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REVIEW

Liver transplantation and neuroendocrine tumors: lessons from a single centre experience and from the literature review

Eliano Bonaccorsi-Riani,[1] Carlos Apestegui,[1] Anne Jouret-Mourin,[2] Christine Sempoux,[2] Pierre Goffette,[3] Olga Ciccarelli,[1] Ivan Borbath,[4] Catherine Hubert,[5] Jean François Gigot,[5] Ziad Hassoun[4] and Jan Lerut[1]

1 Starzl Unit of Abdominal Transplantation, University Hospitals St Luc, Université catholique de Louvain (UCL), Brussels, Belgium
2 Department of Pathology, University Hospitals St Luc, Université catholique de Louvain (UCL), Brussels, Belgium
3 Department of Radiology, University Hospitals St Luc, Université catholique de Louvain (UCL), Brussels, Belgium
4 Department of Gastroenterology, University Hospitals St Luc, Université catholique de Louvain (UCL), Brussels, Belgium
5 Division of Hepatopancreatobiliary Surgery, Department of Abdominal and Transplantation Surgery, University Hospitals St Luc, Université catholique de Louvain (UCL), Brussels, Belgium

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Correspondence
Jan Lerut MD, PhD, FACS, Cliniques Universitaires Saint-Luc, 10 Avenue Hippocrate, 1200, Brussels, Belgium.
Tel.: +32 27641402; fax: 32 27649039;
e-mail: jan.lerut@uclouvain.be

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Summary

Neuroendocrine tumor (NET) metastases represent at this moment the only accepted indication of liver transplantation (LT) for liver secondaries. Between 1984–2007, nine (1.1%) of 824 adult LTs were performed because of NET. There were five well differentiated functioning NETs (four carcinoids and one gastrinoma), three well differentiated non functioning NETs and one poorly differentiated NET. Indications for LT were an invalidating unresectable tumor (4×), and/or a diffuse tumor localization (3×) and/or a refractory hormonal syndrome (5×). Median post-LT patient survival is 60.9 months (range 4.8–119). One-, 3- and 5-year actuarial survival rates are 88%, 77% and 33%; 1, 3 and 5 years disease free survival rates are 67%, 33% and 11%. Due to a more rigorous selection procedure, results improved since 2000; three out of five patients are alive disease-free at 78, 84 and 96 months. Review of these series together with a review of the literature reveals that results of LT for this oncological condition can be improved using better selection criteria, adapted immunosuppression and neo- and adjuvant surgical as well as medical tretament. LT should be considered earlier in the therapeutic algorithm of selected NET patients as it is the only therapy that can offer a cure.

Introduction

Liver transplantation (LT) is considered an accepted indication for the treatment of selected hepatocellular cancers and of some particular liver malignancies such as haemangioendothelioma [1,2]. In contrast LT has been rarely considered as a therapeutical option for the treatment of metastatic neuroendocrine tumors (NETs) [3–6].

Based on a limited single center experience and on a detailed review of the literature, the authors make some propositions to further improve the decision making process and the therapeutical algorithm of metastatic NETs. This thought is important since the incidence of NET has risen markedly during the last years and since more and more patients benefit nowadays from a multimodal approach including LT [3].

Patients and methods

During the period 1984–2007, seven men and two women (nine of 824 adults −1.1%), underwent LT at the University Hospitals St. Luc in Brussels because of NET. Their

median age at diagnosis was 50.9 years (range 25.2–58.9) and at LT was 54 years (range 26.6–61.0). In six patients the primary lesion was previously identified and resected. They were located in the small bowel (2×), bronchial tree (2×) and pancreatic tail (2×). In two patients (1 and 7) the primary lesion was found 13 and 7 months after LT, respectively. These lesions, found in pancreatic tail and in the head respectively, were resected at that time. The last patient had a huge unresectable gastrinoma within the liver, till 6.5 years after LT no primary extrahepatic tumor has been discovered. The retrospectively analyzed clinical data and outcome of all nine patients are summarized in Tables 1–3.

Pretransplant surgery consisted of staging laparoscopy in patients 6 and 8, small bowel resection in patients 5 and 8 and left splenopancreatectomy in patients 3 and 4. Patients 2 and 5 underwent a pulmonary lobectomy; patient 2 had right hepatectomy 3 years later and patient 5 R1 thoracic wall resection 8 years later. Despite this unsatisfactory condition it was decided to replace his 8 kg heavy, invalidating liver tumor. Median time between primary tumor surgery and LT was 48 months (range 2–128) (Table 1).

Seven patients received a non surgical pretransplant treatment for their liver secondaries. Interventional radiology consisting of transarterial chemoembolization (TACE) using cisplatine and adriamycine and percutaneous ethanol injection (PEI) was applied in two patients. Medical treatment consisted of octreotide (two patients), combination of octreotide and interferon (two patients) and 5 FU-streptozocin (one patient) (Table 2).

Primary tumor location was discovered twice after LT: patient 1 underwent splenopancreatectomy 13 months post-LT and patient 7 pylorus-preserving duodenopancreatectomy 7 months post-LT.

The indications for LT were unresectable bilobar metastases (patients 3, 6, 7 and 8) and/or invalidating tumor bulk representing more than 50% of the total liver volume (patients 1, 2, 3, 5 and 9) and/or refractory carcinoid syndrome (patients 2 and 8) and/or hypercalcemia-hyperinsulinemia syndrome due to multiple endocrine neoplasia type I (patient 4) and/or Zollinger–Ellison syndrome (patient 9).

Seven patients received a full graft from a deceased donor; one patient received a right split graft and one a right lobe living donor graft. Induction immunosuppression consisted of cyclosporine-steroids-azathioprine in the first four patients and tacrolimus, low-dose and short-term steroids in the last five patients. Patients 1 and 3 also received antilymphocytic antibodies. Patients 6, 7 and 8 were switched some months after LT to rapamycin in order to take profit of the possible oncological properties of this immunosupressant.

The hepatectomy specimen was examined by our pathologists utilizing the Rindi *et al.*'s classification [7]. Analysis was also done taking into immunohiostochemistry for endocrine markers and recent observations made by Cho *et al.* [8].

Results

Pathological examination and immunohistochemical evaluation was possible in all but one case and is detailed in Table 4. According to ENETs classification there were seven well differentiated NETs, four low grade (G1) and two intermediate grade (G2), one high grade G3 and one poorly differentiated high grade (G3) NET.

One-, 3- and 5-year patient survival (PS) rates are 88%, 77% and 33%. One-, 3- and 5-year disease free survival (DFS) rates are 67%, 33% and 11%.

Mean PS is 64.1 ± 35.5 months (median 59.4 months; range 11.4–96); mean DFS is 26.97 ± 23 months (median 23 months; range 4.8–78.9 (Table 3). There was no early (<3 months) post-LT mortality. The last three patients are actually alive and disease free. Patient 7 is much of interest as she underwent resection of her primary pancreatic head tumor 7 months after LT and re-LT 31 months post-LT because of chronic rejection. The histology of the explanted allograft revealed two unknown small NET lesions. She is alive and disease free 96 and 65 months respectively after the first and second LT. Patient 8 is alive disease free 84 months after LT and 34 months after inter aorto-caval lymphadenectomy and patient 9 is alive disease free 78 months post-LT done because of a primary gastrinoma.

Five patients died due to NET recurrence; one patient died 11 months post-LT due to septic biliary complications in the presence of lumbar and lymph node recurrence (patient 5). The allograft was the site of recurrence in six patients, followed by lymph nodes in five patients and bones in four patients. Despite stable liver disease during 2 years following resection of a well differenciated ileal carcinoid, patient 6 developed early tumor recurrence 12 months after LT. Lymphadenectomy and medical treatment allowed him to survive in good condition during 56 months; he finally died 68 months post-LT of diffuse tumor recurrence.

Four patients underwent surgery because of recurrent disease (Table 2). Patient 1 underwent left hepatectomy, thoracic wall and diaphragmatic resection 12 months after LT and patient 4 underwent liver and pancreas resections 45.5 months post-LT. Despite early recurrence in bones, liver, pancreas and lungs, this patient survived 119 months after LT. Patients 6 and 8 had inter aorto-caval and mesenteric lymphadenectomy 13 and 51 months post-LT respectively.

Table 1. Neuroendocrine tumor (NET) and liver transplantation: pre-transplant characteristics of UCL-series.

Patient	Year	OLT	Age	Sex	CgA (<23 U/l)	5-HIAA (<8 mg/24 h)	Tumor type	Tumor site	Primary tumor surgery	Delay first surgery-LT (months)	Pre-LT treatment	Indication LT/Liver weight
1	1987	84	43	M	NA	NA	Carcinoid	Pancreatic-tail	Splenopancreatectomy 12 months post-OLT (March 1988)	–	–	Tumor bulk (3820 g)
2	1988	167	54	F	NA	NA	Carcinoid	Bronchial-tree	Pulmonary lobectomy (June 1983)	58	Right hepatectomy (tumor mass) (1986)	Endocrine syndrome, tumor bulk (prehepatectomy)
3	1988	229	59	M	NA	<8	Carcinoid	Pancreatic-tail	Splenopancreatectomy Liver nodule resection (May 1987)	11	Adriamycine TACE; Chemotherapy cisplatine, adriamycine	Tumor bulk (2620 g)
4	1989	263	46	M	NA	NA	Carcinoid MEN 1	Pancreatic-tail	Splenopancreatectomy (January 1989)	2	–	Endocrine syndrome, diffuse lesions (2610 g)
5	2000	1094	61	M	35	13.7	Carcinoid	Bronchial	Pulmonary lobectomy (July 1991)	128	Octreotide, R1-pleural and thoracicwall resection	Tumor bulk (8000 g)
6	2001	1195	55	M	52	25.8	Carcinoid	Ileum	Small bowel resection (October 1998)	38	Octreotide, IFN, PEI	Diffuse lesions (1790 g)
7	2002	1224	39	F	20.4	6.2	Undifferent	Pancreatic-head	Duodenopancreatectomy 7 months post-OLT (November 2002)	–	–	Diffuse lesions (1440 g)
8	2003	1290	56	M	15.9	6.6	Carcinoid	Ileum	Small bowel resection (December 1992)	84	Octreotide, IFN	Endocrine syndrome, diffuse lesions (1400 g)
9	2003	1311	26	M	2050	NA	Gastrinoma Zollinger–Ellison syndrome	Liver			Octreotide, PP	Endocrine syndrome tumor bulk (3200 g)

CgA, chromogranine-A; MEN 1, multiple endocrine neoplasia syndrome type 1; R1, resection with remaining microscopic disease; IFN, interferon; PEI, percutaneous ethanol injection; PPI, proton pump inhibitors; NA, not available.

Table 2. Neuroendocrine tumor (NET) and liver transplantation: outcome of UCL-series.

Patient	Type graft	Induction IS	Post-LT complication	Recurrent site	Treatment recurrence	Survival from diagnosis (months)	Survival from LT (months)
1	FS	CyA, AZA, STER, OKT3	Corticoresistant acute rejection, new-onset diabetes	Liver, thoracic wall, diaphragm	Thoracic wall and diaphragmatic resection, liver resection, TACE, 12 months post-LT	51.5	DWD at 51.5
2	FS	CyA, AZA, STER	Acute rejection	Liver, bones	–	104	DWD at 46.2
3	FS	CyA, AZA, STER, ATG	Abdominal bleeding, CMV and urinary infection, new-onset diabetes, incisional hernia	Liver, axillary LN	5FU, STZ, Octreotide	28	DWD at 17
4	FS	CyA, AZA, STER	Pancreatic fistula, acute rejection, CMV infection	Liver, pancreas, lung, bones	Liver and pancreas resection 5FU, STZ, Octreotide, TACE, IFN	121	DWD at 119
5	Right split	TAC STER	Refractory ascites hydrohemothorax biliary tract strictures, hepatic abcess, sepsis, MOF	Mediastinal LN lumbar bones	Octreotide	139	DWD at 11.4
6	FS	TAC, MP, RAPA switch	None	Liver, mesenteric LN pancreas, bones	Mesenteri clymphadenectomy, octreotide	106	DWD at 68.4
7	FS	TAC, MP, RAPA switch	Acute rejection, hepatic recurrence, chronic rejection → re-LT	Liver, coeliac LN	Re-LT Allograft containing two NET lesions	101	AWOD at 96
8	LDLT	TAC, MP, RAPA switch	Biliary stenosis, incisional hernia	Mesenteric and interaortocaval LN	Mesenteric and aortocaval lymphadenectomy	165	AWOD at 84
9	FS	TAC, STER, IS withdrawal	PV stenosis, HA thrombosis, biliary stenosis	–	–	102	AWOD at 78

IS, immunosupression; FS, full size; LDLT, living donor liver transplantation; MOF, multiple organ failure; CyA, cyclosporine A; AZA, azathioprine; OKT3, monoclonal antibodies; STER, steroid; TAC, tacrolimus; MP, methylprednisolone; RAPA, rapamycine; 5-FU, fluoracil; STZ, streptozocin; IFN, interferon; CMV, cytomegalovirus; PV, portal vein; HA, hepatic artery; TACE, transarterial chemoembolization; LN, lymph nodes; DWD, dead with disease; AWOD, alive without disease.

Table 3. Neuroendocrine tumor (NET) and liver transplantation: outcome of UCL-series and selection policy.

			Disease free survival (%)					Patient survival (%)				
Patient	OLT	LT-year	Months	Mean ± SD (months)	1 year	3 years	5 years	Months	Mean ± SD (months)	1 year	3 years	5 years
1	84	1987	10.9	17.4 ± 7.4	75	0	0	51.5	59.3 ± 43.1	10	75	25
2	167	1988	25.3					46.2				
3	229	1988	12.2					17.0				
4	263	1989	22.0					119				
5*	1094	2000	4.8	34.6 ± 29.2	80	40	20	11.4	67.9 ± 33.2	80	80	60
6	1195	2001	12.2					68.4				
7	1224/1395	2002	42.0					96				
8	1290	2002	35.2					84				
9	1311	2003	78.9					78.9				
Total				26.9 ± 23	77	22	0		64.1 ± 35.5	88	77	33

*LT, despite thoracic primary tumor, due to huge tumor bulk.

There was no clear correlation in these small series between the different histological parameters and the tumor recurrence and PS (Table 4).

Discussion

Due to the diagnostic and therapeutic challenges, which are linked to the complexity, heterogeneicity and rarity (0.46% of all malignant diseases) of NET, outcome of this disease was almost not improved over the last three decades. The 5 year overall survival remains indeed invariably around 50–60% [3]. Progress will only be possible if diagnosis can be made earlier and if more patients could be enrolled in clinical trials. This should become feasible as the incidence of patients with NET is steadly rising as well in Europe as in the North-America [3,4].

Gastroenteropancreatic NETs are derived from the widely distributed neuroendrocrine cells which produce and secrete a wide variety of regulatory hormones. Most of them arise from the GI-tract (66%) or bronchopulmonary system and most are sporadic.

In order to make an early diagnosis, one should have a high index of suspicion based on clinical presentation, hormonal assays, tumor makers and pathology including immmunohistochemical investigation. Indeed clinical and biological presentations of NET are slow and protean.

Table 4. Neuroendocrine tumor (NET) and liver transplantation: histology of UCL-series outcome.

Patient	General features	Tumor necrosis	Mitotic fig (/10HPF)	Ki67	Syn	CgA	CK19	Diagnosis	Survival from LT (months)
1	Acinar, well-differentiated	Extensive	8	Failed	Neg	Neg	Weak	Well-differentiated, intermediate grade G2	DWD at 51.5
2	NA	NA	NA	NA	NA	NA	NA	NA	DWD at 46.2
3	Nests, well-differentiated	No	10	30%	Pos	Pos	Pos	Well-differentiated, high grade G3	DWD at 17
4	Nests, well-differentiated	Extensive	3	Failed	Pos	Pos	Neg	Well-differentiated, intermediate grade G2	DWD at 119
5	Trabecular, well-differentiated	No	1	2%	Pos	Weak	Pos	Well-differentiated, low grade G1	DWD at 11.4
6	Nests, well-differentiated	No	0	<2%	Weak	Weak	Neg	Well-differentiated, low grade G1	DWD at 68.4
7	Confluent areas, poorly-differentiated	Extensive	9	35%	Pos	Weak	Weak	Poorly-differentiated, high grade G3	AWOD at 96
8	Nests, well-differentiated	Focal	0	2%	Pos	Pos	Pos	Well-differentiated, low grade G1	AWOD at 84
9	Nests, well-differentiated	No	0	<2%	Pos	Pos	Neg	Well-differentiated, low grade G1	AWOD at 78

NA, no available; Syn, synatophysin; CgA, chromogranine; CK19, cytokeratine 19.

Table 5. Neuroendocrine tumor (NET) and liver transplantation: results from the literature published since 2000.

Author	References	Center	Year	*N*	Symptomatic tumor (%)	Portal venous drainage (primary tumor) (%)	Histology primary		Pre-LTCTH (%)	Delay diagnosis-LT (months)	Operative mortality (%)	Liver involvement (>50%)	5-year PS (%)	5-year DFS (%)
							Carcinoid	Non-carcinoid						
Rosenau *et al.*	38	Hannover	2002	19	90	90	4	15	68	16 med (2–84)	5	94%	80	21
Florman *et al.*	32	Mount Sinai-NY	2004	11	100	90	3	8	NA	NA	27	85 mean 64%	36	9
Frilling *et al.*	33	Essen	2006	15	100	73		15	100	>6 (1–8)	27	88 (med)	67	54
Van Vilsteren *et al.*	34	Mayo	2006	19	84	100	8	11	84	28 med (7–78)	5	NA	87	77
Olausson *et al.*	35	Göteborg	2007	15		93			80	>12	13	>50	71	53
				10 LT	80		9	1	80	(2–120)	0	80%	90	
				5 MVT	100				80		40	100%	40	
Mazzaferro *et al.*	36	Milan	2007	24	10	100		24	55	18 med	NA	0% (all <50%)	90	77
Le Treut *et al.*	37	French MC	2008	85	55	82	74	11	83	30 (1–128)	14	50 med +/−50%	47	20
Present series		Brussels	2008	9	55	66	7	2	55	42 med (2–132)	0	44%	66	20

CHTH, local or systemic chemotherapy, interferon or somatostatin analogue treatment; MVT, multivisceral transplantation; MC, multicenter; NA, non available; PS, patient survival; DFS, disease free survival.

Table 6. Neuroendocrine tumor (NET) and liver transplantation: risk factors for recurrence in recent literature.

	Mazzaferro *et al.* [30,36]	Le Treut *et al.* [26,37]	Rosenau *et al.* [38]	Van Ilsteren *et al.* [34]	Olausson *et al.* [31,35]	Frilling *et al.* [33]	Florman *et al.* [32]
Age over 50 years	>50	No	No	No	No	No	NR
Symptomatic tumor	Yes	No	No	No	No	No	Yes
Primary pancreatic tumor	Yes	Yes if massiveliver involvement	No	Probably yes	No		NR
Non-carcinoid tumor	Yes	(Yes)	No				NR
No portal tumor drainage	Yes	NR	No	Yes	No		NR
Ki 67 index (%)	Yes >5	NR	<5 Yes	Probably yes >2	Yes >10	Yes >10	NR
Aberrant E-Cadherin							
Liver involvement >50% of standard liver volume	Yes	Yes if pancreatic tumor	NR		No	No	NR
Extrahepatic lymph node involvement		No	No	No	No	No	No
Extrahepatic spread	Yes	(Yes)	Yes	Yes	(Yes)	(Yes)	NR
Absent pre-transplant surgery of primary tumor	Yes	(Yes)	Yes	Yes	(Yes)	(Yes)	Yes
Stable period R0-LT (months)	Yes < 6	(Yes)	NR	Yes < 6		Yes <6	NR
Multivisceral transplant	Yes	Yes	Yes		Yes	(Yes)	NR

Small lesions can cause severe endocrine syndromes due to hormonal secretion and very large tumors, replacing nearly all hepatic tissue, can be asymptomatic [3,5]. Based on the secretion of specific peptides and neuroamines, NET tumors are classified as functional or non-functional. NETs are often discovered at an advanced stage and they preferentially metastasize to the liver (40–90% of patients) where they can remain confined for a long time [3,5,6]. This means that curative surgery is theoretically possible when one is able to perform a R0 resection of the primary tumor followed by liver replacement. In order to do so, better tumor localization and staging, uniform histological grading systems and more reliable serum markers are necessary [3]. Optimalization of staging is mandatory not only to detect small metastatic lesions but also to find the primary tumor which is elusive in up to 50% of cases. Endoscopic ultrasound with or without endovenous contrast medium, CT-Scan and magnetic resonance imaging (MRI), selective angiography, bone scanning, endoscopy, videocapsule endoscopy, PET-scan and somatostain receptor scintigraphy (SRS) are the diagnostic procedures used to assess location and extension of NET. It should be noted that many of these examinations have a complementary diagnostic value. The combination of MRI, for the detection of liver metastasis, and of SRS, for the detection of extrahepatic disease is currently considered as the standard imaging for NET. As the sensitivity of SRS only reaches 50–78%, more powerful imaging procedures are necessary [3,9]. The recently introduced DOTATOC and DOPA-PET CT-scans, giving information about both localization and function, have a much higher sensitivity reaching 80–96% [10,11]. These examinations which are based on the fact that all NET-cells can take up catecholamine precursors have a resolution value of 5 mm which contrasts to the classical scintigraphic resolution value of 15 mm.

The histological staging and grading of NETs represents another step forward in the evaluation of the therapeutic algorythm of NET. The recent classifications take into account the tumor location (gastrointestinal versus pancreatic), the degree of differentiation, (well or poor) and the tumor biology (size, vascular invasion, tumor spread and proliferative activity expressed as the number of mitoses and/or the Ki 67 proliferative index) [12,13]. In their study of resected but non-transplanted patients, Cho *et al.* [8] found a correlation between histological classification and outcome. Our series is too small to allow conclusions in relation to this purpose.

Different ablative procedures, arterial embolization, systemic or intra-arterial chemotherapy (CHTH), radiolabelled CHTH, hormonotherapy using somatostatin analogues and interferon-α therapy are all usefull to control or downstage the disease [13–16]. Newer drugs such as V-EGF and mammalian target of rapamycin (m-TOR) inhibitors are currently under evaluation [17–20]. Despite all these treatment modalities, surgery remains an essential part of the treatment of NET [3]. When proposing surgery in NET patients, a full cardiac evaluation is necessary as these tumors have the propensity to cause extensive fibrosis involving the right heart endocardium and valves.

In 'limited' disease, surgery remains the primary method of cure. When proposing surgery for NET in advanced disease, cytoreductive surgery may be useful

[13,14,21,22]. RO resection of the primary tumor, associated with complete, eventually multistep, resection of the liver metastases, is undoubtly the treatment of choice [3]. In those cases, the control of the symtoms can be achieved most of the times, and 5 and 10 years survival rates of 61% and 35% can be reached [3,13,21,22]. Unfortunately only about 10% of patients presenting NET metastases can benefit from liver resection due to the multifocality and/or the extent of the disease.

Because of the frequent limitation of the metastases to the liver for a long period and because of the important technical limitations to liver surgery, LT has been proposed as a potentially curative treatment for selected patients [23–29]. The review of the European Liver Transplant Registry (ELTR) data and of the literature reveals that the transplant experience in NET patients is limited and ill defined. Indeed, only 0.3% (159 carcinoids and 120 other NET) out of 75.530 LT reported to the registry until 2008 have been performed because of NET. Moreover, all usable information about the value of LT in the treatment of NET comes from small, single center series and from two multicentric retrospective studies [25,26] (Table 4). Both facts explain why the place of LT in the treatment of primary and secondary NET is still controversial and not yet validated today. Extremely variable 5-year post-transplant PS rates ranging from 36% to 90% and DFS rates ranging from 9% to 77% point to an important selection bias in the reported series [23–37] and they also indicate that LT may have a cure rate that is superior to the reported 20–30% spontaneous survival of NET patients presenting with bilobar liver metastases. Indeed, complete and sustained remission has not been described in any of the non-surgical treatment modalities. In analogy with the early experience in the field of hepatocellular cancer, LT had initially been proposed in the treatment of NET as a salvage to 'cure' a few desperate patients presenting mostly huge or diffuse tumors with or without invalidating hormonal syndromes refractory to any medical treatment. Our earlier experience confirms this attitude as our first five patients receiving a such a transplant died of tumor recurrence.

The first large NET-liver transplant experience was reported in 1997 by Le Treut *et al.* [26]. The median survival of these 31 patients was 30 months; 1- and 5-year actuarial PS rates were 58% and 36% and 1- and 5-year DFS rates were 45% and 17%. In Lehnert's multicentric survey of 103 cases, 1- and 5-year PS and DFS rates were 68% and 47% and 60% and 24% respectively [25]. The latter study was heterogeneous, incomplete and also included the previously published French experience. Both retrospective studies concluded that gastrointestinal tumors do better than pancreatic tumors, that extensive upper abdominal exenteration should be omitted and that the liver allograft was the most common location of tumor recurrence. In 2008, Le Treut updated the French experience, totaling now 85 patients. Multivisceral transplantation and the combination of pancreatic NET with a liver involvement exceeding 50% of standard liver volume were bad prognostic factors resulting in a 5-year survival rate of 12% only [37].

Based on their former transplant experience with hepatocellular cancer, the Milan group improved the results of LT for NET by prospectively applying strict inclusion criteria. These criteria are: (i) well-differentiated gastroenteropancreatic tumor, (ii) portosystemic tumor drainage, (iii) patient age <55 years, (iv) stable pre-LT disease for at least 6 months, (v) pre-transplant R0 primary tumor resection comprising also extensive lymphadenectomy; (vi) hepatic tumor involvement of <50% of the liver volume; (vii) low tumor aggressiveness (expressed by Ki 67 value <5%) and (viii) absence of extrahepatic disease at the time of LT [30]. Pre-LT staging laparoscopy was also proposed. Following the initial encouraging results in nine patients, fifteen more patients were recruited. Remarkable 5-year PS and DFS survival rates of 90% and 77% were obtained [36]. Despite these excellent results, the Milan selection policy must still be interpreted with caution taking into the account of the Hannover, Mayo, Göteborg and French groups which obtained 5-year survival rates ranging from 73% to 87% using more deliberate selection criteria [28,34–37]. (Table 5). Indeed the prognostic value of primary tumor histology (carcinoid versus non-carcinoid), primary tumor localization (pancreatic versus non-pancreatic), clinical expression (asymptomoatic versus symptomatic), upper age limit (50 years versus 65 years), regional lymph node involvement (present versus absent), degree of liver involvement (less versus more than 50%), Ki 67 index cut off value (2 vs. 5 vs.10 or even 15%), necessity of R0 primary tumor resection (pretransplant resection versus tumor resection during or even after LT) and delay between primary tumor resection and LT (6 months vs. 12 months) all have been questioned in literature [27–29,32–34] (Table 6). Only thoracic and duodenopancreatic tumors with extensive liver involvement, presence of extrahepatic disease other than regional lymph nodes and necessity of multivisceral resection at moment of LT are universally accepted contraindications to LT [3,34,36]. Cytoreductive surgery or chemoembolization combined with hormono- or CHTH are better options for these patiens [9,13,14,16,22].

It becomes evident more information is needed about the biological behaviour of NET in order to further improve the results. The fact that Olausson reported 5-year actuarial PS and DFS rates of 73% and 20% for NET with a Ki-67 index of 10% and even 'hotspots of

15% [35] and the fact that patient 7 of our series is alive, disease free, at 77 months after her first LT despite Ki 67 value of >30%, shows that more discriminative criteria are necessary. The Hannover group analyzed the prognostic value of molecular and cellular tumor markers Ki 67 index and E-cadherin. Ki 67, a nuclear protein involved in the cell cycle regulation, can be detected in all phases of the cell cycle except in G0; E-cadherin is a transmembrane protein related to the dedifferentiation and metastatic potential of tumors. Combination of Ki-67 index <5% and normal staining for E-cadherin were associated with excellent prognosis (100% DFS survival at 7 years post-LT in four patients vs 0% in the other patients) [38].

All reported data indicate that the management of NET should be individualized taking into account patient condition, tumor burden and (clinical) behaviour [3]. It is obvious that a better selection policy is essential in order to improve results. Pluricentric studies, conducted in 'NET centres of excellence' are mandatory in order to further progress in this field of oncological transplantation [3]. Larger numbers of patients are required to validate the value of different diagnostic tools and the recently proposed selection criteria as well as the different treatment modallities. Evaluation protocols containing more sensitive scanning, better inclusion criteria and optimal follow-up must also be further refined in order to improve the results of LT. Three to six monthly follow-up of tumor markers such as chromogranine A or B (CgA CgB), neuron specific enolase and chorionic gonadotropin, specific serum pancreatic polypeptide (i.e. VIP, pancreostatin…), urinary hormonal markers (5-HIAA as the breakdown product of serotonin) and adequate imaging using repetitive thoraco-abdominal scanning, MRI, SRS and more specific imaging such as DOTATOC-gallium and/or DOPA PET scanning are all necessary as well during the pre- and post-transplant period in order to detect and treat tumor recurrence timely and also to exclude timely patients waiting for a liver transplant [3,30,33,34]. The use of CgA during follow-up is hampered by the fact that this marker is increased only in 60–80% NET and that it can be falsely elevated after transplantation due to renal insufficiency caused by calcineurin-inhibition based immunosuppression and/or due to hyperplasia of enterochromaffin-like cells caused by the frequently prescribed proton-pump inhibitors. CgB, which is less sensitive to reduced glomerular filtration, should be preferentially used in the post-LT follow-up [35]. Targetted complementary (metabolic) surgery, chemo-, immuno-, hormono- and peptide receptor radiotherapy as well as adapted immunosuppressive schemes are other crucial factors to further improve results of LT [20,30]. The recent introduction of anti-angiogenic immunosuppressant rapamycine and of endothelial growth factor inhibitors will become part of the treatment of these liver recipients. The m-TOR inhibitor everolimus has an *in-vitro* antiproliferative activity on BON1 cells, derived from the human pancreatic carcinoid [19,20].

One hundred years after the first description of carcinoid tumors by Oberndorfer, the place of LT for NET metastases becomes slowly unraffled. LT is a valid option for very well selected NET patients with unresectable hepatic primaries and secondaries. We propose to limit nowadays the indication for tranplantation in gastro-enteropancreatic NET patients to the (till now successful) criteria advocated by the Milan group. Indeed following these recommendations survival rates after LT for NET of around 80% can be obtained, a number which is close to the survival rates obtained after LT for cirrhotic diseases. Liver transplantation should however only be considered in the therapeutic algorithm of this disease after multidisciplinary work-up, done following the diagnostic and (medical and surgical) therapeutic standards put forward at the ENETS experts conference held in 2007 in Palma de Mallorca and very recently published in the 'Consensus guidelines for the standard of care for patients with digestive neuro-endocrine tumors' [39]. Cautious inclusion of NET-patients in a liver transplant program, based on all aforementioned conditions, should be the best guarantee to avoid futile liver transplantations. This attitude should be especially kept in mind taking into account the more liberal and widespread application ('too much, too rapid') of living liver donation in hepatobiliary oncology, it is also clear that clinical trials with new pharmacological agents and more detailed analysis of larger transplant experiences are necessary to further improve our knowledge and to optimise the use of a scarce organ resource. If results of LT or NET will further improve living liver donation clearly has an important role to play in this field of LT, as NET patients cannot (and will never) benefit from prioritization in the MELD allocation system.

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