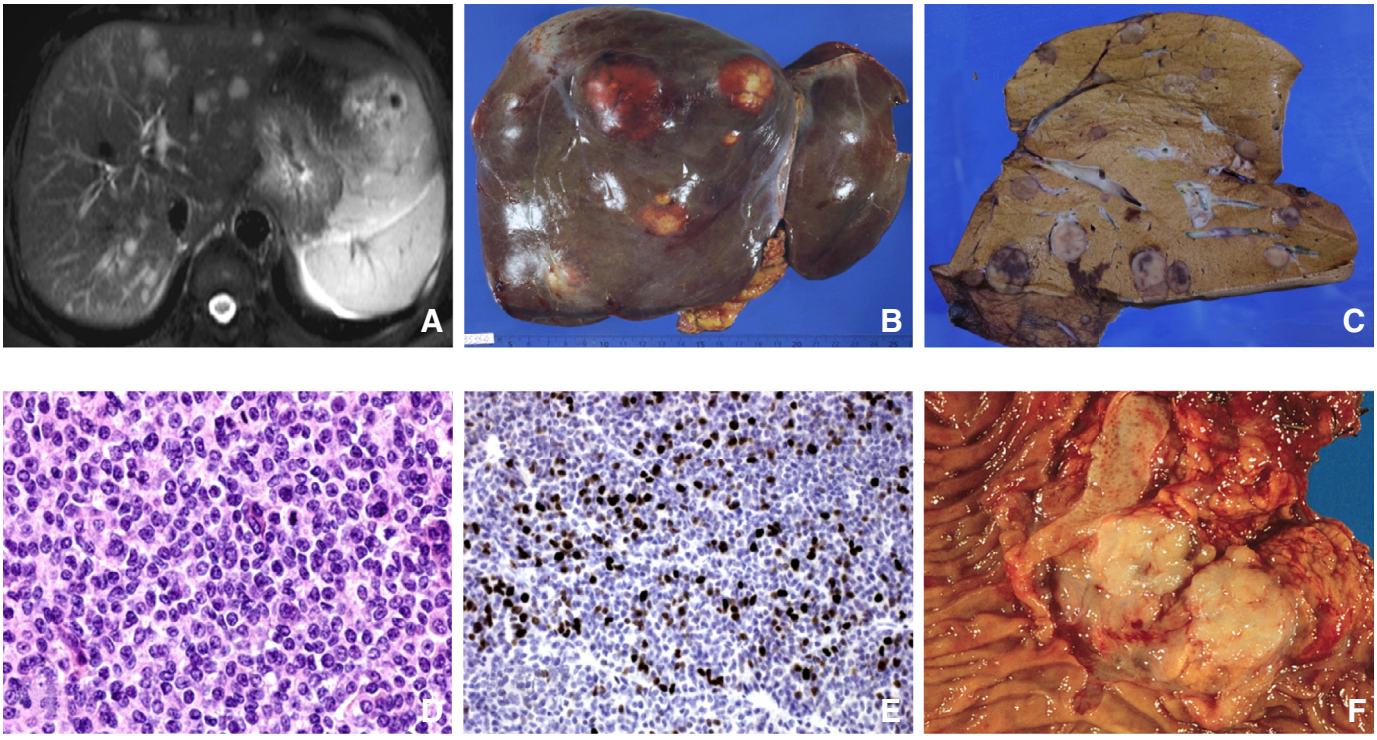


**Fig. 1.** Case No. 1224: a 39-year old female patient undergoing deceased-donor liver transplantation for neuroendocrine liver metastases. **A**: CT scan showing multiple, bi-lobar (biopsy proven) metastases; **B** and **C**: The pathological examination of the hepatectomy specimen revealed innumerable lesions; **D** and **E**: HE staining shows a high mitotic index and immunohistochemistry shows a Ki67 expression of 35% (original magnification × 100); F: Seven months after LT, a poorly differentiated (G3) primary tumor was found in the pancreatic head and a pylorus preserving pancreatoduodenectomy was performed. This patient is alive and disease-free 225 months after diagnosis and 210 months after transplantation.

Liver Transplant Registry (ELTR) and Milan National Cancer Center reports [4,5].

In living-donor recipients, CR-LM originated from sigma and transverse colon and, in deceased-donor recipients, from rectum and left colon. One LDLT CR-LM patient had neoadjuvant chemotherapy followed by primary transverse colic tumor resection, extensive loco-regional lymphadenectomy, debulking of liver disease and cytoreductive chemotherapy; the other patient received upfront sigmoidectomy and extensive loco-regional lymphadenectomy, followed by cytoreductive chemotherapy. Both DDLT recipients underwent primary anterior resection and left colectomy with extensive lymphadenectomy completed with adjuvant (first-line only) chemotherapy; both had massive bi-lobar involvement. Over time, the indications were adapted to the Oslo experiences [6].

All recipients had thorough pre-transplant evaluations including three-monthly thoraco-abdominal CT scan, bone scintigraphy, and determination of tumor markers CEA, CA19-9; chromogranin A determination and semi-annual DOTATOC PET/CT scan were added in NET-LM. The multidisciplinary tumor board confirmed the indication for LT [7]. In accordance with local institutional regulations, all live donors underwent a workup including counselling by a psychiatrist and the head-internist as “donor’s advocates”.

All but one procedure included a vena cava sparing technique, without use of veno-venous bypass. In NET-LM recipients, graft implantation was completed with extensive celio-mesenteric lymphadenectomy to fulfil staging [7].

Considering the absence of portal hypertension, a progressive shift was made with time in LDLT from the larger right (segments V–VIII) to the smaller left liver (segments I–IV) (Fig. 2) [8–12]. The final choice for right or left graft was decided on graft-to-recipient weight recipient ratio (GRWR) and digital liver reconstruction (MeVisLab, MeVis AG, Bremen, Germany) of segmental anatomy and venous outflow. Venous outflow reconstruction was considered for segmental hepatic veins having a diameter $\geq$5 mm [13]. Graft inflow modulation, through splenic artery obliteration,

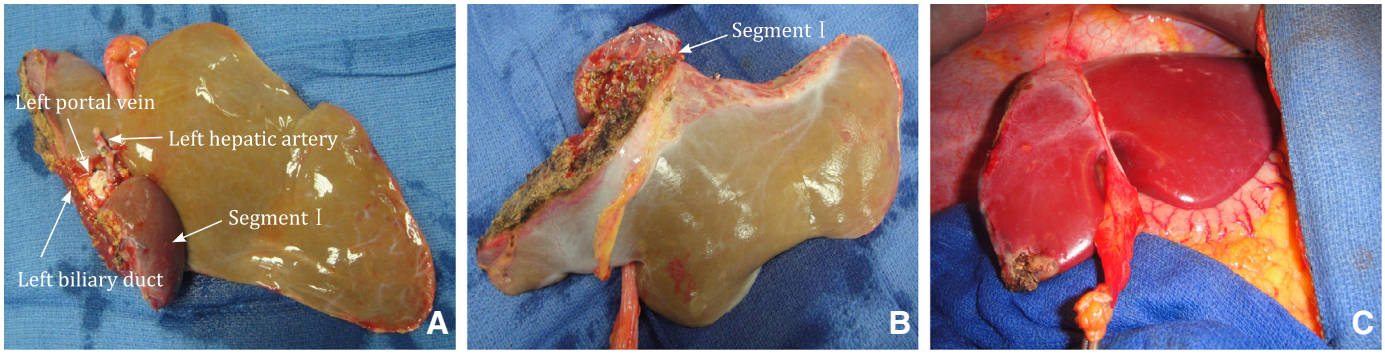


**Fig. 2.** Back-table (**A** and **B**) and intra-operative (**C**) view of a very small-for-size (454 g, GRWR 0.59%) live-donor left-liver graft.

was decided on real back-table graft weight and intra-operative flow measurements, done using adapted VeriQ flow probes (Medistim, Oslo, Norway) [14]. All donor procedures were performed by the same surgeon (Lerut J).

Since 1991, the initial triple immunosuppressive scheme, comprising cyclosporine, azathioprine and corticosteroids ($n=4$), was progressively replaced by a tacrolimus-based minimized immunosuppression ($n=18$) [15]. Based on the final pathology report, the oncological evolution and the renal function, m-TOR inhibitors were introduced in maintaining immunosuppression of some patients, allowing thereby also to further minimize calcineurin inhibitors. All patients had a similar outpatient follow-up, with regular blood testing and oncological screening, including three-monthly determinations of tumor markers and thoraco-abdominal CT scan. NET-LM patients initially had six-monthly and, after 3 years, annual DOTATOC PET/CT scans.

DDLT and LDLT recipients were compared in terms of overall survival, graft survival, postoperative complications and recurrence. Because of the small sample size, NET- and CR-LM were grouped, despite their different biologic behavior. Morbidity and mortality were ranked following the Clavien–Dindo classification and the Comprehensive Complication Index [16,17].

### *Statistical analysis*

Continuous data were reported as median and interquartile range (IQR) and tested with the Mann–Whitney *U* test. Binomial variables were reported as number and percentage and tested with Fisher's exact test. Survivals were analyzed with the Kaplan-Meier method and compared with the log-rank test. The significance of statistical tests was taken at $P < 0.05$. Analyses were run using SPSS (version 23.0; IBM, Armonk, USA).

## Results

The characteristics of the DDLT and LDLT cohorts are displayed in Table 5. They differed in favor of LDLT with regard to cold ischemia time [56 min (IQR 48–78) vs. 502 min (IQR 442–588) in DDLT; $P < 0.01$], and diameter of the biggest hepatic lesion [16 mm (IQR 15–20) vs. 35 mm (IQR 20–60) in DDLT; $P < 0.01$], reflecting a more appropriate recent patient selection adapted to the literature findings [4–6].

In LDLT, the median GRWR was lower in left-liver recipients [0.59% (IQR 0.51–0.91%)] than in right-liver recipients [1.03% (IQR 0.86–1.30%), $P=0.02$], like the median weight of left grafts [423 g (IQR 383–542)] compared to right grafts [908 g (IQR 705–1121), $P=0.01$] (Tables 6 and 7, Fig. 2). Graft inflow modulation was performed in four recipients. No case of small-for-size syndrome (SFSS) developed, according to the Kyushu definition [11]. The median length of hospital stay of the living-donor recipients was 11 days (IQR 9–12) for right-liver donors and 10 days (IQR 9–11) for left-liver donors ($P=1.00$). There was no donor mortality. Five donors experienced Clavien–Dindo I complications (mostly pain); one donor experienced early biliary leak requiring surgery (Clavien–Dindo IIIb, without sequelae). The early postoperative biochemical evolution between the two groups was comparable concerning INR and ALT peak; total bilirubin peak was significantly higher after right hepatectomy [3.3 mg/dL (IQR 2.3–5.2) vs. 1.3 mg/dL (IQR 1.2–2.2), $P=0.02$]. This finding correlates with the significantly lower estimated liver remnant/body-weight ratio in right versus left liver LDLT [0.68% (0.59%–0.70%) vs. 1.15% (1.09%–1.39%); $P=0.04$]. No psychological disorders were recorded after living donation (Table 6).

From the first diagnosis, the median follow-up numbered 90 months (IQR 51–123) in the DDLT group and 143 months (IQR 56–194) in the LDLT group ($P=0.40$). The 1- and 5-year overall survival was 100% and 73% for DDLT recipients, and 100% and 100% for LDLT recipients respectively ($P < 0.01$).

From the time of transplantation, the median follow-up numbered 64 months (IQR 17–107) in the DDLT group and 40 months (IQR 35–116) in the LDLT group ($P=0.70$). The 1- and 5-year overall survival was 82% and 55% for DDLT recipients, and 100% and 100% for LDLT recipients respectively ($P < 0.01$). The 1- and 5-year graft survival was 73% and 36% for DDLT recipients and 91% and 91% for LDLT recipients respectively ($P < 0.01$) (Fig. 3, Table 8).

In NET-LM patients, causes of death after DDLT were recurrent disease ($n=4$; at 17, 50, 68 and 107 months after LT), sepsis ($n=1$ at day 1), and myocardial infarction ($n=1$, at day 7); all LDLT patients are alive. Overall, nine patients experienced tumor recurrence, of whom six in the DDLT group (at 11, 12, 17, 19, 20 and 24 months) and three in the LDLT group (at 15, 48 and 53 months). Two recurrences were disseminated while other affected organs included locoregional lymph nodes ($n=4$), bones ($n=3$), liver ($n=2$), lungs ($n=1$), pancreas ($n=1$), kidney ($n=1$), diaphragm ($n=1$), and skin ($n=1$). Notably, five of those recipients experienced episodes of single-site recurrence and, thus, underwent further surgical resection. In four of those cases (two LDLT and two DDLT), surgery granted patients 173, 136, 40, and 10 additional disease-free months, one recipient still being tumor-free after almost 15 years (Table 7). Two patients, one with a solitary costal lesion and one with a retro-portal lymph node recurrence, do not show any evidence of disease progression under treatment with somatostatin analogues. Three of the four patients whose primary tumor was found after LT are disease-free and well at 114, 188 and 204 months after LT; one (the first patient of our series) died of recurrent disease 50 months after LT.

The two CR-LM DDLT patients died after 17 and 64 months of recurrent disease, diagnosed at 6 months (widespread recurrence) and 47 months (pulmonary, mediastinal, cerebral and liver

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**Table 5**
Baseline characteristics of patients undergoing liver transplantation for secondary liver malignancies.

| Characteristics | DDLT ($n=11$) | LDLT ($n=11$) | $P$ value |
|---|---|---|---|
| Indication | | | 1.00 |
| NET-LM | 9 (82%) | 9 (82%) | |
| CR-LM | 2 (18%) | 2 (18%) | |
| Recipient sex | | | 1.00 |
| Male | 9 (82%) | 9 (82%) | |
| Female | 2 (18%) | 2 (18%) | |
| Age (yr) | 51 (34–57) | 52 (44–53) | 0.70 |
| BMI (kg/m$^2$) | 27 (22–31) | 25 (24–27) | 0.43 |
| Cold ischemia time (min) | 502 (442–588) | 56 (48–78) | <0.01 |
| Warm ischemia time (min) | 40 (31–47) | 44 (32–59) | 0.85 |
| Diameter of the major lesion (mm) | 60 (10–210) | 16 (7–40) | <0.01 |
| Surgery-to-LT delay (mon) | 18 (0–40) | 30 (19–100) | 0.17 |
| Follow-up from LT (mon) | 64 (17–107) | 40 (35–116) | 0.70 |
| Follow-up from first diagnosis (mon) | 90 (51–123) | 143 (56–194) | 0.40 |

DDLT: deceased-donor liver transplantation; LDLT: living donor liver transplantation; NET-LM: neuroendocrine tumor liver metastases; CR-LM: colorectal cancer liver metastases.

**Table 6**
Characteristics of living donors.

| Graft type | Right liver (S5–8) ($n=4$) | Left liver (S1–4) ($n=7$) | $P$ value |
|---|---|---|---|
| Age (yr) | 26.2 (23.0–40.4) | 27.4 (25.7–48.0) | 0.32 |
| BMI (kg/m$^2$) | 22.7 (19.8–27.8) | 24.2 (24.0–27.1) | 0.41 |
| Estimated liver remnant/body-weight ratio (%) | 0.68 (0.59–0.70) | 1.15 (1.09–1.39) | 0.04 |
| *GRWR (%)* | *1.03 (0.86–1.30)* | *0.59 (0.51–0.91)* | *0.02* |
| Duration of the procedure (min) | 525 (435–701) | 450 (420–482) | 0.41 |
| Estimated intraoperative blood loss (mL)[a] | 237 (59–1184) | 300 (0–482) | 1.00 |
| Length of hospital stay (d) | 11 (9–12) | 10 (9–11) | 1.00 |
| Recipient length of ICU stay (d) | 1 (1–1) | 1 (1–1) | 1.00 |
| Total bilirubin peak (mg/dL)[b] | 3.3 (2.3–5.2) | 1.3 (1.2–2.2) | 0.02 |
| ALT peak (IU/L)[b] | 289 (196–331) | 214 (168–429) | 0.65 |
| INR peak[b] | 1.50 (1.35–1.63) | 1.16 (1.12–1.57) | 0.23 |
| Clavien–Dindo complication score [c] | | | |
| I | 1 (25.0%) | 4 (57.1%) | 0.55 |
| IIIb | 0 | 1 (14.3%) | 1.00 |
| Comprehensive complication index[c] | 0 (0–6.5) | 8.7 (0–8.7) | 0.23 |

ALT: alanine aminotransferase; BMI: body mass index; GRWR: graft-to-recipient-weight ratio; ICU: intensive care unit; INR: international normalized ratio.
[a] Through CellSaver® recovery.
[b] During the first postoperative month.
[c] Until discharge.

recurrence). One LDLT recipient is still disease-free after 32 months; the other one recurred at 4 months after LT (lungs, re-resected), and is still alive, having chemotherapy, after 28 months.

## Discussion

Since the introduction of the first adult-to-adult LDLT in 1994 by Hashikura et al., a marked evolution has occurred in the field [18]. LDLT has become a fertile ground to explore the boundaries of transplantation for HCC and cholangiocellular cancer, since this approach controls both factors "tumor" and "time" [19–23]. Simultaneously, the transplant world has resumed interest in transplanting secondary liver tumors.

Recent experiences have shown that patients with non-resectable liver metastases from NETs can be successfully transplanted by adhering to strict selection criteria. The ELTR survey conducted by Le Treut showed a 52% 5-year patient survival and a 30% recurrence-free survival [4]. Poor prognostic factors are recipient age >45 years, previous major simultaneous resection, and hepatomegaly. Mazzaferro et al. improved these results to 92% 5-year recurrence-free survival through selection refinement, comprising primary tumor within portal drainage territory, age <55 years, tumor mass <50% of the liver volume, response to pre-transplant treatment, and stable disease for six months minimum [5].

In 2006, the Rikshospitalet group in Oslo launched a prospective project about LT for unresectable CR-LM (SECA-1 study) [6]. This Norwegian group relaunched the idea developed in the early 1970s by the Vienna LT center [24]. Indeed, by 1995, more than half of the European CR-LM LT experience originated from this Austrian group. Although the European collective showed a disappointing 19% 5-year patient survival, nine (25%) patients survived more than 5 years [25]. The critical appraisal of this experience learned that nearly half of patients died of perioperative events and two thirds of them received heavy immunosuppression. Years later, the Vienna group demonstrated that extra-hepatic micrometastases, detected using specific amplification in "histologically negative" lymph nodes, entailed universal recurrence [26]. The SECA-1 trial brought transplant oncology forward, reaching a 35% 1-year recurrence-free survival. Adjuvant surgery raised 5-year recurrence-free survival to 60%. Liver recurrence (occurring in one third of cases) had a worse outcome than pulmonary recurrence (80% of cases) [27]. CEA <80 μg/L, delay between primary tumor and occurrence of metastases >2 years, largest diameter <5.5 cm, and stable disease under chemotherapy were favorable prognostic factors [6]. These low-risk CR-LM patients fared well compared to HCC MC-in patients [28]. Retrospective analysis of the pre-transplant imaging revealed that pulmonary metastases were misdiagnosed as atypical lesions in one third of patients and that pulmonary recurrences did not grow faster, despite on-going immunosuppression, compared to non-immunosuppressed patients

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**Table 7**
Characteristics of living-donor liver transplant recipients.

| Graft type | Right liver (S5–8) ($n=4$) | Left liver (S1–4) ($n=7$) | *P* value |
|---|---|---|---|
| Age (yr) | 53.7 (47.8–55.3) | 49.6 (36.2–52.7) | 0.16 |
| BMI (kg/m$^2$) | 26.2 (24.5–27.1) | 24.7 (23.3–26.3) | 0.32 |
| Donor-recipient relationship | | | |
| Related | 4 (100%) | 5 (71.4%) | 0.49 |
| Daughter to father | 2 (50.0%) | 2 (28.6%) | 0.58 |
| Son to father | 0 | 2 (28.6%) | 0.49 |
| Daughter to mother | 1 (25.0%) | 0 | 0.36 |
| Sister to sister | 1 (25.0%) | 0 | 0.36 |
| Brother to brother | 0 | 1 (14.3%) | 1.00 |
| Unrelated | 0 | 2 (28.6%) | 0.49 |
| Friend to friend | 0 | 1 (14.3%) | 1.00 |
| Mother-in-law to son-in-law | 0 | 1 (14.3%) | 1.00 |
| ABO-incompatibility | 1 (25.0%) | 0 | 0.36 |
| Graft weight (g) | 908 (705–1121) | 423 (383–542) | **0.01** |
| GRWR (%) | 1.03 (0.86–1.30) | 0.59 (0.51–0.91) | **0.02** |
| Middle hepatic vein in graft | 2 (50.0%) | 7 (100%) | 0.11 |
| Outflow venous reconstruction | 3 (75.0%) | 1 (14.3%) | 0.09 |
| Splenic artery flow modulation | 1 (25.0%)[a] | 3 (42.9%)[b] | 1.00 |
| Multiple hepatic arteries | 0 | 1 (14.3%) | 1.00 |
| Multiple bile ducts | 0 | 1 (14.3%) | 1.00 |
| Bile duct anastomosis | | | 1.00 |
| Duct-to-duct | 3 (75.0%) | 4 (57.1%) | |
| Hepatico-jejunal | 1 (25.0%) | 3 (42.9%) | |
| T-tube insertion | 1 (25.0%) | 3/7 (42.9%) | 1.00 |
| End-procedure hepatic arterial flow (mL/min) | 150 (120–363) | 265 (95–378) | 1.00 |
| End-procedure portal vein flow (mL/min) | 660 (553–768) | 342 (314–750) | 0.41 |
| Portal vein flow/100 g GW (mL/min/100 g) | 69.1 (58.5–98.8) | 86.1 (69.9–171.3) | 0.29 |
| Cold ischemia time (min) | 73 (45–138) | 55 (48–75) | 0.41 |
| Warm ischemia time (min) | 44 (29–78) | 56 (32–59) | 0.79 |
| Operation time (min) | 607 (349–806) | 675 (502–750) | 0.65 |
| Intraoperative auto-transfusion | 1 (25.0%) | 3 (42.9%) | 1.00 |
| Intraoperative allo-transfusion (mL) | 0 (0–740) | 0 (0–260) | 0.93 |
| Recipient hospital stay (d) | 16 (13–22) | 18 (17–20) | 0.32 |
| Recipient ICU stay (d) | 2 (2–3) | 2 (1–7) | 0.93 |
| SFSS[c] | 0 | 0 | – |
| Clavien–Dindo complication score[d] | | | |
| I | 1 (25.0%) | 1 (14.3%) | 1.00 |
| II | 4 (100%) | 2 (28.6%) | 0.06 |
| IIIa | 0 | 1 (14.3%) | 1.00 |
| IIIb | 1 (25.0%) | 4 (57.1%) | 0.55 |
| IVb | 0 | 1 (14.3%) | 1.00 |
| Comprehensive Complication Index[c] | 21.8 (20.9–35.4) | 33.7 (20.9–33.7) | 0.65 |

BMI: body mass index; ICU: intensive care unit; GRWR: graft-to-recipient-weight ratio; GW: graft weight; SFSS: small-for-size syndrome.
[a] Ligation.
[b] Two cases of splenic artery ligation, one case of splenic artery embolization.
[c] Total bilirubin >20 mg/mL for seven consecutive days after post-LT day seven in absence of technical and immunologic factors [11].
[d] Until discharge.

[29]. Due to difficult recruitment, this pilot cohort was heterogeneous in relation to number (from 4 to >30), diameter (from <5 to >10 cm) of lesions and pre-transplant response to different chemotherapy lines (from 1 to 3). Another point of concern was the quadruple sirolimus-based immunosuppression, administered to most patients. Nevertheless, the comparison of SECA-1 results with the Nordic VII trial interestingly showed a striking difference in 5-year patient survival in favor of LT of 55% vs. 6% [30,31]. The "Compagnons Hépato-biliaires" group confirmed CEA level >80 μg/L and delay <2 years between primary diagnosis and LT as unfavorable prognostic factors [32].

The growing evidence led the Oslo group to the SECA-2 study. Selection was adapted and included $^{18}$F-FDG PET/CT imaging [33]. The analysis of the 15 included patients showed 1-, 3-, and 5-year patient survival of 100%, 83%, and 83%, with recurrence-free survival of 53%, 44%, and 35%, respectively. Eight patients who recurred received surgery. Thirteen patients are alive and 11 (73%) are disease-free after a median follow-up of 36 months [34].

Presently, a multicenter randomized controlled trial, comparing LT and chemotherapy to chemotherapy alone, in non-resectable CR-LM, is on-going in France. The French Health Authority and Allocation Organism have endorsed this "Transmet study" by giving priority to patients randomized to transplantation. To date, 63 patients have been enrolled; 30 have been transplanted (August 2019, personal communication by René Adam). Recently, the Toronto General Hospital group has started an open label trial combining LDLT and neo-adjuvant chemotherapy. Likewise, a large Italian study group has launched a prospective parallel trial comparing LT to chemotherapy for non-resectable CR-LM (ClinicalTrials.gov NCT03803436).

The SECA experience gave rise also to an innovative two-stage transplant technique, the RAPID concept [35]. First, a deceased-donor split left lobe is implanted following left hepatectomy. Then, once the split-graft regenerates enough, the remaining metastatic liver is removed. This procedure might shortcut discussion about organ shortage, avoid the risk of liver failure or SFSS, and dull LDLT morbidity and mortality. Till now, three patients have been included in this open-label trial (December 2018, personal communication by Pål-Dag Line); several other procedures have been done in other European centers, including ours. Still, the indication of LT for secondary liver tumors can be safely extended through one-step LDLT using small left-liver grafts. Although the use of left hemi-livers shifts the risk from donor to recipient, several

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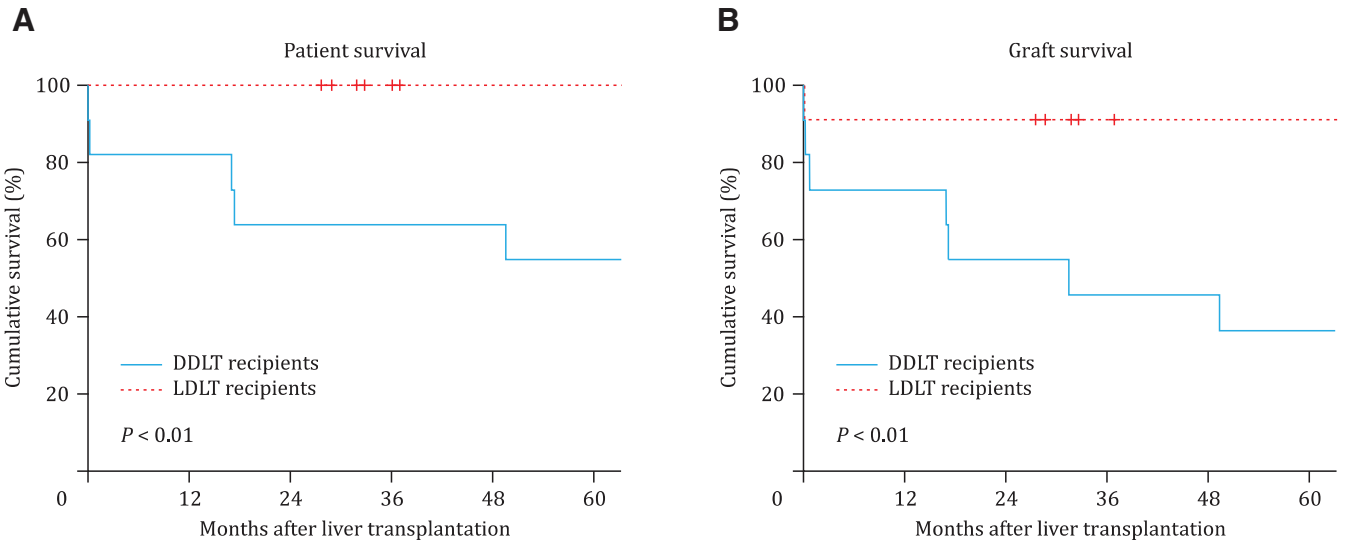
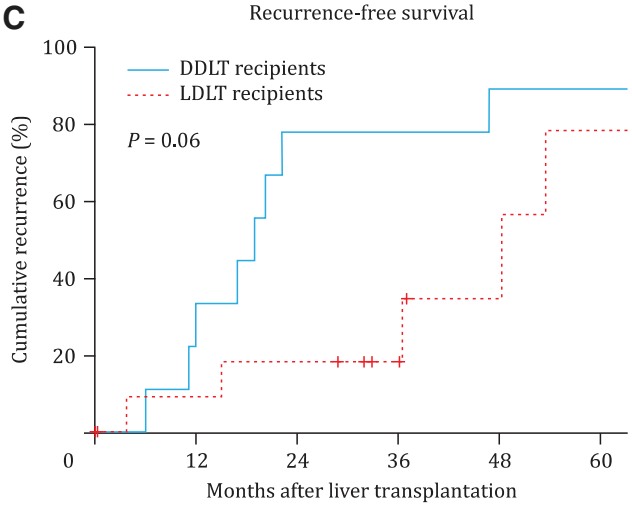



| | Baseline | 3-mon | 1-yr | 5-yr |
|---|---|---|---|---|
| Patient survival | | | | |
| DDLT | 100% | 82% | 82% | 55% |
| LDLT | 100% | 100% | 100% | 100% |
| No. of patients exposed to the risk of death | | | | |
| DDLT | 11 | 11 | 9 | 6 |
| LDLT | 11 | 11 | 11 | 5 |

| | Baseline | 3-mon | 1-yr | 5-yr |
|---|---|---|---|---|
| Graft survival | | | | |
| DDLT | 100% | 73% | 73% | 36% |
| LDLT | 100% | 91% | 91% | 91% |
| No. of patients exposed to the risk of graft loss | | | | |
| DDLT | 11 | 11 | 8 | 4 |
| LDLT | 11 | 11 | 10 | 5 |




| | Baseline | 3-mon | 1-yr | 5-yr |
|---|---|---|---|---|
| Recurrence | | | | |
| DDLT | 0 | 0 | 22% | 89% |
| LDLT | 0 | 0 | 9% | 78% |
| No. of patients exposed to the risk of recurrence | | | | |
| DDLT | 11 | 10 | 8 | 1 |
| LDLT | 11 | 11 | 10 | 1 |

**Fig. 3.** Patient and graft survival and recurrence after liver transplantation for secondary liver malignancies.

Eastern (Kyoto and Kyushu) and Western (Ghent, Cleveland and San Francisco) groups showed that small left grafts (segments I or II to IV) can be successfully implanted by optimizing hepatic venous outflow and portal venous inflow [8–14]. The absence of portal hypertension makes low GRWRs safe(r) (up to 0.51 in our series). Moreover, if SFSS occurs, it can be handled easier, in the absence of portal hypertension, by intensive albumin and somatostatin administration [36]. Additionally, the familiar environment of these oncological patients typically accepts left-liver LDLT, considering their desperate cancer-driven swift deterioration.

Indeed, the current absence of prioritization for these non-yet-validated indications makes LDLT the treatment of last resort. Early adjuvant chemotherapy and immunotherapy are likely to improve the outcomes meanwhile minimized immunosuppression is the best prophylactic strategy to reduce the incidence of possible recurrences [15,28]. These arguments and the obtained, comparable

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**Table 8**
Results of liver transplantation for secondary liver malignancies.

| LT No. | Year of LT | Recurrence | RFS (mon) | Site of recurrence | Recurrence treatment | Overall DFS (mon) | Re-LT | Indication for Re-LT | GS (mon) | Death | Cancer-related death | Survival (mon)[a] | | | Status[a,d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | From diagnosis | From pre-LT surgery | From LT | |
| Living-donor liver transplantation – neuroendocrine tumor liver metastases | | | | | | | | | | | | | | | |
| 1290 | 2003 | Yes | 48 | 1. Mesenteric LNs;<br>2. Solitary bone lesion | 1. Surgery;<br>2. Lanreotide | 184 | No | – | 190 | No | – | 318 | 318 | 192 | Alive w/ stable disease |
| 1695 | 2009 | Yes | 53 | 1. Pancreatic head;<br>2. Right kidney;<br>3. Lungs | 1. Surgery;<br>2. Surgery;<br>3. Surgery and CT | 93 | No | – | 117 | No | – | 176 | 174 | 119 | Alive w/ stable disease |
| 1723 | 2009 | No | 77 | – | – | 77 | No | – | 111 | No | – | 218 | 114 | 114 | Alive w/o disease |
| 1732 | 2009 | Yes | 15 | Multiple bone lesions | Sunitinib, CT and radiotherapy | 15 | No | – | 110 | No | – | 160 | 159 | 112 | Alive w/ disease |
| 2028 | 2013 | No | 64 | – | – | 64 | No | – | 62 | No | – | 191 | 190 | 64 | Alive w/o disease |
| 2197 | 2016 | No | 37 | – | – | 37 | No | – | 35 | No | – | 140 | 137 | 37 | Alive w/o disease |
| 2200 | 2016 | No | 36 | – | – | 36 | Yes | Portal vein thrombosis | 0 | No | – | 67 | 66 | 36 | Alive w/o disease |
| 2225 | 2016 | No | 33 | – | – | 33 | No | – | 31 | No | – | 53 | 52 | 33 | Alive w/o disease |
| 2246 | 2016 | No | 29 | – | – | 29 | No | – | 27 | No | – | 57 | 55 | 29 | Alive w/o disease |
| Deceased-donor liver transplantation – neuroendocrine tumor liver metastases | | | | | | | | | | | | | | | |
| 84 | 1987 | Yes | 11 | Liver, diaphragm, skin | Surgery and TACE | 11 | No | – | 52 | Yes | Yes | 51 | 50 | 50 | Dead w/ disease |
| 229 | 1988 | Yes | 12 | Widespread | CT and octreotide | 12 | No | – | 17 | Yes | Yes | 44 | 35 | 17 | Dead w/ disease |
| 263 | 1989 | Yes | 20 | Widespread | Octreotide | 20 | No | – | 119 | Yes | Yes | 110 | 109 | 107 | Dead w/ disease |
| 1195 | 2001 | Yes | 19 | 1. Mesenteric LN;<br>2. Bones. | 1. Surgery;<br>2. Octreotide | 29 | No | – | 68 | Yes | Yes | 108 | 108 | 68 | Dead w/ disease |
| 1224 | 2002 | Yes | 24 | Liver and coeliac LN | Surgery | 197 | Yes | Chronic rejection | 32 | No | – | 219 | 204 | 204 | Alive w/o disease |
| 1311 | 2003 | No | 188 | – | – | 188 | No | – | 186 | No | – | 204 | 188 | 188 | Alive w/o disease |
| 1942 | 2012 | No | 0[b] | – | – | 0 | No | – | 0 | Yes | No[b] | 63 | 63 | 0 | NA |
| 2005 | 2013 | Yes | 17 | Solitary retroportal LN | Octreotide | 17 | Yes | Biliary duct necrosis | 1 | No | – | 120 | 67 | 67 | Alive w/ stable disease |
| 2261 | 2016 | No | 0[c] | – | – | 0 | No | – | 0 | Yes | No[c] | 29 | 24 | 0 | NA |
| Living-donor liver transplantation – colorectal cancer liver metastases | | | | | | | | | | | | | | | |
| 2230 | 2016 | No | 32 | – | – | 32 | No | – | 30 | No | – | 49 | 39 | 32 | Alive w/o disease |
| 2257 | 2016 | Yes | 4 | Lungs | Surgery and CT | 4 | No | – | 26 | No | – | 53 | 49 | 28 | Alive w/ disease |
| Deceased-donor liver transplantation – colorectal cancer liver metastases | | | | | | | | | | | | | | | |
| 11 | 1985 | Yes | 47 | Lungs, mediastinum, brain, liver | Palliative CT | 47 | No | – | 62 | Yes | Yes | 90 | 90 | 64 | Dead w/ disease |
| 31 | 1986 | Yes | 6 | Widespread | Palliation | 6 | No | – | 17 | Yes | Yes | 66 | 66 | 17 | Dead w/ disease |

CT: chemotherapy; DFS: disease-free survival; GS: graft survival; LN: lymph node; LT: liver transplantation; NA: not applicable due to early postoperative death; Re-LT: retransplantation; RFS: recurrence-free survival; TACE: transarterial chemoembolization.

[a] Since the first submission of the manuscript, all patients have six months more follow-up without any change in their general as well as oncologic status.

[b] Myocardial infarction.

[c] Sepsis.

[d] w with; w/o without.

results, in terms of survival and recurrence, counteract the ethical debate about the use of a scarce resource for unverified indications for LT.

Criticisms of this study include the reduced sample size and the long-time span, which implies major advances in the oncological approach of secondary liver malignancies [37–42]. Notwithstanding latest progress, careful review confirmed the unresectability of these tumors in all patients in our series, even considering modern medical and surgical techniques. All patients transplanted during the period 1985–2003 had an advanced bi-lobar liver involvement, making them candidate for LT even today. Our results confirmed that not only better selection (see lower tumor burden in LDLT recipients) and management (see lower immunosuppressive burden), but also the introduction of LDLT *per se* in the therapeutic algorithm of these patients improved overall outcomes. Ninety percent of NET-LDLT patients showed long disease-free intervals, in contrast with the 29% of the surviving NET-DDLT recipients (Table 8). When total hepatectomy is envisaged, selection features and the choice of transplantation from living-donors steer patients' outcomes. Moreover, resectable recurrence or primary-tumor identification after LT does not erode survival *per se*, provided that resection of these lesions is R0 [4–7,33,34]. This has been clearly shown in our series. This implicates that strict post-transplant follow-up of these liver recipients is an absolute necessity in order to timely allow eventual surgical treatment of recurrent disease. In the field of LT for CR-LM, progress is still much warranted. Nevertheless, LDLT offers the advantage to timely schedule R0 surgery between optimized neo- and adjuvant treatments. The benefit of such concept has been already shown in the field of hepatoblastoma [43]. LT for CR-LM has recently proved to be beneficial also in terms of quality of life and costs [44].

Immunosuppression fine-tuning (e.g. with the use of the antiangiogenic properties of mTOR inhibitors) is another means to optimize outcomes. The minimization of immunosuppression is crucial because this approach epitomizes the best available immunotherapy, in this context, and because it allows a safe and prompt start of adjuvant chemotherapy after LT, adapted to the molecular tumor biology and the final pathological report of the hepatectomy specimen.

In conclusion, LT is progressively gaining its place in the treatment of secondary liver malignancies. In this scenario, our experience shows that LDLT favorably compares to DDLT. The combination of small left-liver LDLT and graft inflow modulation guarantees a safe procedure in both donor and recipient and, thus, makes this approach attractive, on a larger scale. LDLT does not interfere with the scarce allograft resource and will foster progress in transplant oncology.

## Addendum

Since first submission of this paper, all patients had 6 more months of follow-up without any change in their general and oncologic status.

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## Contributors

LJ and IS designed the work, collected analyzed and interpreted the data and drafted the manuscript. IS performed the statistical analysis. LJ and IS contributed to the acquisition of data, critically revised the intellectual content thoroughly, and approved the final version to be published. VG, FT, AK and INME contributed to acquisition of data. INME, KM, CL, CO and BRE contributed to the medical care and approved the final version to be published. LJ and IS contributed equally to this article. LJ is the guarantor.

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## Ethical approval

This study was approved by the local Institutional Ethical Committee. Informed consent was obtained from all individual participants included in the study.

## Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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