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Liver transplantation for symptomatic liver metastases of neuroendocrine tumours

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ABSTRACT

Numerous reports have demonstrated that liver transplantation for neuroendocrine tumour metastasis is feasible. However, perioperative risks and long-term recurrences remain significant concerns. When liver transplantation is combined with extensive intestinal or pancreatic resection, the risk is particularly high.

We report our institutional experience of liver transplantations performed for liver metastases secondary to neuroendocrine tumours, and in combination with a review of the literature, we propose a set of selection criteria. The key points include unresectable hepatic metastases of neuroendocrine origin, absence of extrahepatic metastases, symptomatic disease that is refractory to medical therapy, a Ki-67 level less than 2%, previous resection of the primary disease, and previous therapy for metastatic neuroendocrine tumour.

In our experience, the patient in the first case had, post-transplantation, rapid disease progression because of an unidentified primary, and patient in the second case had primary non-function of the liver graft, requiring urgent re-transplantation. More recently, two liver transplantations were successfully performed. The indications were, in the first case, refractory hormonal secretion and, in the other, secondary biliary cirrhosis attributable to hepatic artery therapy with tumour *in situ*. Subclinical and stable recurrent disease has been detected by scintigraphy in the mesentery and lumbar spine in the former patient. A mesenteric recurrence developed in the latter patient 2 years post transplantation and was subsequently completely resected. At 4 and 5 years post transplantation, both patients are symptom-free.

Recurrence after transplantation remains a significant concern, even with careful patient selection, but recurrences may remain indolent. If recurrences are progressive, they may still be amenable to additional medical or surgical therapy. A national or international consensus between oncologists and transplant specialists regarding the indications for liver transplantation is vital, because future progress will depend on careful patient selection and prospective study.

KEY WORDS

Liver transplantation, neuroendocrine tumour, liver metastases

1. INTRODUCTION

A role for liver transplantation in the treatment of liver metastasis from neuroendocrine tumours (mNET) is recognized and yet still undefined[1,2]. A review of the literature reveals a collection of studies with heterogeneous populations, wide-ranging tumour burdens, and a variety of operative procedures.

The four largest institutional studies published have included between 15 and 19 patients (Table I). The 5-year overall survival in those series ranged between 67% and 90%; the 5-year recurrence-free survival rates were much lower, between 20% and 48%. In the experience of the group from Hannover, Germany, long-term survival was associated with a Ki-67 index of less than 5% and normal E-cadherin expression[4]. In the Swedish report, postoperative mortality after multi-visceral transplantation was very high at 40%[7]. The Mayo Clinic published the only prospective study protocol conducted to date[6]. The Mayo criteria for inclusion were a prior complete resection of the primary tumour; bilobar, unresectable, and progressive liver disease; and the absence of extrahepatic disease. The exclusion criteria for the study included prior nonselective hepatic arterial embolization, a rectal primary, anaplastic or poorly differentiated primary NET, or right atrial pressure exceeding 15 mmHg. Long-term survival has yet to be reported. Finally, a series from Essen, Germany, described a heterogeneous cohort of patients with lung, pancreas, ileum, and colon primaries, with operations such as deceased-donor liver, living-donor liver, and cluster

TABLE I Case series and reviews of liver transplantation for metastatic neuroendocrine tumours

Reference	*Patients (n)*			*Concurrent resections*	*Follow-up (years)*	*OS (%)*	*RFS (%)*
	Overall	*OLT*	*MVT*				
Lehnert *et al.,* 1998 [3]	103	103	0	39	5	47	24
Rosenau *et al.,* 2002 [4]	19	19	0	6	5	80	21
Frilling *et al.,* 2006 [5]	15	14	1	2	5	67.2	48.3
van Vilsteren *et al.,* 2006 [6]	19	19	0	1	1	88	80
Olausson *et al.,* 2007 [7]	15	10	5	5	5	90[a]	20
Le Treut *et al.,* 2008 [8]	85	85	0	34	5	47	20
Gedaly *et al.,* 2011 [9]	150	133	13	—	5	49	32
Máthé *et al.,* 2011 [10]	89	89	0	45	5	44	—

[a] Includes only the OLT patients.
OLT = orthotopic liver transplantation; MVT = multi-visceral transplantation; OS = overall survival; RFS = recurrence-free survival.

transplantation[5]. In that series, the perioperative mortality was also quite high at 20%.

Three multicenter reviews[5,8,10] and a retrospective review of the United Network for Organ Sharing (UNOS) database[9] reported the prognostic factors associated with long-term survival (Table I). The long-term survivals reported in those reviews were quite similar: between 44% and 49% at 5 years post transplantation. In 2008, the multivariate analysis in a French series of 85 patients identified 3 risk factors for poor outcome: concomitant upper abdominal exenteration, duodenal or pancreatic primary, and hepatomegaly. Mathé *et al.*[10] reviewed the literature for documented cases of liver transplantation for pancreatic neuroendocrine tumours. The analysis of that series of 89 patients identified an age greater than 55 years and simultaneous pancreatic resection and liver transplantation to be risk factors for poor survival. Of the 9 patients who died within a month of the operation, 8 had undergone simultaneous resection and transplantation procedures. The multivariate analysis of an earlier European series of 103 patients showed that greater age (>50 years) and combined resection and transplantation procedures were adverse prognostic factors. The UNOS review demonstrated that post-transplantation survival was comparable to that in transplantation for hepatocellular carcinoma[9]. Interestingly, patients whose waiting time was longer than the median of 67 days had better outcomes in terms of 5-year survival, although an explanation of that finding was not presented[9]. A different analysis of the UNOS database over a similar period found that patients transplanted since 2002 enjoyed an improved overall survival of 57.8%[11].

The purpose of the present analysis was to report the institutional experience at a Canadian centre. In combination with the literature review, we propose a set of selection criteria for liver transplantation for MNET.

2. METHODS

Patients referred to the London Regional Cancer Programme for MNET are presented at a multidisciplinary tumour board. All patients are assessed by an oncologist, a nuclear medicine physician specializing in radioisotope therapy, an interventional radiologist, a surgical oncologist, a hepatobiliary surgeon, and a pathologist. The standard investigations for initial assessment and follow-up included abdominal computed tomography (CT) imaging, multiphasic CT imaging of liver, CT imaging of other disease-bearing regions, somatostatin receptor scintigraphy, MIBG scintigraphy for all non-pancreatic neuroendocrine neoplasms, complete blood count, creatinine, urea, international normalized ratio, serum biochemistry, liver function tests, and plasma chromogranin A. All patients are required to have pathology specifying the Ki-67 index. Patients undergoing potentially renotoxic therapies such radioisotope targeted therapy, hepatic arterial chemoembolization (TACE), or certain chemotherapies will have their glomerular filtration rate determined on a nuclear medicine renal scan. Select patients may undergo magnetic resonance imaging of the liver at the discretion of the tumour board. All patients were given slow-release octreotide (Sandostatin LAR: Novartis Oncology Canada, Dorval, QC).

The standard treatment at the London Regional Cancer Programme for MNET includes systemic chemotherapy combined with hepatic artery radioisotope therapy. The chemotherapy regimen is 5-fluorouracil 250 mg/m^2 by continuous intravenous infusion daily for 14 days starting day 1 or oral capecitabine 2000 mg/m^2 daily for 14 days; epirubicin 50 mg/m^2 intravenously on day 8; and carboplatin AUC 5 intravenously on day 8. The chemotherapy is combined with intrahepatic radioisotope therapy given on day 8, as ^{111}In-octretate 3.7 GBq or ^{131}MIBG 5.55–7.4 GBq (depending on patient weight). Hepatic

TACE included doxorubicin 50 mg in 10 mL ethiodized oil, or cisplatin 50 mg with ^{131}I–ethiodized oil 10 mL.

All candidates for transplantation are assessed and approved by the multidisciplinary liver transplantation team at the University Hospital, University of Western Ontario. All candidates are assessed by a hepatologist, a transplant surgeon, a nurse practitioner, and a social worker before being wait-listed. Orthotopic liver transplantations are performed using the caval replacement technique. Post-transplant immunosuppression includes tacrolimus, mycophenolate mofetil, and prednisone. No antibody induction immunosuppression is used.

Follow-up after transplantation includes routine clinical visits at the neuroendocrine tumour clinic and the transplant hepatology clinic. Routine laboratory tests (including a complete blood count, renal and liver function, international normalized ratio, electrolytes, Ca, Mg, and plasma chromogranin A) and CT imaging of the thorax, abdomen, and pelvis are performed every 6 months. All recurrences or clinical changes are discussed at the multidisciplinary tumour board.

3. RESULTS

3.1 Early Experience

In 1988, a 35-year-old woman underwent liver transplantation without perioperative complications for a MNET of presumed hepatic origin. She had first presented 17 years before transplantation with diarrhea, nausea, anorexia, and asthma. No surgical or antineoplastic therapy was given before transplantation. At 9 months post transplantation, she developed a mass in the head of the pancreas and numerous retroperitoneal lesions for which enucleation of the pancreatic primary and debulking of the retroperitoneal metastases were performed. The patient died of metastatic disease 3 years after transplantation.

In 1991, a 61-year-old man underwent liver transplantation for hepatic metastases from a gastrointestinal NET. At 20 years before transplantation, the patient had undergone resection of an ileal primary and right hepatectomy for metastatic disease. At wait-listing, the remnant left lobe had been almost completely replaced by recurrent tumour. The transplantation was complicated by primary nonfunction of the graft; repeat transplantation was performed urgently on the 4th postoperative day. Unfortunately, this patient died of sepsis and multiorgan failure 1 month later.

3.2 Recent Experience

In 2007, a 65-year-old man presented with symptoms of secondary biliary cirrhosis because of a complication of TACE for MNET. This patient had initially presented 7 years previously with diarrhea and flushing, at which point the primary tumour in the ileum was resected and the hepatic metastases were diagnosed. The Ki-67 index was 1%. Treatment for the metastatic disease included long-acting somatostatin analogues and two treatments of TACE combined with radioisotope therapy. The second treatment was complicated by biliary abscesses and strictures requiring multiple endoscopic and percutaneous drainage procedures. Eventually, secondary biliary cirrhosis developed, with jaundice, anorexia, weight loss, abdominal cramps, and fatigue.

At transplantation, the disease burden consisted of a 3-cm mass in the atrophic right lobe, with no evidence of extrahepatic disease. After liver transplantation, the patient had an uneventful recovery. At 1 year post transplantation, chronic renal dysfunction because of calcineurin inhibitor toxicity prompted conversion of immunosuppression from tacrolimus to sirolimus. At 30 months post transplant, a recurrence in the small bowel mesentery was noted; it was subsequently resected. The patient is now 5 years post transplantation without evidence of disease.

A 34-year-old man presented with unresectable metastatic disease and progressive symptoms of carcinoid syndrome that were refractory to slow-release octreotide (monthly doses up to 240 mg). His symptoms were dominated by severe diarrhea and flushing. There was also evidence of asymptomatic endomyocardial fibrosis and moderate tricuspid regurgitation. Pre-transplant treatment of the MNET included 7 combined chemotherapy and hepatic artery radio-nucleotide therapy procedures. In 2007, 8 months before transplantation, a jejunal resection of the primary disease was performed. The Ki-67 index was 1%. Hepatomegaly because of innumerable carcinoid metastases was noted. Additional consultation with the cardiology service found an acceptable risk for transplantation despite the moderate valvular disease. The post-transplant recovery was uncomplicated, and this patient is now 4 years post transplant with no symptoms. Two areas of questionable recurrence have been noted in the mesentery and the lumbar spine on the somatostatin receptor scintigraphy, although no mass has been demonstrated on CT imaging. The areas have been stable on subsequent scintigraphy exams.

4. DISCUSSION AND CONCLUSIONS

The early experience of our centre with liver transplantation for MNET highlights the major risks associated the procedure. The rapid progression of unidentified primary tumours to unresectable disease can occur coincident with the introduction of immunosuppressive therapy. It is vital that this type of disease recurrence be minimized through careful and detailed work-up of potential candidates. Also, liver transplantation in general is associated with significant perioperative mortality and morbidity risks. Advances in perioperative transplant care have brought those risks to new lows, but the clinical benefit must be weighed against

the perioperative and long-term risks associated with liver transplantation.

The need for defined patient selection criteria is vital to validating a specific role of liver transplantation in the treatment of liver metastasis from neuroendocrine tumours. The minimum goals of liver transplantation should include a complete oncologic resection (R0); symptomatic relief of the endocrine syndrome, if necessary; and a reasonable chance of long-term cure. Most publications have described small study populations and only one study was prospective[6]. The data necessary to the formulation of selection criteria are based on this limited published evidence, but only prospective study will establish the role in the future.

Multivariate analysis of published studies[3] and a review of the French experience[8] demonstrate several prognostic factors associated with long-term success. The significant factors included older age (>50 years[3] to 55 years[8]), concomitant radical resections[3,8,10], hepatomegaly[8], and pancreatic or duodenal primaries[8], all of which were associated with poor long-term outcomes. Here, we propose criteria (Table II) in addition to those used in the Mayo Clinic study. The goal is to balance clinical benefit in terms of overall survival, disease-free survival, and symptomatic relief against patient risk and judicious organ utilization.

The site of primary disease must be identified and resected, including all involved lymph nodes, before the liver transplantation. This sequencing avoids the combination of pancreatic or radical intestinal resections with the transplantation operation, which has a very high perioperative risk[8,10]. Separation of the operations avoids the possibility of an unresectable primary and a discarded graft or a prolonged cold ischemia time for the back-up recipient. Prior resection also provides a comprehensive histopathologic evaluation of the NET—in particular, Ki-67 index, mitotic count, and degree of differentiation, which are critical to patient selection for transplantation.

TABLE II Selection criteria for liver transplantation for liver metastases of neuroendocrine tumours

Criterion	*Centre*		
	UWO	*Mayo*[6]	*ENETS*[12]
Previous resection of primary disease site	+	+	+
Unresectable hepatic metastases	+	+	+
Absence of extrahepatic metastases	+	+	+
Low-grade tumour with Ki-67 < 2%	+		+[a]
Duration of stable disease (months) before listing for transplantation[b]	12	6	+
Trial of therapy for metastatic neuroendocrine tumour	+		+
Refractory symptomatic disease	+		+
Otherwise eligible for transplantation	+	+	

[a] The suggestion of the ENETS consensus was that Ki-67 should not, as a maximum, exceed 10%.

[b] The UWO calculates its waiting period from the date of the initial consultation for metastatic neuroendocrine tumour. The Mayo clinic calculates its waiting period from the date of operation for the primary disease.

UWO = University of Western Ontario; Mayo = May Clinic; ENETS = European Neuroendocrine Tumor Society.

Only unresectable liver-only disease should be considered for transplantation, and the projected surgical outcome should be R0. Any resectable hepatic disease should undergo partial hepatectomy to avoid the complications related to liver transplantation and to obviate the risk of long-term immunosuppression. Previous hepatic resection or hepatic angio-embolization can make subsequent transplantation technically more difficult, but is certainly not an absolute contraindication.

Oncologic therapy for liver metastasis from NET should be considered according to local practice and NET multidisciplinary board decision. Transcatheter arterial embolization and TACE are generally considered standard therapies[2] and may be able to provide a significant period of disease control. In our view, hepatic artery therapy, including the newer selective internal radiation therapy, need not be avoided as previously suggested as a relative technical contraindication to transplantation[5]. Therapy is particularly important because the waiting time for a graft is uncertain. To ensure the absence of extrahepatic disease, any suspicion of such disease should be addressed by an exploratory laparoscopy or laparotomy or by a biopsy (depending on the site) before wait-listing proceeds[6,5].

Recurrence after transplantation remains a significant problem, although some patients remain manageable either surgically or medically. Selection of patients for transplantation should focus on those with the least chance of developing aggressive recurrence after transplantation. The tumour should be low grade, G1, with a Ki-67 index less than 2% and fewer than 2 mitoses per high-power field[12]. In the future, it is possible that this Ki-67 limit maybe increased to 10%[13].

The year of clinical observation provides another important tool for assessing the biologic behaviour of the tumour and for allowing subclinical metastases to declare themselves. This period could begin retrospectively from the initial date of diagnosis of the liver metastases, when the histopathology and the degree of disease burden are established, continuing until the day of listing for liver transplantation. As part of their study criteria, van Vilsteren *et al.*[6] included a similar 6-month waiting period between resection of the primary tumour and liver transplantation to allow for the development of recurrent disease. During the minimum 12-month wait, resection of the primary tumour and an initial trial of standard therapy for mNET could be realized. The disease burden would

be documented with serial cross-sectional imaging and scintigraphy.

The selection criteria for transplantation should ensure a clinical benefit. A survival benefit under such specific conditions will be difficult to demonstrate for such a rare disease. As a result, the indication of symptom relief alone must outweigh the significant risks of both the operation and the subsequent immunosuppression[3,5,8,14]. The indications can include symptoms of intractable carcinoid syndrome, hepatomegaly, secondary biliary cirrhosis because of complications from prior oncologic therapy, or liver failure because of metastatic invasion. These symptoms must be the cause of moderate or severe debility, which would lead to an obvious improvement in the post-transplantation quality of life.

The small sample size in the present report limits our ability to definitively determine the feasibility of these proposed selection criteria. However, our initial experience should lay the groundwork for further discussion or a consensus conference with the participation of oncologists and transplant specialists alike. In conjunction with the published literature, the present study demonstrates that transplantation is feasible and that the key to long-term success stems from careful patient selection. That selectivity will be further accentuated by the significant risk of recurrence, even with very conservative criteria. The hope is that such failures will remain indolent and amenable to subsequent surgical resection or oncologic therapy. Thus, it may be possible to provide adequate disease control such that long-term survival is not jeopardized by recurrences post transplantation. Future consideration might also be given to alternative immunosuppression regimens that include everolimus (an inhibitor of the mammalian target of rapamycin) for its antineoplastic[15] and immunosuppressive effects. A consensus conference will be necessary to set the stage for a multicentre prospective study of liver transplantation for mNET in Canada. It is crucial that any set of criteria be studied prospectively to permit proper interpretation and application of the study outcomes.

5. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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