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REVIEW ARTICLE

Liver transplantation for neuroendocrine tumour liver metastases

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Abstract

Objective: Search and review of available literature were made to define the indications for and timing of liver transplantation for neuroendocrine tumour (NET) liver metastases.

Methods: Electronic bibliographical databases were searched. Prospective and retrospective cohort studies and case–controlled studies were used for qualitative and quantitative synthesis of the systematic review. Reports of patients with liver transplantation alone for NET liver metastases of any origin or combined with resection of extrahepatic tumour deposits were recruited.

Results: The number of patients who have undergone liver transplantation for NET liver metastases is 706. The post-transplant 5-year survival rate from the time of diagnosis was approximately 70%. NET patients with metastases confined to the liver and not poorly differentiated are favourable candidates for liver transplantation. Selection of patients based on evolution of tumours over 6 months is not recommended.

Conclusion: Non-resectable NET liver metastasis resistant to medical treatment and confined to the liver is an accepted indication for liver transplantation.

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Introduction

Neuroendocrine tumour (NET) metastasis localized to the liver is an accepted indication for liver transplantation as such tumours have a low biological aggressiveness in terms of malignancy and are slow growing. Moreover, the long-term results are comparable with and in some cases even better than those of transplantations performed for primary liver cancer.[1] However, compared with non-malignant conditions, NET liver metastasis may result in an inferior outcome of transplantation.[2] In the face of the scarcity of donated organs and recent improved results of non-surgical treatment for NET liver metastases, controversy over patient selection and timing for liver transplantation continues. A systematic review of the recent literature was made to answer the following questions:

1 In patients with non-resectable NET liver metastases, does liver transplantation improve the outcome as opposed to R2 liver resection (debulking) or non-surgical treatment?
2 In patients with NET liver metastases, which selection criteria should be used for liver transplantation in order to improve the outcome (disease-free survival, overall survival, quality of life)?
3 In patients with NET liver metastases and consideration for liver transplantation, does a delay (>6 months) to assess tumour progression before transplantation improve the selection of patients as opposed to early transplantation (<6 months)?

The paper is based on a previous communication to the 2012 International Consensus Conference on Neuroendocrine Liver Metastases, 12–13 December 2012, London, UK.

4 In patients with NET liver metastases listed for transplantation, do downstaging techniques (locally ablative techniques, percutaneous liver-directed techniques, peptide receptor radionuclide treatment, chemotherapy, target therapy and biotherapy) improve the post-transplant outcome?
5 In patients with non-resectable NET liver metastases, does living donor liver transplantation (LDLT) improve the outcome as opposed to deceased donor liver transplantation (DDLT) or non-surgical treatment?
6 Does the outcome of the recipient justify the risk of the donor in the setting of liver transplantation for NET liver metastases?

Methods

Searches

The following electronic bibliographic databases were searched: MEDLINE, EMBASE and the Cochrane Library [Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and Central Register of Controlled Trials (CENTRAL)].[3]

Types of study included

Prospective and retrospective comparative cohort studies and case-controlled studies were used for the qualitative and quantitative synthesis of the systematic review. Patient series were included in a separate database for descriptive purposes. Single patient reports were not included. The review protocol was published by Stump *et al.*[3]

Patient population

The patient population included in this analysis was composed of (i) patients with non-resectable NET liver metastases of any origin, patients who underwent liver transplantation or palliative liver resection or non-surgical treatment, (ii) patients with pre-operative/intra-operative diagnosis of primary tumours and lymph node secondaries and (iii) patients with liver transplantation combined with surgical resection of extrahepatic tumour deposits.

Exclusion criteria

Patients under the age of 18 years and studies that did not report overall survival were excluded.

Comparator/control

Liver transplantation versus palliative liver resection versus non-surgical treatment.

Outcomes

Primary outcome: overall survival
Secondary outcome: disease-free survival

Results

The literature search resulted in 46 relevant publications on liver transplantation for NET liver metastasis (Fig. 1). A total of 873 patients were reported in these publications. Excluding obvious overlaps or duplications, the number of liver transplantations for NET liver metastases was 706. The reported 5-year overall survival rates in the different series varied from 0% to 100%. Disease-free survival was not routinely reported but the reported 5-year disease-free survival rates varied from 0 to 80%. Most reports described frequent and early recurrences of NET after liver transplantation. The wide ranges of survival rates reflect the small number of patients in each report, short duration of follow-up and significant selection bias. In series with more than 100 patients,[1,4] the average 5-year overall survival rate and disease-free survival rate were about 50% and 30%, respectively (Table 1). There was no study that addressed the quality of life after liver transplantation.

Table 1 NET liver metastases and liver transplantation: recurrence and survival rates

	Rosenau *et al.* (2002)[12]	van Vilsteren *et al.* (2006)[14]	Olausson *et al.* (2007)[13]	Le Treut *et al.* (2008)[7]	Frilling *et al.* (2009)[5]	Mazzaferro *et al.* (2010)[16]	Gedaly *et al.* (2011)[1]	Nguyen *et al.* (2011)[4]	Le Treut *et al.* (2013)[8]
Number of patients	19	19	15	85	15	24	150	184	213
5-year post-transplant survival	80%	NR	90%	47%	67.2%	90%	49%	49.2%	52%
5-year post-transplant disease-free survival	22%	NR	18%	20%	48.3%	77%	32%	NR	30%
Number of patients surviving without disease	3	16	4	NR	5	NR	NR	NR	63
5-year survival after diagnosis of liver metastasis	NR	NR	NR	69%	NR	NR	NR	NR	73%

NR, Not reported.

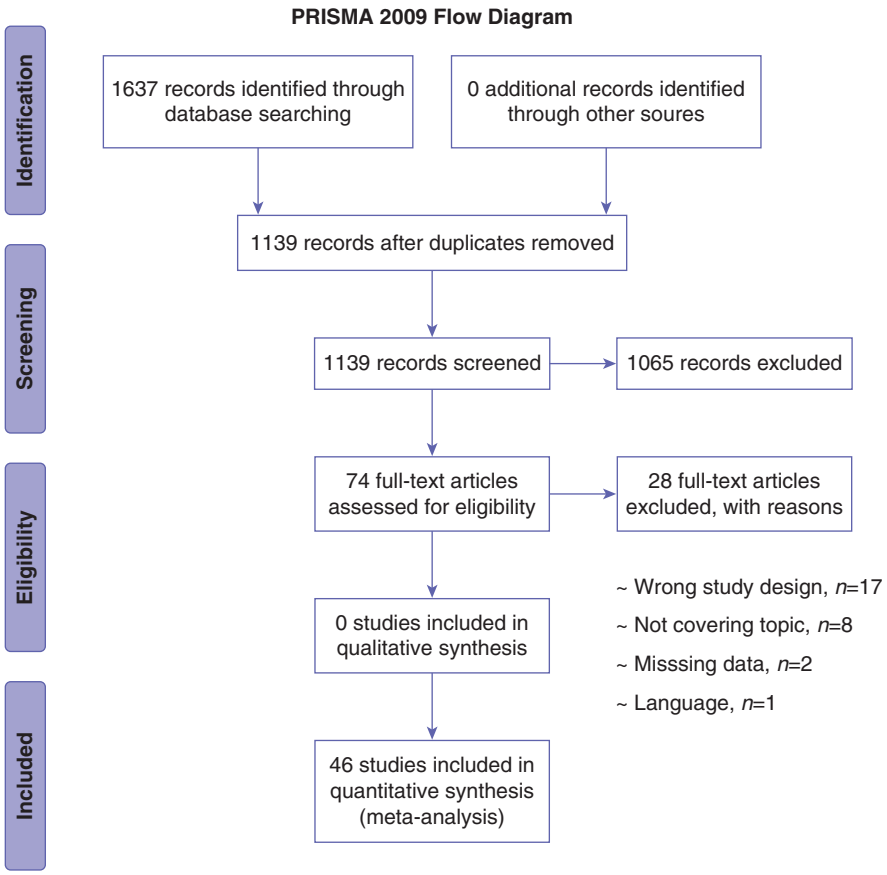

Figure 1 Flow diagram demonstrating retrieval of reports of neuroendocrine tumour liver-metastases from the literature

Response to Question 1

There was no prospective randomized trial to show the superiority of liver transplantation over resection or non-surgical treatment. In the very few comparative studies[5,6] that included resection or non-surgical treatment as a control, the overall 5-year survival of transplanted patients was about the same as non-transplanted patients, but the rate of 5-year disease-free survival was higher for transplanted patients (50% versus 34%) (Table 1). As liver transplantation is often performed after all other treatment modalities have been exhausted, evaluation of outcome using post-transplant survival duration may not be valid when liver transplantation is compared with non-transplant treatment. A better measurement would be duration of survival after diagnosis of liver metastases. The rate of 5-year survival after diagnosis of liver metastases was 69–84% for patients who received transplantation,[7,8] 34% for patients who underwent non-surgical treatment,[5,6] and 20–30% for patients not treated.[9,10] An alternative measurement would be survival from the time of uncontrolled tumour progression because transplantation is frequently performed when the tumour is observed growing at a faster pace. However, such survival data were not available in the reports. Because of the highly selective nature of patients chosen for non-surgical treatment, resection or transplantation, randomized controlled trials evaluating patient outcomes with these treatment modalities would be difficult to perform.

Response to Question 2

Patients with NET liver metastases were frequently subjected to liver transplantation when surgical or non-surgical treatment failed to control the tumours. The risk factors for recurrence or inferior survival derived from experiences at major centres were: age over 50 years, a symptomatic tumour, a primary tumour in the pancreas or a non-gastrointestinal location, a non-carcinoid tumour, a high Ki-67 index, involvement of liver >50% and poor tumour differentiation.[1,4–7,11–15] Multivisceral transplantation and additional major resection were found to have adverse effects on long-term outcome.[8,13] Thus, extrahepatic spread and a primary tumour not resected (necessitating an additional procedure or graft) are to be considered definite contraindications to liver transplantation. However, the majority of the adverse risk factors have not been validated in prospective studies. Moreover, the risk factors were not all derived from multivariate analysis (Table 2). Based on multivariate analysis of the data of 213 patients in the European Liver Transplant Registry, the significant risk factors

Table 2 NET liver metastases and liver transplantation: risk factors for recurrence and survival

	Rosenau *et al.* (2002)[12]	van Vilsteren *et al.* (2006)[14]	Olausson *et al.* (2007)[13]	Le Treut *et al.* (2008)[7]	Frilling *et al.* (2009)[5]	Mazzaferro *et al.* (2010)[16]	Gedaly *et al.* (2011)[1]	Nguyen *et al.* (2011)[4]	Le Treut *et al.* (2013)[8]
Age over 50 years	No	No	No	No	No	Yes	No	No	Yes
Symptomatic tumour	No	No	No	No	No	Yes	NR	NR	NR
Primary tumour in the pancreas	No	No	No	Yes	NR	Yes	NR	NR	Yes
Non-carcinoid tumour	No	No	NR	No	NR	Yes	No	NR	NR
Primary tumour at non-portal drainage site	No	NR	No	NR	NR	Yes	NR	NR	NR
Ki-67 index (%) or aberrant E-cadherin	Yes	No	Yes >10	NR	Yes >10	Yes >5	NR	NR	NR
Liver involvement >50% of standard liver volume or hepatomegaly	NR	NR	No	Yes	No	Yes	NR	NR	Yes
Extrahepatic spread	Yes	NR	Yes	Yes	Yes	Yes	No	No	Yes
Primary tumour not resected	Yes	NR	Yes	Yes	Yes	Yes	No	No	Yes
Stable period (months)	NR	Yes <6	NR	NR	Yes <6	Yes <6	Yes <2	Yes	NR
Multivisceral transplant or additional major resection	Yes	NR	Yes	Yes	Yes	Yes	No	No	Yes
Histology (poor differentiation)	NR	No	NR	Yes	Yes	NR	NR	NR	Yes

NET, neuroendocrine tumour; NR, Not reported.

were multivisceral resections or multivisceral grafts, a poorly differentiated tumour and hepatomegaly as a surrogate of intrahepatic tumour burden.[8] If patients without such risk factors are selected, the rate of 5-year survival can reach 60–80%.[8] In summary, liver transplantation is suitable for patients with disease burden confined to the liver. Patients with well-differentiated tumours appeared to be the best candidates for liver transplantation.

Response to Question 3

In a study by Mazzaferro *et al.*, a delay (>6 months) to assess tumour progression before transplantation was arbitrarily chosen as an inclusion criterion, and remarkable transplant results were produced.[16] However, the cause-to-effect relationship between this criterion and the results was not proven as there were many other stringent selection parameters in the criteria adopted by them. It is possible to assume that NET liver metastasis having evolved over a long time would have a better outcome after liver transplantation (Fig. 2). This hypothesis has found confirmation in retrospective data on transplantation for NET.[1] Currently, many physicians have the perception that asymptomatic patients with stable diseases may not require liver transplantation whereas patients with progressive diseases refractory to non-surgical treatment may require liver transplantation. The available evidence does not permit any strong conclusion. Further prospective studies are needed before 'disease with a stable period of 6 months' can be established as an important criterion in the selection.

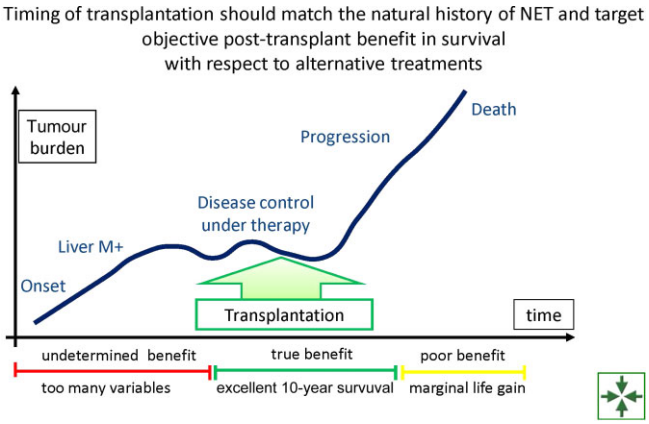

Figure 2 Benefit of liver transplantation for neuroendocrine tumour (NET) metastases in liver

Response to Question 4

There are scarce data on the improvement of outcome of liver transplantation for NET liver metastases by downstaging of disease. Analysis of the 35 000 patients in the Surveillance, Epidemiology and End Results (SEER) database demonstrated that the use of somatostatin analogues correlates with survival

benefit.[17] It is expected that a similar benefit should be observed in a pre-transplant setting. However, data are not available. Properly designed studies would address the issue of the possible ameliorating effect of downstaging therapies on prolonging the time to progression of tumours and hence delaying the need for transplantation.

Response to Question 5

There are only 21 reported LDLTs for NET liver metastases.[1,11,14,15,18] No separate analysis of the efficacy of LDLT versus DDLT was done in these reports. It is therefore impossible to identify any advantage of LDLT over DDLT or vice versa. As patients with NET liver metastases may not have access to deceased donor organs owing to organ allocation regulations, LDLT may be their only hope of a cure. However, as the long-term results of LDLT for NET liver metastases are not known, criteria for selection of patients for LDLT should not differ from those for DDLT. Further studies are needed to document the advantages of LDLT over DDLT, if any.

Response to Question 6

The outcome of LDLT for NET liver metastases is not known exactly. Assuming the 5-year overall survival rate of LDLT for NET liver metastases is similar to that of DDLT or that for hepatocellular carcinoma (60%), it seems that such an outcome can justify the 0.1–0.5% mortality risk posed to donors.[19]

Summary

- In carefully selected patients, non-resectable NET liver metastasis resistant to medical treatment is an accepted indication for liver transplantation. (Recommendation: Strong)
- NET patients with metastases confined to the liver and not poorly differentiated are favourable candidates for liver transplantation. (Recommendation: Strong)
- The selection of patients with NET liver metastases based on evolution of tumour over 6 months is still controversial. The available evidence does not allow any conclusion. (Recommendation: Weak)
- Balancing the survival rate of NET liver metastases patients after transplantation with the donor risk, LDLT may be justified. The criteria for selection of patients with NET liver metastases for LDLT should not differ from those for DDLT. (Recommendation: Weak)

Future perspectives

As liver transplantation is uncommonly performed for NET liver metastases and data are scarce, a strong recommendation for most of the concerns of liver transplantation cannot be made at the present time. Documentation of benefits of liver transplantation for NET liver metastases is likely in a subgroup of patients. However, this would require detailed and prospective collection of clinical, radiological and biological data. A worldwide registry of liver transplantations for NET liver metastases is needed.

Conflicts of interest

None declared.

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