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REVIEW

Liver transplantation for primary or secondary endocrine tumors

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Summary

Endocrine tumors comprise a heterogeneous group of rare neoplasms. Liver metastatic endocrine tumors (MET) are amenable to various therapeutic modalities including liver transplantation (LT). However, LT for MET remains controversial because of the lack of clear selection criteria. The purpose of this study based on thorough perusal of English and French literature since 1989 was to identify prognostic factors and propose recommendations for selecting patients most likely to benefit LT for primary and secondary endocrine tumors.

Introduction

Endocrine tumors comprise a heterogeneous group of rare neoplasms. Most (90%) occur in the gastrointestinal tract and pancreas, but the primary tumor site remains unknown in 15–25% of cases [1–4]. Endocrine tumors can cause severe illness and lead to life-threatening situations because of massive hormonal release (up to 50% functioning tumors) and large tumor bulk. Metastasis is an extremely unfavorable event associated with a 5-year survival of 20–30% when compared to 96% in absence of metastasis [5–7]. Liver metastatic endocrine tumors (MET) are amenable to a wide range of therapeutic options including abstention, somatostatin analogs, interferon therapy, systemic chemotherapy, targeted therapies, transarterial chemo-embolization, peptide receptor radionuclide therapy, radioembolization (Y90), and ablative therapy.

Metastatic endocrine tumor remain confined to the liver for a long period during which there is theoretically a 'surgical window'. In practice, 80% of MET are bilateral and multilocular at diagnosis and thus not amenable to liver surgery [8–10]. Although total hepatectomy and liver transplantation (LT) have been proposed to achieve symptomatic relief and long-term survival in patients with unresectable MET, outcome in terms of survival has been variable. This inconsistency suggests that a more selective approach may be needed. The purpose of this study based on thorough perusal of English and French literature since 1989 was to identify prognostic factors and propose recommendations regarding LT for primary and secondary endocrine tumors.

Liver transplantation for metastatic endocrine tumors

Literature review: monocentric and multicentric series

All monocentric (Table 1) and multicentric (Table 2) series including four or more patients published between 1989 and 2009 were included in this study. Several

Table 1. Liver transplantation for metastatic endocrine tumor in monocentric series.

First author, year of publication	*N*	1-year survival (%)	5-year survival (%)	Disease-free survival (%)
Makowka, 1989 [11]	5	60	–	
Arnold, 1989 [14]	4	50	–	
Routley, 1995 [13]	11	82	57	54 (1 year)
Alessiani, 1995 [12]	14	–	64 (3-year)	
Anthuber, 1996 [37]	4	25	0	0
Dousset, 1996 [46]	9	33	11	–
Lang, 1997 [2]	12	81	81	34 (5-year)
Frilling, 1998 [16]	4	50	50	–
Pilchmayr, 1998 [24]	15	–	87	–
Lang, 1999 [23]	10	100	100	11
Pascher, 2000 [47]	4	100	50	–
Coppa, 2001 [21]	9	100	70	53 (5-year)
Ringe, 2001 [48]	5	80	–	–
Rosenau, 2002 [25]	19	89	80	21 (5-year)
Olausson, 2002 [17]	9	89	–	44 (3-year)
Fernandez, 2003 [49]	5	80	40 (3-year)	40 (2-year)
Cahlin, 2003 [19]	10	80	–	50 (2-year)
	Carcinoids 4	100 (2-year)		75 (2-year)
	Noncarcinoids 6	67 (2-year)		33 (2-year)
Florman, 2004 [34]	11	73	36	9 (5-year)
Ahlman, 2004 [20]	12	78	–	–
Von Vilsteren, 2006 [28]	19	87	–	77 (1-year)
Frilling, 2006 [15]	15	78	67	48 (5-year)
Mazzaferro, 2007 [22]	24	–	90	77 (5-year)
Olausson, 2007 [18]	15		71	20 (5-year)
	LT 10	90	90	–
	MVT 5	40		
Marin, 2007 [50]	10	86	57 (3-year)	33 (5-year)

LT, liver transplantation; MVT, multivisceral transplantation.

Table 2. Liver transplantation for metastatic endocrine tumor in multicentric series.

Author, year of publication	Prognostic factors	*N*	1-year survival (%)	3-year survival (%)	5-year survival (%)	5-year disease-free survival (%)
Bechstein & Neuhaus, 1994* [40]		30	52	52	–	–
Le Treut *et al.*, 1997 [32]		31	59	47	36	17
	Carcinoids	15	80	80	69	
	Non carcinoids	16	38	15	–	
Le Treut *et al.*, 1997* [32]		37	66	46	46	–
	Carcinoids	17		34 (2-year)		
	Non carcinoids	20		83 (2-year)		
Lehnert, 1998* [26]		103	68	53	47	24
	0 factor**	36	90	77	65	
	1 factor	38	57	47	32	
	2 factors	11	12	0	0	
Le Treut *et al.*, 2008 [27]		85	72	59	47	20
	0 factor***	20	85	85	76	
	1 factor	35	86	76	66	
	2 factors	23	57	26	12	

*Results from literature compilation.

**Prognostic factors (85 documented cases): extended operation and age >50 years.

***Prognostic factors (78 cases, UAE excluded): primary tumor site in duodenum or pancreas, and hepatomegaly.

institutional reports, such as Pittsburgh reports [11,12], London reports [13,14], Essen reports [15,16], Göteborg reports [17–20], Milan reports [21,22], and Hannover reports [2,23–25], contained overlapping data but were included to highlight the improvement of outcomes during the past 20 years.

Prognostic factors and survival

Extrahepatic disease

According to all authors, extrahepatic disease found in almost 50% of MET patients at the time of diagnosis is a contraindication for LT as systemic and peritoneal involvement prevents complete tumor resection [1]. Analysis of 103 cases of LT for MET reported in the literature confirmed that 40% of the patients presented extrahepatic disease at time of operation and consequently showed poor survival [26]. In a previous study, our group also reported significantly poorer 5-year survival after LT in which resection was classified as R1-R2 than as R0 (9% vs. 53%) [27]. Mazzaferro *et al.* [22] stated that primary tumor resection must be performed by an experienced team with precise curative intent including loco-regional and distant lymph node dissection (R0). Based on this experience, R0 resection of the primary tumor should be considered as mandatory for long-term survival after LT.

Careful staging to detect extrahepatic disease is an important part of pre-LT assessment. Various work-up procedures have been proposed to detect extrahepatic lesions. Frilling *et al.* used [^{68}gallium]-DOTATOC-PET and somatostatin receptor scintigraphy (SRS) in combination with standard imaging modalities (MRI, CTscan). Results showed that SRS and DOTATOC-PET detected extrahepatic metastases that were not diagnosed by usual imaging procedures in 10 of 28 (35%) patients [15]. For detection of peritoneal involvement before LT, the Mayo Clinic group systematically performed staging laparotomy to identify peritoneal deposits [28]. Frilling *et al.* [15] also recommended staging laparotomy as a component of pretransplant work-up in case of suspicious extrahepatic CT findings.

Bone is a preferential location for extrahepatic involvement even in patients with well-differentiated MET. In a prospective series of 79 patients Leboulleux *et al.* reported bone metastasis in 46% [29]. In that study, multivariate analysis showed that the presence and extent of liver involvement and bronchial-thymic primaries were independently correlated with a higher risk of bone metastases. Bone metastasis was found in more than 50% of patients presenting duodenopancreatic and ileal primaries, in association with liver involvement exceeding 25%. Regarding bone staging, the authors recommended SRS and spine MRI as these techniques allow detection of more than 90% of metastatic bone lesions [29]. Recent advancements have further improved diagnosis of extrahepatic involvement. Putzer *et al.* reported 97% sensitivity and 92% specificity in bone metastasis detection using [^{68}gallium]-DOTATOC-PET that achieves better detection of distant metastases than CT-scan or conventional bone scintigraphy [30].

Upper abdominal exenteration, multivisceral transplantation, and other extended procedures

Upper abdominal exenteration (UAE) and multivisceral transplantation (MVT) have been proposed for upper abdominal malignancy since 1990. Twenty years ago, Starzl *et al.* reported a 10-patient series describing UAE and MVT including two MET [31]. An update published in 1995 including 14 MET showed better 3-year survival for endocrine tumors (63%) than sarcoma (44%), hepatocellular carcinoma (25%), cholangiocarcinoma (20%), and other adenocarcinomas (20%) [12]. Despite a 3-month mortality of 18%, the authors stated that 'the greatest benefit was in patients with endocrine tumors' [12]. In a more recent 15-patient series using both LT and MVT, the Göteborg group provided evidence that MVT could be a viable option for MET [18]. In the five patients who underwent MVT, two died from transplantation-related causes within 4 months, one died from recurrence after 27 months, one was tumor-free after 12 months and one was alive with recurrent disease at 4 years [18]. Multivariate analysis of the 103 cases compiled from the literature, showed that extended procedures, e.g., LT with UAE or duodenopancreatectomy, led to poor outcomes with a fivefold higher mortality risk [26]. Two other reports also demonstrated that UAE was an unfavorable prognostic factor associated with a 3.27-fold increase in mortality risk in both univariate and multivariate analysis [27,32]. Based on these findings, it can be recommended that UAE and MVT be performed only by experienced teams in carefully selected patients. In as far as possible, a two-step approach should be used with resection of the pancreatic primary tumor prior to LT [22].

Tumor biology and histology

Several aspects of tumor biology and histology have been correlated with the outcome of LT for MET. In 2002, the Hannover group reported that analysis of the nuclear protein Ki67 (involved in cell proliferation) and glycoprotein E-cadherin (involved in cell–cell adhesion) could be used to identify patients with favorable prognosis [25]. Patients with tumors in which immunostaining showed Ki67 expression greater than 10% were at higher risk for recurrence and poor survival. Identical results were reported in a 14-case series showing that patients with an

MIB-1, an anti-Ki67 antibody, index less than 5% exhibited longer disease-free and overall survival rates (median, 69 and 80 months respectively) than patients with an MIB-1 index greater than 5% (median, 11 and 13 months respectively) [33]. In a multicentric series of 85 patients, univariate analysis showed that the 5-year survival rate was lower for poorly differentiated tumors ($n = 11$) than for well-differentiated tumors ($n = 74$): 27% vs. 50% ($P = 0.004$) [27]. As a result of the small sample size of the poorly differentiated tumors group, histologic differentiation was no longer a predictor of the outcome of LT for MET in multivariate analysis. However, it must be underlined that many authors have reported poor outcome after LT for poorly differentiated MET [11,34]. Based on these observations, patients with well-differentiated MET exhibiting Ki67 level below 10% appear the most likely to benefit from LT.

With regard to differentiation, it is interesting to compare the main endocrine tumor classifications, i.e., the World Health Organization (WHO) and tumor node metastasis (TNM) classifications. The most recently updated WHO classification stratifies endocrine tumors according to location, histological features, and hormone production [35]. However, the WHO classification still does not distinguish well-differentiated tumors from tumors with other unfavorable prognostic signs such as high proliferation index or necrosis. The latest TNM classification proposes a three-group grading system that takes into account mitosis number and proliferation index (Ki67) [36]. Well-differentiated endocrine tumors are divided into two groups, i.e., G1 for well-differentiated endocrine tumors with low-proliferation rates and G2 for aggressive well-differentiated endocrine tumors. The third group (G3) corresponds to poorly differentiated endocrine tumors (Table 3).

Primary tumor site

The prognostic implications of primary tumor site remain unclear. Many authors have identified primary tumor location in the pancreas as an unfavorable factor [19,27,32,37]. In Lehnert's review series, pancreatic primary tumor was also an unfavorable factor in univariate analysis (almost significant, $P = 0.07$), but not in multivariate analysis [26]. In a retrospective series including 31 cases, pancreatic primary tumor was a risk factor with a survival rate of only 8% at 4 years versus 69% at 5 years for carcinoid tumors in the digestive tract or bronchial tree (Fig. 1) [32]. This could be explained in part by higher postoperative mortality as a result of extended procedures associated with LT in patients with pancreatic primary tumors. These results were confirmed by a large retrospective series in which pancreatic location of the primary tumor was a factor of poor prognosis in both univariate (Fig. 2) and multivariate analysis [27]. In glar-

Table 3. Tumor node metastasis classification, grading system [36].

Grade	Mitotic Index (10 High Power Fields)	Ki-67(%)
Grade 1	≤2	≤2
Grade 2	2–20	2–20
Grade 3	>20	>20

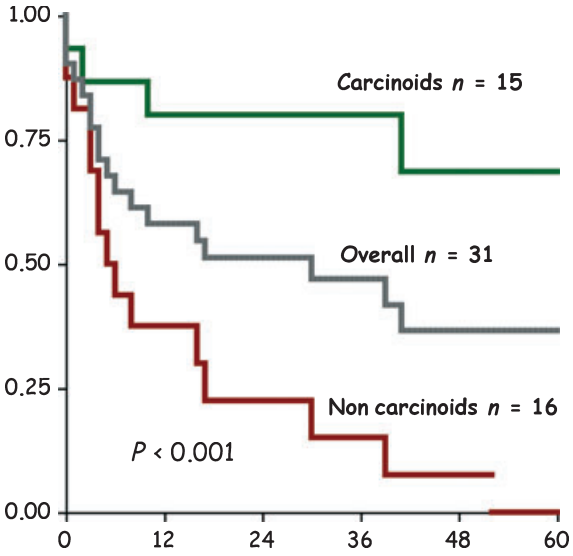

Figure 1 Actuarial survival of patients with carcinoid and noncarcinoid metastatic tumors in a 31-case multicentric series. Adapted from Le Treut *et al.* [32].

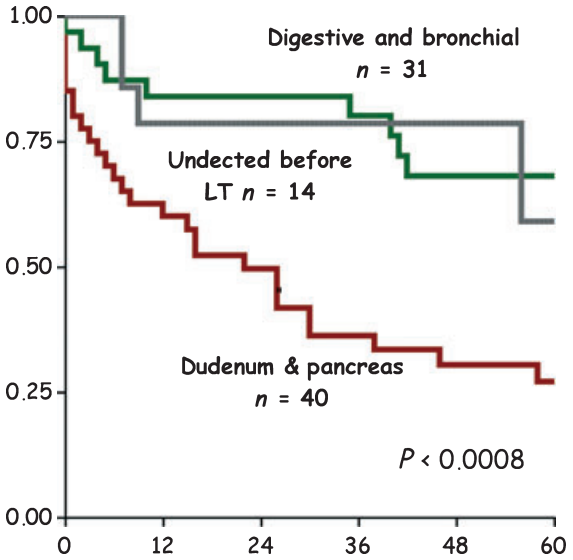

Figure 2 Actuarial survival of patients according to primary site location in a 85-case multicentric series. Adapted from Le Treut *et al.* [27].

ing contradiction with these findings, a 37-case series compiled from the literature showed a significantly higher 2-year survival rate for pancreatic MET than for carcinoids: 83% vs. 34% and a 10-case monocentric series of LT for pancreatic MET showed a spectacular 100% 5-year survival [32].

Several recommendations have been made regarding the use of LT for MET associated with primary tumors located in the bronchial tree. Based on their prospective study, the Milan group stated that LT should only be used for patients presenting endocrine carcinomas with portal drainage in which case the liver is the 'first station' colonized during hematogenous spread of malignant cells from the primary site [22]. Application of this recommendation rules out LT for bronchial (and rectal) MET. In one multicentric series including 85 patients, endocrine tumors of the bronchial tree or digestive tract were grouped together because they share the same embryological origin, i.e., the foregut, and often have similar symptoms, i.e., carcinoid syndrome [27]. Univariate analysis indicated that neither of these two primary locations was correlated with poor prognosis (Fig. 1). The authors concluded that primary location in the bronchial tree was not a contraindication for LT but these patients should benefit from exhaustive preoperative work-up to rule out bone metastasis [27,29].

Liver involvement

Extent of liver involvement has also been described as a prognostic factor. In a 60-patient MET series, Touzios *et al.* reported that involvement of more versus less than 50% of the liver was a major predictor of 5-year survival: 8% vs. 67% respectively [38]. The authors concluded that LT could be useful in patients with extensive liver involvement whereas hepatic resection would likely lead to poor results. As mentioned above, extensive liver involvement was an independent predictor associated with higher risk of bone metastases even in well-differentiated MET [29]. Various authors have confirmed the correlation between extent of liver involvement and survival. Lang *et al.* reported that all disease-free survivors had less than 40 to 50% of tumor liver involvement [2]. The Milan group arbitrarily set less than 50% metastatic liver involvement as a selection criterion for LT and obtained excellent disease-free survival [22].

Precise evaluation of the extent of hepatic involvement on CT-scan can be difficult in patients presenting poorly visible lesions scattered throughout the liver. To overcome this problem, a possible alternative involves preoperative screening for hepatomegaly based on estimation of liver volume from CT-scans. In a previous report, Le Treut *et al.* identified hepatomegaly, defined as explanted liver volume more than 20% greater than standard liver volume calculated using the formula proposed by Heinemann *et al.*, as an independent predictor of poor prognosis [27,39]. Results also showed that hepatomegaly was a more relevant prognostic factor than percentage of liver involvement regardless of the cutoff used for stratification [27].

Regarding liver involvement, it must be underlined that bulk alone should not considered as an absolute contraindication for LT. Large tumor size can itself seriously impair quality of life and lead to life-threatening situations. Several long-term survivors of LT for MET reported in the literature have been patients with massive tumors [15,17,25]. Bechstein and Neuhaus reported a case of LT involving a woman with disabling hepatomegaly [40]. The patient's preoperative weight was 48 kg and the explanted liver weighed 17.4 kg. One year later, metastatic nodules were detected in the transplanted liver and the patient finally succumbed 3.5 years after LT. Although survival was less than 5 years, this outcome seems acceptable considering the severity of symptoms.

Selection criteria and prognostic scoring system

Three main series, i.e., two large retrospective series and one prospective series, have proposed criteria to select patients to undergo LT for MET [22,26,27]. As a prelude to presenting these series, however, it is important to recognize that as organs are in short supply, careful patient selection is necessary to ensure best benefit from this demanding procedure. Benefit of LT must be defined not only in terms of cancer-related factors but also of quality of life and symptom relief. However, it must also be emphasized that MET patients get no Model for End-stage Liver Disease points and thus timely procurement of a suitable liver from a deceased donor is problematic. This results in long waiting times with high risk for disease progression. In this context, the possibility of living donor LT becomes a crucial decision-making factor [41].

In 1998, Lehnert reported a metaanalysis of 103 cases involving LT for MET [26]. Only patients with complete data sets ($n = 85$) were included in multivariate analysis which identified two risk factors for poor survival: extended procedures, i.e., LT associated with UAE or duodenopancreatectomy [hazard ratio (HR) = 4.8] and age over 50 years (HR = 2.1). The 5-year survival rate was 65% in patients without either of the factors, 32% in patients with one or the other factor, and 0% in patients with both factors. Only one patient with both risk factors was alive 10 months after LT (Table 2). The author concluded that LT for MET could be effective in young patients if not be associated with extended operations. This study is subject to two major biases, i.e., analysis of cases compiled from the literature and heterogeneous fol-

low-up data. It is also interesting to note that subsequent reports have failed to confirm the age-related risk.

In 2007, the Milan group reported a prospective 24-case series of LT for MT using stringent patient selection criteria, i.e., well-differentiated endocrine carcinoma, primary tumor drained by the portal venous system, primary tumor resection before LT, extent of liver involvement less than 50%, stable disease for 6 months prior to transplant, and age under 55 years [22]. Only 10% of patients presented symptoms. The authors achieved remarkable 5-year survival rates, i.e., 90% overall and 77% disease-free. The authors drew two conclusions. The first was that further multi-institutional study was necessary to validate the proposed model before LT for MET could be considered as outside clinical trials. The second conclusion was LT for MET should not be considered as a rescue treatment for patients with no other alternatives but as a possibility for a prospective, valuable set of individuals requiring innovative approaches.

In 2008, Le Treut *et al.* reported a multicentric study compiled in France in which overall 5-year survival was 47% but disease-free 5-year survival was only 20% [27]. Multivariate analysis identified three risk factors for poor outcome, i.e., UAE, pancreatic primary tumor, and hepatomegaly as defined above. When patients who underwent UAE were excluded from calculation, pancreatic location and hepatomegaly remained as risk factors associated with a threefold increase in mortality. Based on this finding, a prognostic score was devised by assigning one point to each factor so that patients with both pancreatic primary tumor and hepatomegaly had two points, patients with one or the other factor had one point, and patients with neither factor had 0 points. The corresponding 5-year survival rates were 76%, 66%, and 12% (Fig. 3). The authors concluded that patients presenting pancreatic endocrine tumors and hepatomegaly were unlikely to benefit from LT.

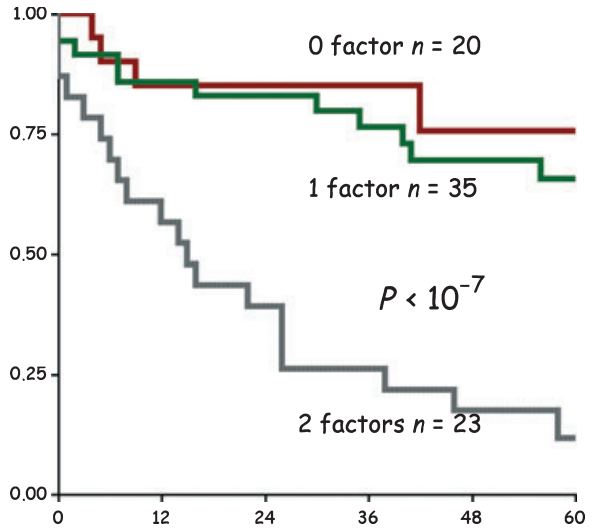

Figure 3 Actuarial survival of patients according to prognostic factors (pancreatic primary and hepatomegaly) in a 78-case multicentric series. Adapted from Le Treut *et al.* [27].

Survival rates reported by Le Treut *et al.* were disappointing in comparison with those reported by the Milan group. To assess the role of patient selection, a virtual study was performed to determine what outcome would have been obtained if the more stringent Milan criteria had been applied to the 85 patients in the French study. A total 24 patients (28%) would have met the Milan criteria and 61 (72%) would have been excluded. The 5-year survival rate would have been 66% in the selected group and 38% in the unselected group. However, after exclusion of patients who underwent UAE, the difference between the two groups would no longer have been significant. This finding suggests that further study will be needed to confirm the real efficacy of stringent patient selection criteria.

Primary hepatic endocrine carcinoma and metastases of unknown primary

Although the liver is a common site for endocrine metastases, primary hepatic endocrine carcinoma (PHEC) is rare. Classically PHEC are large, solitary, centrally located, nonfunctioning tumors [42]. However, the presence of all these features does not rule out the possibility of metastasis from an unknown primary tumor. Careful preoperative work-up including SRS and other nuclear studies, CT scan, gastrointestinal endoscopy and even staging laparotomy is mandatory to differentiate primary and secondary endocrine tumors. Histology alone is not effective.

More than 100 patients presenting PHEC have been described in the literature and most have been single case reports [43]. The first case treated by LT was reported in 1989 involving a 35-year-old woman with a symptomatic unresectable lesion [14]. This patient remained disease-free 38 months after LT. In an 8-case series of PHEC, Fenwick *et al.* reported two patients managed by LT. Disease-free survival was achieved in both cases for 45 and 95 months [42]. On the basis of their experience, the authors recommended LT as a suitable alternative in case of failure or ineligibility for hepatic resection.

In many patients presenting MET, the location of the primary tumor cannot be determined. This was the case for 14 patients (16%) who underwent LT in the multicentric French series including four patients in whom the primary tumor was subsequently found in the small bowel ($n = 3$) or the pancreatic head ($n = 1$). Unidentified primary tumors had better survival than primary

pancreatic endocrine carcinomas (Fig. 2) [27]. Based on these findings, it appears that unknown primary location is not an absolute contraindication for LT.

Conclusion

The use of LT for MET is controversial. As organs are in short supply, it is important to select patients who are most likely to benefit from this demanding procedure.

Beyond the consensual criteria, i.e., unresectable liver metastasis, no extrahepatic disease and well-differentiated tumors (Ki67 < 10%), it has been shown that the use of stringent criteria to select patients for LT could achieve spectacular overall and disease-free survival rates. In addition to requiring further study to determine the reproducibility of these results, this attitude is subject to two criticisms. The first is that most oncologists recommend a 'wait-and-see' policy for asymptomatic patients with limited liver involvement and stable disease [44]. The second is that it probably excludes many patients that might benefit greatly from symptom relief. Nevertheless, use of some kind of stringent criteria can be useful to determine the exact benefit of LT in relation to disease extent in case of MET.

Benefit cannot be defined based simply on cancer-related factors. Selection must also take into account the quality of life that LT can provide. In this respect LT could be considered as a valid option for symptomatic patients who have exhausted other treatment options. Overall survival in this case should exceed 50% at 5 years [45]. Our perusal of the literature indicates that is necessary to avoid association of several risk factors in order to enhance survival after LT for MET. We advise against use of LT in patients with pancreatic primary tumor and hepatomegaly or extensive liver involvement. Our findings also indicate that major resection in addition to LT and MVT should only be performed by highly experienced teams.

References

1. Chamberlain RS, Canes D, Brown KT, *et al.* Hepatic neuroendocrine metastases: does intervention alter outcomes? *J Am Coll Surg* 2000; **190**: 432.
2. Lang H, Oldhafer KJ, Weimann A, *et al.* Liver transplantation for metastatic neuroendocrine tumors. *Ann Surg* 1997; **225**: 347.
3. Neumann KH, Nystrom JS. Metastatic cancer of unknown origin: nonsquamous cell type. *Semin Oncol* 1982; **9**: 427.
4. Spigel DR, Hainsworth JD, Greco FA. Neuroendocrine carcinoma of unknown primary site. *Semin Oncol* 2009; **36**: 52.
5. Thompson GB, van Heerden JA, Grant CS, Carney JA, Ilstrup DM. Islet cell carcinomas of the pancreas: a twenty-year experience. *Surgery* 1988; **104**: 1011.
6. Jensen R. Natural history of digestive endocrine tumors. In: Mignon MCJ, ed. *Recent Advances in Pathophysiology and Management of Inflammatory Bowel Disease and Digestive Endocrine Tumors*. Paris: John Libbey Eurotext Publishing Co, 1999: 192–219.
7. Soreide O, Berstad T, Bakka A, *et al.* Surgical treatment as a principle in patients with advanced abdominal carcinoid tumors. *Surgery* 1992; **111**: 48.
8. Soga J, Yakuwa Y, Osaka M. Carcinoid syndrome: a statistical evaluation of 748 reported cases. *J Exp Clin Cancer Res* 1999; **18**: 133.
9. Moertel CG. Treatment of the carcinoid tumor and the malignant carcinoid syndrome. *J Clin Oncol* 1983; **1**: 727.
10. McEntee GP, Nagorney DM, Kvols LK, Moertel CG, Grant CS. Cytoreductive hepatic surgery for neuroendocrine tumors. *Surgery* 1990; **108**: 1091.
11. Makowka L, Tzakis AG, Mazzaferro V, *et al.* Transplantation of the liver for metastatic endocrine tumors of the intestine and pancreas. *Surg Gynecol Obstet* 1989; **168**: 107.
12. Alessiani M, Tzakis A, Todo S, Demetris AJ, Fung JJ, Starzl TE. Assessment of five-year experience with abdominal organ cluster transplantation. *J Am Coll Surg* 1995; **180**: 1.
13. Routley D, Ramage JK, McPeake J, Tan KC, Williams R. Orthotopic liver transplantation in the treatment of metastatic neuroendocrine tumors of the liver. *Liver Transpl Surg* 1995; **1**: 118.
14. Arnold JC, O'Grady JG, Bird GL, Calne RY, Williams R. Liver transplantation for primary and secondary hepatic apudomas. *Br J Surg* 1989; **76**: 248.
15. Frilling A, Malago M, Weber F, *et al.* Liver transplantation for patients with metastatic endocrine tumors: single-center experience with 15 patients. *Liver Transpl* 2006; **12**: 1089.
16. Frilling A, Rogiers X, Malago M, Liedke O, Kaun M, Broelsch CE. Liver transplantation in patients with liver metastases of neuroendocrine tumors. *Transplant Proc* 1998; **30**: 3298.
17. Olausson M, Friman S, Cahlin C, *et al.* Indications and results of liver transplantation in patients with neuroendocrine tumors. *World J Surg* 2002; **26**: 998.
18. Olausson M, Friman S, Herlenius G, *et al.* Orthotopic liver or multivisceral transplantation as treatment of metastatic neuroendocrine tumors. *Liver Transpl* 2007; **13**: 327.
19. Cahlin C, Friman S, Ahlman H, *et al.* Liver transplantation for metastatic neuroendocrine tumor disease. *Transplant Proc* 2003; **35**: 809.
20. Ahlman H, Friman S, Cahlin C, *et al.* Liver transplantation for treatment of metastatic neuroendocrine tumors. *Ann N Y Acad Sci* 2004; **1014**: 265.
21. Coppa J, Pulvirenti A, Schiavo M, *et al.* Resection versus transplantation for liver metastases from neuroendocrine tumors. *Transplant Proc* 2001; **33**: 1537.

22. Mazzaferro V, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? *J Hepatol* 2007; **47**: 460.
23. Lang H, Schlitt HJ, Schmidt H, *et al.* Total hepatectomy and liver transplantation for metastatic neuroendocrine tumors of the pancreas – a single center experience with ten patients. *Langenbecks Arch Surg* 1999; **384**: 370.
24. Pichlmayr R, Weimann A, Oldhafer KJ, Schlitt HJ, Tusch G, Raab R. Appraisal of transplantation for malignant tumours of the liver with special reference to early stage hepatocellular carcinoma. *Eur J Surg Oncol* 1998; **24**: 60.
25. Rosenau J, Bahr MJ, von Wasielewski R, *et al.* Ki67, E-cadherin, and p53 as prognostic indicators of long-term outcome after liver transplantation for metastatic neuroendocrine tumors. *Transplantation* 2002; **73**: 386.
26. Lehnert T. Liver transplantation for metastatic neuroendocrine carcinoma: an analysis of 103 patients. *Transplantation* 1998; **66**: 1307.
27. Le Treut YP, Gregoire E, Belghiti J, *et al.* Predictors of long-term survival after liver transplantation for metastatic endocrine tumors: an 85-case French multicentric report. *Am J Transplant* 2008; **8**: 1205.
28. van Vilsteren FG, Baskin-Bey ES, Nagorney DM, *et al.* Liver transplantation for gastroenteropancreatic neuroendocrine cancers: defining selection criteria to improve survival. *Liver Transpl* 2006; **12**: 448.
29. Leboulleux S, Dromain C, Vataire AL, *et al.* Prediction and diagnosis of bone metastases in well-differentiated gastro-entero-pancreatic endocrine cancer: a prospective comparison of whole body magnetic resonance imaging and somatostatin receptor scintigraphy. *J Clin Endocrinol Metab* 2008; **93**: 3021.
30. Putzer D, Gabriel M, Henninger B, *et al.* Bone metastases in patients with neuroendocrine tumor: 68Ga-DOTA-Tyr3-octreotide PET in comparison to CT and bone scintigraphy. *J Nucl Med* 2009; **50**: 1214.
31. Starzl TE, Todo S, Tzakis A, *et al.* Abdominal organ cluster transplantation for the treatment of upper abdominal malignancies. *Ann Surg* 1989; **210**: 374. Discussion 85–6.
32. Le Treut YP, Delpero JR, Dousset B, *et al.* Results of liver transplantation in the treatment of metastatic neuroendocrine tumors. A 31-case French multicentric report. *Ann Surg* 1997; **225**: 355.
33. Amarapurkar AD, Davies A, Ramage JK, Stangou AJ, Wight DG, Portmann BC. Proliferation of antigen MIB-1 in metastatic carcinoid tumours removed at liver transplantation: relevance to prognosis. *Eur J Gastroenterol Hepatol* 2003; **15**: 139.
34. Florman S, Toure B, Kim L, *et al.* Liver transplantation for neuroendocrine tumors. *J Gastrointest Surg* 2004; **8**: 208.
35. Solcia E, Klöppel G, Sobin L. *Histological typing of Endocrine Tumors. WHO International Histological Classification of Tumors*, 2nd edn. New York: Springer Verlag, 2000.
36. Rindi G, Kloppel G, Alhman H, *et al.* TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2006; **449**: 395.
37. Anthuber M, Jauch KW, Briegel J, Groh J, Schildberg FW. Results of liver transplantation for gastroenteropancreatic tumor metastases. *World J Surg* 1996; **20**: 73.
38. Touzios JG, Kiely JM, Pitt SC, *et al.* Neuroendocrine hepatic metastases: does aggressive management improve survival? *Ann Surg* 2005; **241**: 776. Discussion 83–5.
39. Heinemann A, Wischhusen F, Puschel K, Rogiers X. Standard liver volume in the Caucasian population. *Liver Transpl Surg* 1999; **5**: 366.
40. Bechstein WO, Neuhaus P. Liver transplantation for hepatic metastases of neuroendocrine tumors. *Ann N Y Acad Sci* 1994; **733**: 507.
41. Abreu de Carvalho LE, Troisi R, de Hemptinne B. Living donor liver transplantation combined with Whipple's procedure for metastatic gastrinoma: a clinical case with 5 years follow-up. *Acta Chir Belg* 2009; **109**: 498.
42. Fenwick SW, Wyatt JI, Toogood GJ, Lodge JP. Hepatic resection and transplantation for primary carcinoid tumors of the liver. *Ann Surg* 2004; **239**: 210.
43. Gravante G, De Liguori Carino N, Overton J, Manzia TM, Orlando G. Primary carcinoids of the liver: a review of symptoms, diagnosis and treatments. *Dig Surg* 2008; **25**: 364.
44. Cadiot G, Baudin E, Partensky C, Ruszniewski P. Digestive endocrine tumors. *Gastroenterol Clin Biol* 2006; **30**: 2S91.
45. O'Grady JG. Treatment options for other hepatic malignancies. *Liver Transpl* 2000; **6**(6 Suppl. 2): S23.
46. Dousset B, Saint-Marc O, Pitre J, Soubrane O, Houssin D, Chapuis Y. Metastatic endocrine tumors: medical treatment, surgical resection, or liver transplantation. *World J Surg* 1996; **20**: 908. Discussion 14–5.
47. Pascher A, Steinmuller T, Radke C, *et al.* Primary and secondary hepatic manifestation of neuroendocrine tumors. *Langenbecks Arch Surg* 2000; **385**: 265.
48. Ringe B, Lorf T, Dopkens K, Canelo R. Treatment of hepatic metastases from gastroenteropancreatic neuroendocrine tumors: role of liver transplantation. *World J Surg* 2001; **25**: 697.
49. Fernandez JA, Robles R, Marin C, *et al.* Role of liver transplantation in the management of metastatic neuroendocrine tumors. *Transplant Proc* 2003; **35**: 1832.
50. Marin C, Robles R, Fernandez JA, *et al.* Role of liver transplantation in the management of unresectable neuroendocrine liver metastases. *Transplant Proc* 2007; **39**: 2302.

