Liver transplantation in patients with liver metastases from neuroendocrine tumors: A systematic review

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Background. *Liver transplantation to treat neuroendocrine tumors, especially in the setting of diffuse liver involvement not amenable to operative resection remains controversial. We sought to perform a systematic review of the current literature to summarize data on patients undergoing liver transplantation with neuroendocrine tumors liver metastases as the indication.*

Methods. *A systematic review was conducted in accordance to the Preferred Reporting Items for Systematic reviews and Meta-Analysis guidelines. Eligible studies were identified using 3 distinct databases through March 2017: Medline (PubMed), ClinicalTrials.gov, and Cochrane library, Cochrane Central Register of Controlled Trials using a search algorithm: "(neuroendocrine or NET) and transplantation and liver."*

Results. *From the 1,216 records retrieved, 64 studies were eligible. Overall, 4 studies presented data from registries, namely the European Liver Transplant Registry and the United Network for Organ Transplantation/Organ Procurement and Transplantation Network databases, 3 were multicenter studies. The largest cohort of data on patients undergoing liver transplantation for neuroendocrine tumors liver metastasis indication were from single center studies comprising a total of 279 patients. Pancreas was the primary tumor site for most patients followed by the ileum. Several studies reported that more than half of patients presented with synchronous disease (55.9% and 57.7%); in contrast, metachronous neuroendocrine tumors liver metastasis ranged from 17.7% to 38.7%. Overall, recurrence after liver transplantation ranged from 31.3% to 56.8%. Reported 1-, 3-, and 5-year overall survival was 89%, 69%, and 63%, respectively. Several prognostic factors associated with worse long-term survival including transplantation >50% liver tumor involvement, high Ki67, as well as a pancreatic neuroendocrine tumors versus gastrointestinal neuroendocrine tumors tumor location.*

Conclusion. *Liver transplantation may provide a survival benefit among patients with diffuse neuroendocrine tumors metastases to the liver. However, due to high recurrence rates, strict selection of patients is critical. Due to the scarcity of available grafts and the lack of level 1 evidence, the recommendations to endorse liver transplantation for extensive liver neuroendocrine tumors metastases warrants ongoing deliberations. (Surgery 2017;162:525-36.)*

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Neuroendocrine tumors (NET) are rare neoplasms that arise from cells of the neuroendocrine system. The biologic behavior of these tumors can be heterogenous with clinical presentation varying from an incidental diagnosis in an asymptomatic patient to extensive metastatic disease and

Accepted for publication May 2, 2017.

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0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2017.05.006

refractory carcinoid syndrome.[1,2] For patients with metastatic disease, the liver is one of the most common sites of NET metastases, with up to 50% of patients developing liver metastasis.[3,4] Numerous treatment options for cure and disease control have been investigated. The optimal management of hepatic NET metastases remains, however, a topic of debate. Operative resection with curative intent (R0 or R1) is associated with long-term survival, despite a high incidence of recurrence after operation.[5,6] Unfortunately at diagnosis, >80% of patients present with multifocal or bilobar hepatic metastatic disease that may exclude them from operative cure.[4,7,8] Palliative cytoreduction or debulking by surgical resection (R2 resection) can be offered to these patients, as cytoreduction may offer symptom relief and improved survival without compromising liver function.[9-11] In general, palliative treatments for NET aim to relieve symptoms induced by excess serotonin, in the case of functional tumors, or to relieve symptoms caused by the hepatic tumor burden itself.[12]

Many nonoperative palliative treatment modalities also have been used for patients with extensive NET liver disease. These liver-directed therapies for NET liver metastases have included ablative techniques, as well as transarterial chemoembolization or radionuclide therapy (111 indium-pentetreotide, Ytrium DOTATOC, Lutetium DOTA or meta-iodobenzylguanidine). These locoregional therapies can be effective in slowing tumor progression and palliating symptoms.[13-16] Other systemic treatment options include chemotherapy, immunotherapy alone or in combination with octreotide, and medical treatment using octreotide or lanreotide.[15,17,18] Although these therapies may provide some therapeutic benefit, current locoregional and systemic treatment options do not, however, provide a chance for cure.

Although some of the first cases of liver transplantation (LT) reported in the literature were performed for metastatic liver tumors, contemporary LT largely has been restricted to hepatocellular carcinoma and, in select settings, hilar cholangiocarcinoma.[19,20] More recently, some investigators have advocated that LT may be an option to treat NET, especially in the setting of diffuse liver involvement not amenable to operative resection.[21,22]

The role of LT for NET remains, however, controversial. As such, we sought to perform a systematic review of the current literature to summarize data on patients undergoing LT with NET liver metastases as the indication.

MATERIAL AND METHODS

Search strategy, data sources, and eligibility criteria. A systematic review was conducted in accordance to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (Supplemental Table I).[23] A study protocol, agreed beforehand, was strictly followed by all authors. Eligible studies were identified using 3 distinct databases through March 2017; Medline (PubMed), ClinicalTrials.gov, and Cochrane library, Cochrane Central Register of Controlled Trials (CENTRAL). The following algorithm was applied: "(neuroendocrine or NET) and transplantation and liver." Two independent reviewers (D.I.T., I.N.S.) screened all articles retrieved by the aforementioned algorithm. Reference lists of eligible studies were assessed manually so that no relevant article was missed.

Eligible studies were considered if data were report on patients undergoing LT with NET liver metastasis as the indication. Exclusion criteria included: 1) animal studies, 2) studies reporting on LT for an indication other than NET, 3) studies involving both NET and another primary cancer without referring specifically to the NET cohort, 4) reviews and meta-analyses, 5) editorials and letters to the editors, and 6) overlapping studies. Regarding any overlapping reports, only the most recent or most informative study for a single center was included in the analyses. There were no study restrictions with regards to language or study sample size.

Data extraction and tabulation. After reviewing the full-texts of eligible studies, 2 independent authors (D.I.T., I.N.S.) performed the data extraction and cross-checked all results. Extracted variables included: general study characteristics (eg, author, year of publication, country of enrollment, study design, number of patients), patient demographics (eg, age, sex), primary tumor site, history of hormone therapy and chemotherapy, tumor status (functional, nonfunctional), indications for LT, concomitant multivisceral transplantation, donor classification, immunosuppressive therapy, adjuvant chemotherapy, 1-, 3-, and 5-year overall survival (OS), 1-, 3-, and 5- disease-free survival (DFS), recurrence, mortality (eg, overall and disease-related) and patient status at the end of follow-up. When coding the data, any disagreements were adjudicated by a third reviewer (D.M.).

Data were tabulated and cumulative analysis was performed when possible. Categorical variables were extracted as numbers and reported as proportions. Regarding continuous variables,

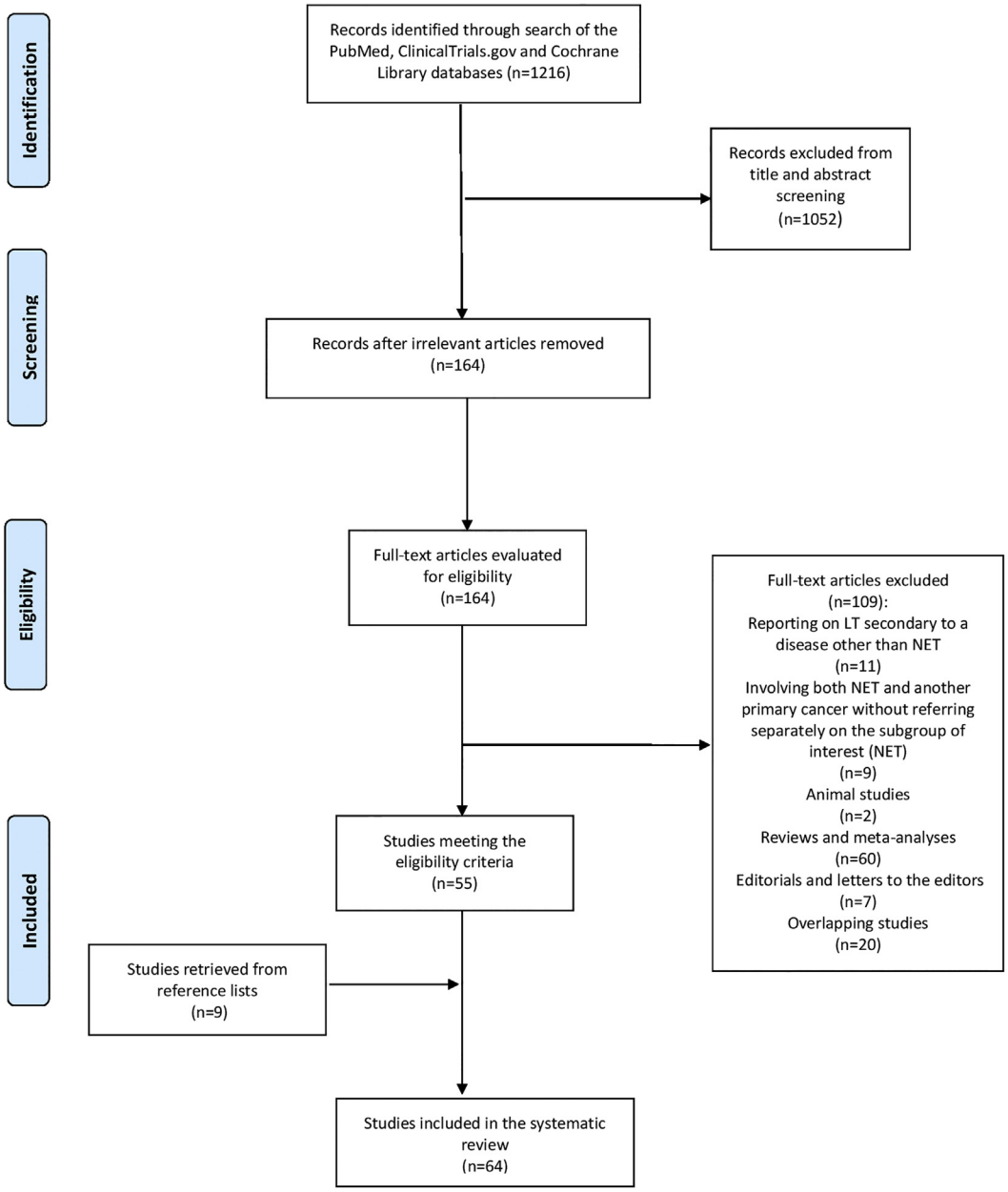

Fig. Flowchart of search strategy.

the method proposed by Hozo et al was utilized when data were presented as medians with a range to estimate the respective means and standard deviations.[24] DFS was defined as the time from liver transplantation to metastatic or locoregional disease recurrence or occurrence of a new NET tumor. OS was defined as the time from liver transplantation to death or last follow-up. Finally, "absolute survival" rates were estimated to calculate OS and DFS at 1-, 3-, and 5-years after LT.

RESULTS

Search results and study characteristics. The results yielded by the initial algorithm and the successive steps of the selection process are depicted in Fig. Twenty studies were excluded as obvious overlaps or duplications (Supplemental Table II). From the 1,216 records retrieved, 64 studies were finally considered eligible. Due to possible overlap of cohort populations among the studies, registry analyses and multicenter studies were described in a narrative fashion, while single

Table I. Features and demographics of eligible studies

	PMID	First author (year of publication)	Years of enrollment	Country/ database	Study design	No. of patients	Male: Female	Age (y)	
								Mean (SD)	Range
Registry databases	25989503	Nobel (2015)	2002–2014	UNOS database	Retrospective	120	NR	NR	NR
	23532105	Le Treut (2013)	1982–2009	ELTR database	Retrospective	213	114:99	46 (11)	16–71
	22254141	Nguyen (2011)	1988–2011	UNOS database	Retrospective	184	100:84	44.9 (NR)	11–69
	21844436	Gedaly (2011)	1988–2008	UNOS database	Retrospective	150	84:66	45.1 (SE:12.5)	11–69
Multicenter experience	27900037	Pasqual (2016)	1990–2012	Italy	Retrospective	4	0:4	48.75 (11.84)	N/R
	26171686	Sher (2015)	1988–2012	USA	Retrospective	85	51:34	46.75 (17)	16–75
	18444921	Le Treut (2008)	1989–2005	France	Retrospective	85	46:39	45 (11)	18–64
Single center experience	*	*	1974–2016	*	*	279	147:115	42 (10)	13–67

*Details on single center experience are provided in Supplemental Table III.

center studies were described cumulatively. Overall, 4 studies presented data from registries, namely the European Liver Transplant Registry (ELTR)[22] and the United Network for Organ Transplantation (UNOS)/Organ Procurement and Transplantation Network databases.[25-27] Three were multicenter studies,[28-30] while the majority of studies were single center reports (57 out of 64).[31-87] In turn, the largest cohort of data on patients undergoing LT for NET liver metastasis indication were from single center studies comprising a total of 279 patients (Supplemental Table III).

Patient and primary tumor characteristics. The demographic and clinical data of patients who underwent LT for NET liver metastases between 1974 and 2016 are summarized in Table I. Among the included studies, mean patient age ranged from 44.9 to 48.7 (age range, 11 to 75) with more male versus female patients. Pancreas was the primary tumor site for most patients followed by the ileum. Specifically, in analyzing the ELTR database, Le Treut et al reported 44.1% (94/213) and 22.5% (48/213) of primary tumors originated from the pancreas and the ileum, respectively.[22] Sher et al described pancreas/duodenum as the primary tumor site in 49.4% (42/85) of cases,[30] which was similar to another study by Le Treut et al that analyzed the records from 17 French centers (48.2%).[28] In addition, cumulative analysis from single center studies demonstrated the pancreas to be the most common site of primary tumor origin (53.4%, 149/279) followed by the ileum (23%, (64/279).

Only 3 studies provided details on the histologic type of primary tumors.[22,26,28] Among functional tumors, carcinoid was the most common subtype, whereas the incidence of nonfunctional tumors ranged from 30.3% (single center analysis) to 52.6%.[22] With regard to liver involvement, NET metastases seemed to occupy <60% of liver parenchyma in most cases (Table II).[22,28]

Several studies reported that more than half of patients presented with synchronous disease (55.9% and 57.7%); in contrast, metachronous NET liver metastasis ranged from 17.7% to 38.7%.[22,28] Of note, diagnosis of liver metastases before the identification of the primary tumor was reported as 20.6%[22] and 24.6%[28] in 2 multicenter studies and 18.7% in the cumulative single center analysis.[31-87]

Pretransplant treatment history. Le Treut et al reported that 161 out of 213 (76%) patients in the ELTR database had a history of hormone therapy or chemotherapy prior to LT.[22] Similarly, in a separate study, 70 out of 85 (82%) patients were noted to have received hormone therapy or chemotherapy in the French multicenter analysis.[28] Data from our cumulative single center analysis noted that 137 out of 184 (74.4%) patients received such pre-LT therapy.[31-87] In another study, pre-LT treatment included operative resection of the primary tumor in 74.2% (158/213) of patients, resection of NET liver metastasis in 26.3% (56/213), while 5.6% (12 patients) had no therapy used before LT.[22] In a different multicenter study, the proportion of patients treated with these different pre-LT options were 64.7%, 33% and 8%, respectively.[28] When considering aggregate data from single center studies, 77.8% (179/230) of patients had pre-LT resection of the primary tumor, whereas 5.6% (13/230) did not receive any treatment preoperatively.

Table II. Primary tumor characteristics

	Registry databases				*Multicenter experience*			
Author (year of publication)	*Nobel (2015)*	*Le Treut (2013)*	*Nguyen (2011)*	*Gedaly (2011)*	*Pasqual (2016)*	*Sher (2015)*	*Le Treut (2008)*	*Single center experience*
Primary tumor site								
Bronchial tree	NR	16 (10 carcinoids, 6NF)	NR	NR*	0	0	5 (3 carcinoids, 2 NF)	14
Stomach	NR	8 (1carcinoid, 7NF)	NR	NR*	0	0	3 (3 NF)	7
Duodenum	NR	3 (2 gastrinomas, 1NF)	NR	NR*	0		41 (13 gastrinomas, 2 VIPomas, 2	20
Pancreas	NR	94 (18 gastrinomas, 6 insulinomas, 6 VIPomas, 4 polymorphs, 3 glucagonomas, 3 carcinoids, 54NF)	NR	NR*	1	42	glucagonomas, 2 insulinomas, 1 carcinoid, 1 polymorph, 20 NF)	149
Jejunum	NR	16 (2 carcinoids, 1 GFRHoma, 1 VIPoma,1 gastrinoma, 11NF)	NR	NR*	0	0	6 (2 carcinoids, 1 VIPoma, 3 NF)	21
Ileum	NR	48 (38 carcinoids, 10NF)	NR	NR*	3	0	16 (14 carcinoids, 2 NF)	64
Right colon	NR	4 (4NF)	NR	NR*	0	0	0	8
Sigmoid colon	NR	1 (1NF)	NR	NR*	0	0	4 (4 NF)	6
Rectum	NR	5 (5NF)	NR	NR*	0	0		6
Common bile duct	NR	1 (1 carcinoid)	NR	NR*	0	0	0	0
Undetected	NR	17 (3 carcinoids, 1 gastrinoma, 13NF)	NR	NR*	0	16	10 (2 carcinoids, 8 NF)	13
Other	NR	0	NR	NR*	0	24 digestive tract, 1 lung, 1 both pancreas and bowel, 1 choledochal cyst	0	7
Functional status of the tumor, *n* (%)								
Functional	NR	101 (47.4)	NR	NR	2 (50)	NR	43 (50.6)	136 (69.7)
Nonfunctional	NR	112 (52.6)	NR	NR	2 (50)	NR	42 (49.4)	59 (30.3)
Extent of liver involvement (%)								
<60	NR	113	NR	NR	NR	NR	61	<50: 50
>60		85					24	>50: 46

*51 carcinoids, 6 insulinomas, 3 glucagonomas, 11 gastrinomas, 9 VIP-secreting tumors, and 70 unspecified NETs.

Table III. Liver transplantation and outcomes

	PMID	*First author (year of publication)*	*No. of patients*	*No. of retransplantations*	*No. of MVT*	*OS, %*			*DFS, %*		
						1-year OS	*3-year OS*	*5-year OS*	*1-year DFS*	*3-year DFS*	*5-year DFS*
Registry databases	25989503	Nobel (2015)	120	NA	NA	87 (95% CI, 79–92)	69 (95% CI, 59–77)	63 (95% CI, 53–72)	NR	NR	NR
	23532105	Le Treut (2013)	213	24	6	81	65	52	65	40	30
	22254141	Nguyen (2011)	184	14	0	79.5 (Post-MELD: 84.7)	61.4 (Post-MELD: 65)	49.2 (Post-MELD: 57.8)	NR	NR	NR
	21844436	Gedaly (2011)	150	0	13	80	64	48	77†	50†	32†
Multicenter experience	27900037	Pasqual (2016)	4	0	0	100‡	50‡	50 (95% CI, 12.5–100)	NR	NR	NR
	26171686	Sher (2015)	85	NR	17	83	60	52	NR	NR	NR
	18444921	Le Treut (2008)	85	7	3	72	59	47	56	37	20
Single center experience	*	*	279	14	16	81.4	64.9	70.7§	59.5	41	26.3

*Details on single center experience are provided in Supplemental Table III.
†As described by the authors, DFS rates were estimated for the 83 patients for whom recurrence information was available.
‡Not clearly written in the text but obviously extracted from Fig. *D* of the same study.
§5-year survival seems greater than 3-year survival due to the study by Mazzaferro et al[32] that did not provide details on 1- and 3-year survival rates but contributed with a 5-year OS of 97.2%.
NA, Not applicable; *NR*, not reported; *MELD*, model for end-stage liver disease score.

Indication for LT. Indications for LT were categorized according to the study by Le Treut et al into 3 distinct groups: "hormonal syndrome" including patients with life-threatening or debilitating hormone-related symptoms, "tumor bulk" including patients with pain or debility associated with enlargement of the liver, and "oncological" including patients with low-grade symptoms.[22] Two studies provided details on the indications for LT. One study noted that LT was performed for hormonal syndrome in 12%, tumor bulk in 24%, and oncologic reasons in 54%,[22] whereas in another study, the proportion of patients that met each indication were 23.5%, 27.1% and 42.4%, respectively.[28] Analysis of aggregate data from single center reports demonstrated that the indications for LT were presentation of symptoms, either debilitating or low-grade, related to the underlying NET in 66.1% (129/195) followed by tumor bulk in 33.8% (66/195).

Liver transplantation. Apart from liver only transplantation, multivisceral transplantation (MVT) was used in cases of widespread disease and involvement of more organs. In general, the utilization of MVT was <20%. Most cases of MVT were reported by Sher et al (17 out of 85)[30] and Gedaly et al (13 out of 150),[26] whereas 2 studies mentioned no MVTs.[25,29] Analysis of single center studies revealed 16 out of 279 (5.7%) cases of MVT.

Most cases of retransplantation (24 cases) were reported by Le Treut et al, of which 10 were performed due to hepatic artery thrombosis, 6 for primary nonfunction of the graft, 2 for portal/hepatic vein thrombosis, 1 for each of biliary complication, recurrent hepatitis C and chronic rejection as well as 3 undetermined causes.[22] Nguyen et al,[25] as well as single center studies[38,39,44,47,58,71,75,76,81,86] reported a total of 14 cases of retransplantation (Table III). Of note, one patient described by Ortiz et al underwent 3 liver transplantations due to consecutive events of primary graft non-function. This patient was alive at 16 years of follow-up.[38]

Among those studies that provided details on donor classification, the use of deceased donor grafts was about 90% with only a small minority of grafts derived from living donors.[22,26,28] In analyzing the ELTR database, Le Treut et al reported a domino procedure in 7 cases,[22] while 2 were reported in the French multicenter analysis.[28]

Only a few studies provided transplantation-related perioperative data. For example, mean operative time was 7.8 ± 3.1 hours in the ELTR database,[22] whereas mean length of stay was

Table IV. Recurrence and mortality rates

	PMID	First Author (year of publication)	No. of patients	Recurrence, n (%)	Mortality, n (%)		Alive patients, n (%)	
					Overall mortality	Disease-related	With disease	Disease-free
Registry databases	25989503	Nobel (2015)	120	NR	46 (38.3)	20/38 (52.6)*	74 (61.7)	
	23532105	Le Treut (2013)	213	112 (52.6)	124 (58.2)	87 (40.8)	26 (12.2)	63 (29.6)
	22254141	Nguyen (2011)	184	NR	86 (46.7)	46 (25)	98 (53.3)	
	21844436	Gedaly (2011)	150	26/83 (31.3) †	NR	NR	NR	NR
Multicenter experience	27900037	Pasqual (2016)	4	NR	NR	NR	NR	NR
	26171686	Sher (2015)	85	46/81 (56.8)	40 (47)	20 (23.5)	45 (53)	
	18444921	Le Treut (2008)	85	44 (51.8)	61 (71.8)	44 (51.8)	24 (28.2)	
Single center experience	‡	‡	279	107/267 (39.8)	90/272 (33.1)	57/272 (21)	182/272§	(66.9)

*Cause of death was identified in 38 out of 46 deceased patients.
†Tumor recurrence was seen in 26 of 83 patients who underwent LT after 1999, when information about tumor recurrence became available.
‡Details on single center experience are provided in Supplemental Table III.
§45 with disease, 97 disease-free, and 40 alive with no disease status.
NR, Not reported.

23 days (range, 15–52) in one report[25] and 22.2 days (range, 3–160) in another,[26] both derived from the UNOS database. The amount of blood loss during operation, as well as the need for blood transfusion was not reported in any study.

Immunosuppressive therapy. None of the large cohort studies reported on the immunosuppressive therapy used. Mazzaferro et al did report on 41 patients with LT for NET liver metastases and described the use of tapering of steroids within the third posttransplant month with initiation of calcineurin inhibitor monotherapy (tacrolimus and cyclosporine in 81% and 19% of patients, respectively).[32] Tacrolimus-based immunosuppression, along with the use of additional regimens such as cyclosporine and steroids, was applied in other single center studies.[44,47,48,53-55] In the case of calcineurin inhibitors intolerance, use of sirolimus was also reported.[48] Finally, use of adjuvant chemotherapy after LT was not described except in 4 cases: combination of cisplatin, doxorubicin, 5-flurouracil, and vincristine for a metastatic gastrinoma,[42] leukovorin and 5-FU for a metastatic islet cell carcinoma,[80] adriamycin for a metastatic glucagonoma[86] and 5-FU for a mixed carcinoid tumor-cholangiocarcinoma.[86]

Long-term outcomes. Overall, recurrence after LT ranged from 31.3% to 56.8% (Table IV). In analyzing the ELTR database, Le Treut et al reported that a total of 112 out of 213 (52.6%) patients recurred,[22] whereas analysis of aggregate single center data demonstrated a recurrence in 107 out of 267 (39.8%) patients. At the time of last follow-up, reported overall mortality ranged from 33.1% to 71.8%, whereas disease-related mortality ranged from 21% to 52.6%. In turn, the proportion of patients alive at reported last follow-up ranged from 28.2% to 66.9%, with single center studies reporting higher proportions of patient survival.

Analyzing the UNOS database from 2002 to 2014, Nobel et al reported a 1-, 3-, and 5-year OS of 89%, 69% and 63%, respectively.[27] Survival was much greater than that reported by 2 other studies from the same database that reported a 1-year survival of 79.5% and 80%, a 3-year OS of 61.4% and 64%, and a 5-year OS of 48.0% and 49.2%.[25,26] These data may relate to more unfavorable outcomes in the early 1990s because the latter 2 studies include patients from 1988.[25,26] Of note, NET patients transplanted after 2002, with the introduction of the model for end-stage liver disease/pediatric end-stage liver disease scoring systems for organ allocation, were associated with an increase in 5-year survival from 49.2% to 57.8%

compared with patients transplanted since 1988 (Table III).[25] The ELTR database analysis, which incorporated a total of 213 patients, noted a 1-, 3-, and 5-year survival of 81%, 65%, and 52%, respectively.[22]

In assessing multicenter data, Sher et al reported the results from 28 US centers and noted a 1-, 3-, and 5-year OS of 83%, 60%, and 52%, respectively.[30] Survival from this study was more favorable than the data previously report by Le Treut et al that analyzed the results of 17 French centers (1-, 3-, 5-year OS: 72%, 59%, and 47%).[28] In a more recent report by Pasqual et al 5-year OS was 50% (95% CI, 12.5–100).[29] Aggregate data from 57 single center studies was notable for an estimated cumulative 1-, 3-, and 5-year survival of 81.4%, 64.9%, and 70.7%, respectively. Although the cumulative 5-year survival was greater than noted in the larger cohort studies, this difference was likely related to data from the Mazzfero et al study that reported a 5-year OS of 97.2% among transplanted patients versus only 50.9% among those patients treated with nontransplant strategies.[32]

Survival according to the primary tumor site. Among the studies included in the current study, only four reported on outcomes stratified by primary tumor site.[22,28,55] Le Treut et al reported that patients with a pancreatic NET (PNET) had a worse 5-year survival compared with patients who had a gastrointestinal NET (GI NET; 44% vs 62%, $P < .05$).[22] In addition, a French multicenter study reported a worse 5-year survival LT among patients with a PNET versus patients with a GI NET (27% vs 69%, $P = .0008$).[28] In another study, while not statistically significant, the data did suggest that 1-year OS (77% vs 100%, $P = .2$) and 1-year DFS (60% vs 100%, $P = .1$) were both inferior among PNET versus GI NETs patients.[55] In a different study, Sher et al reported a comparable 5-year survival among patients with tumors arising from the duodenum/pancreas versus remaining digestive tract (53% vs 51%, $P = .83$).[30]

DISCUSSION

LT was originally conceived as a therapy for advanced liver malignancies as it offered the potential for total tumor removal and elimination of recurrence in the liver remnant compared with standard hepatic resection.[88] Several attempts to implement an LT strategy for both primary and metastatic tumors led to poor results, and therefore LT was not considered for this indication.[88] Rather, based on data from Mazzaferro et al in the mid-1990s, LT was restricted largely to patients with early hepatocellular carcinoma who met strict selection criteria.[20] In contrast, LT for unresectable metastases to the liver essentially was abandoned. More recently, however, LT has been reconsidered as a possible option for highly selected patients with NET liver metastasis. Many patients with NET will develop liver metastasis during the course of their disease. Although resection of the primary tumor and the liver metastases are sometimes amenable to operative resection, a subset of patients will not be candidates for expiration of their disease.[6] While cytoreductive operation aimed at removing the bulk of disease may be a possible therapeutic option, this therapeutic approach does not offer the chance at long-term cure.[89] As such, Mazzaferro et al[90] and others have suggested possible selection criteria for patients with NET (Table V). In particular, it is a prerequisite to exclude the possibility of extrahepatic disease through careful staging using SRI or gallium-68 octreotate PET-CT scan with a specific focus on ruling out bone and lymph node metastases.[6,21,47,54,91,92] In addition, at the time of operation, exploratory laparotomy or laparoscopy to detect peritoneal deposits also should be considered.[53-55]

Le Treut et al have published the largest cohort study to date of 213 patients with metastatic liver NET who underwent transplantation throughout a 27-year time interval from the European Liver Transplant Registry.[22] In this study, 90-day postoperative mortality was 10%, whereas 5-year OS was 52% yet almost 60% of the patients had disease recurrence.[22] One strength of the current study was the analysis of aggregate data amassed from the varied single center studies, which provided one of the largest analytic cohorts of patients to date on the topic of NET LT ($n = 279$). In assessing these aggregate data, 1- and 3-year survival following LT was similar to that reported by Le Treut et al[22] at 81.4% and 64.9%, respectively. In contrast, 5-year survival derived from the aggregate data was 70.7%, which was indeed greater than the 52% reported in other multicenter studies.[22,30] The difference in reported long-term outcomes was likely due to both differences in data reporting as well as patient selection. Specifically, patients eligible for LT according to the Milan-NET criteria had a more favorable long-term.[32]

Le Treut et al have identified a number of important prognostic factors associated with worse long-term survival, including resection of the primary tumor during liver transplantation, the presence of hepatomegaly (presumably a surrogate for extensive metastatic disease within the liver),

Table V. Milan criteria for liver transplantation in patients with hepatic metastases from neuroendocrine tumors

Inclusion criteria
1. Confirmed histology of low-grade neuroendocrine tumors with or without the presence of syndrome
2. Primary tumor drained by the portal system (pancreas and intermediate gut: from distal stomach to sigmoid colon) already removed with a curative resection (removal of all extra-hepatic tumor deposits prior to liver transplantations)
3. <50% involvement of liver parenchyma
4. Good response or stable disease for at least 6 mo during the pretransplantation period
5. Age <55 years
Exclusion criteria
1. Small-cell carcinoma and high-grade neuroendocrine carcinomas (noncarcinoid tumors)
2. Other medical/operative conditions contraindicating liver transplantation, including previous tumors
3. Nongastrointestinal carcinoids or tumors not drained by the portal system

transplantation with <50% liver tumor involvement, and tumor bulk as the primary indication for transplantation. In addition, poorly differentiated tumors, a margin-positive resection, and lymph node-positive disease were all associated with worse long-term outcomes.[22] Other factors related to poor prognosis include the association of LT with major resection, especially upper abdominal exenteration, liver enlargement >50% and Ki-67 proliferation index>10%.[21,22,28,93,94] Similarly, the ENETS Consensus guidelines note that LT should only be considered based on criteria including well-differentiated (G1, G2) NET with a Ki-67 index of <10%, stable disease for at least 6 months before LT, age <55 years, absence of extrahepatic disease, a <50% liver involvement or <75% for patients with refractory hormonal symptoms, and primary tumor removed before transplantation (at least 6 months ago).[21] The site of the primary tumor is thought to have an important role since gastrointestinal tumors usually have better outcomes compared with PNETs consistent with data in the current study.[22,28,55,95] For those patients with an unknown primary tumor, Le Treut et al reported a 59% long-term overall survival.[22]

Based on the relative good long-term results, LT may indeed be a viable option for selected patients with diffuse hepatic metastases, especially patients meeting the criteria established by Mazzaferro et al.[90] In fact, the Organ Procurement and Transplantation Network has established recommendations for selecting patients in the United States for LT with NET. Selection criteria include recipient age <60 years, limitation of the NET metastases to the liver with a bilobar involvement and not amenable to resection and resection of the primary malignancy without evidence for recurrence for at least 6 months. Only patients with well to moderately differentiated NETs (G1/G2) with a low mitotic rate (<20 per 10 high power fields) and a Ki67 value <20%, which originate from the gastroenteropancreatic system with portal system drainage should undergo LT. Furthermore, the guidelines contain instructions for radiologic workup including time interval, type of diagnostics, and radiographic characteristics.[96] Patients who do not meet these guidelines should be considered for other liver directed therapies such as yittrium-90 or peptide receptor radionuclide therapy.

In conclusion, LT seems to provide a survival benefit among patients with diffuse NET metastases to the liver who have no evidence of extrahepatic disease. The total number of liver transplants performed for neuroendocrine liver metastases is, however, small. As such, while the survival data seems favorable, caution should be taken and the benefit of LT for NET should be balanced against the world organ shortage and potential clinical benefit.

Due to high recurrence rates, strict selection of patients is critical. In addition to a multidisciplinary approach, standardization of patient selection criteria, as well as post-LT immunosuppressive regimens are needed. Due to the scarcity of available grafts and the lack of level 1 evidence, the recommendations to endorse LT for extensive liver NET metastases warrants ongoing deliberations.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.surg.2017.05.006.

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