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Long term results of hepatic resection or orthotopic liver transplantation in patients with liver metastases from gastrointestinal neuroendocrine tumors

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Abstract. Hepatic metastases are one of the most important prognostic factors for survival among patients affected by gastrointestinal neuroendocrine tumors (NETs). The present study aims to evaluate the impact of surgery, including hepatic resection or orthotopic liver transplantation (OLT), on the outcome of patients affected by hepatic metastases from NETs, in terms of overall survival (OS). In this multicentric retrospective study, data was collected on 26 patients, who underwent surgery for hepatic metastases from NETs in two Italian University Clinics between January 1990 and December 2012; of which, 22 patients underwent hepatic resective surgery and 4 patients OLT. Hepatic metastases were synchronous in the 53.8% of cases and metachronous in the 46.2% of cases. The median number of resected hepatic metastases was 3. Surgical radicalness (R0) was reached in the 84.6% of cases. In total, 57.7% of patients had a recurrence, 66.7% of which were intra- and 33.3% extra-hepatic. The OS of patients that underwent hepatic resections and OLT was 44.9% [95% confidence interval (CI95), 26.0-77.7%] and 50% (CI95, 12.5-100.0%) at 5 years, respectively. Although the data regarding the survival of patients receiving surgery for hepatic metastases from NETs are encouraging, randomized clinical trials are necessary to more adequately evaluate the effect of surgery on survival of this group of patients.

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Abbreviations: NET, neuroendocrine tumor; OLT, orthotopic liver transplantation

Key words: gastroenteropancreatic neuroendocrine tumors, liver metastases, orthotopic liver transplantation, hepatic resection, overall survival

Introduction

Neuroendocrine tumors (NETs) include numerous heterogeneous types of cancers with extremely varied biological behaviors (1-3). The literature published on the subject commonly divides NETs into two major classes, based on their primary origin: Pancreatic neuroendocrine (islet cell) tumors and gastrointestinal neuroendocrine tumors (carcinoids) (4-6). In particular, gastrointestinal NETs are usually characterized by a slow growth pattern, are commonly diagnosed in the advanced stages of disease (5,7-12), and present with liver metastases in 50-75% of cases (13-15).

The frequent occurrence of liver secondaries in patients affected by gastrointestinal NETs is a clear sign of clinical controversy. NETs represent a rare group of neoplastic diseases; therefore, affected patients are recommended to be transferred into larger, more experienced centers that can more appropriately treat rare hepatic metastasis. Furthermore, although metastatic malignancies were once commonly considered as a terminal neoplastic stage, numerous therapeutic options have now been introduced in order to improve the quantity and quality of life in patients affected by rare liver metastasis (11,16-18).

However, the role of liver surgery for patients with metastatic gastrointestinal NETs remains an argument of great debate; the inert growth and long term natural history of gastrointestinal NETs makes determining the real effectiveness of the hepatic surgical approach on overall survival (OS) even more challenging. In particular, in an analysis of 13,715 patients conducted by Modlin *et al* (3), synchronous distant metastases were already evident in the 12.9% of patients with gastrointestinal NETs, and demonstrated a 5-year OS rate of 67.2%. As a consequence, the widely promulgated benignity of these neoplasms has been brought into question, so that the current literature recognizes their malignant potential (2,19-22).

In patients with NETs, the occurrence of hepatic secondaries is one of the most important prognostic factors for survival (11,23-25). Therefore, the present study aims to evaluate the impact of surgery, including hepatic resection and orthotopic liver transplantation (OLT), on the outcome of patients affected by hepatic metastases from NETs, in terms of OS.

Materials and methods

Data collection. For this multicentric retrospective study, data was collected on 26 patients, who underwent surgery for hepatic metastases from NETs at the Departments of Surgery of 'Santa Maria della Misericordia' University Hospital (Udine, Italy) and 'Ospedali Riuniti Umberto I, G.M. Lancisi, G. Salesi' University Hospital (Ancona, Italy) between January 1990 and December 2012; of which, 22 patients underwent hepatic resective surgery and 4 underwent OLT. In the present study, only patients treated with surgical treatment were considered; as a result, none of the included patients underwent intraoperative treatments associated with surgical resection.

The present study was conducted in accordance with the Declaration of Helsinki and following the dictates of the general authorization to process personal data for scientific research purposes by the Italian Data Protection Authority (Rome, Italy). Furthermore, the present study was also approved by the Internal Review Board of the Department of Experimental and Clinical Medical Sciences, University of Udine (Udine, Italy).

Data collection took into consideration patients' characteristics (age at diagnosis, presence of symptoms, bioumoral markers and imaging findings), tumor characteristics (histotype, stage, primary tumor and secondary localizations), and treatments (hepatic resections or OLT). The main outcome considered in the present study was the OS of the included patients.

Patient profiling. The imaging techniques used to diagnose and stage patients affected by NETs included chest-abdominal-pelvic computerized tomography (CT) scans, magnetic resonance imaging (MRI), octreoscan and positron emission tomography- computed tomography (PET/CT) with 111In-pentetreotide. CT or PET/CT scans obtained by initial diagnosis were also used to determine the percentage of diseased hepatic parenchyma. In addition, hepatic parenchyma involvement was divided into lobar and bi-lobar, and the major diameter of the greatest hepatic metastasis was also registered.

Every patient was investigated for the presence of symptoms, including tachycardia or flushing. Among the bioumoral markers of NETs, the following were routinely preoperatively tested: Urinary vanilmandelic acid dosage in the 24 h; urinary catecolamine dosage; urinary 5-idrossi-indolo-acetic acid dosage; seric cromogranin A; seric neuronal specific enolase; seric insulin; seric glucagon; seric gastrin; seric vasoactive intestinal peptide; and seric somatostatin. To complete the preoperative assessment of patients, an electrocardiograph and endocrinological, oncological and anaesthesiological evaluations were also undertaken.

Patients with unresectable hepatic metastases were candidates for OLT, and were required to satisfy the following inclusion criteria: Histological confirmation of NET; diffuse unresectable hepatic disease; substitution of ≤50% hepatic parenchyma; stable disease during the preoperative period; absent or stable extra-hepatic disease during the preoperative period; and hepatic insufficiency following the hepatic resection of stable disease (rescue OLT).

For the follow-up, bioumoral markers were tested at 3, 6 and 12 months, where appropriate. The instrumental follow-up consisted of imaging repetition after 6 and 12 months from surgery. All patients included in the present study were monitored for at least 12 months following surgery. For patients that were monitored for >12 months, bioumoral markers and imaging were then assessed yearly for the first 5 years, or more frequently in case of recurrence suspicion.

Statistical analysis. Statistical analysis was performed using R (version 3.0.1; www.r-project.org; The R Foundation for Statistical Computing, Vienna, Austria). Distribution normality was evaluated through the Kolmogorov-Smirnov test. In addition, the following statistical tests were applied where appropriate: Student's *t*-test, Wilcoxon test, one way analysis of variance and Kruskal-Wallis test for continuous variables; chi-square test and Fisher's exact test for categorical variables. To analyze the OS of patients, Kaplan-Meier curves were drawn, and the differences between various groups were tested using the Log-rank test.

Results

Description of the population. In total, 26 patients, whose characteristics are exhibited in Table I, received surgery for hepatic metastases from NETs. The mean age at the diagnosis of hepatic metastases was 58.04±13.05 years, 59.73±12.78 years for patients that received hepatic resections and 48.75±11.84 years for those that underwent OLT. Among the patients that received surgery, vasomotoric symptoms were reported in 4 cases (15.4%). Primary tumors were located in the pancreas in 8 cases (30.8%) and in the ileum in 6 cases (23.1%).

In 53.8% of cases (14/26), hepatic metastases were synchronous, 13 cases of which were surgically treated together with the primary tumor. For these patients, the majority of cases received a partial pancreasectomy (35.7%, 5/14), followed in terms of prevalence by gastrectomy (21.4%, 3/14), right emicolectomy (21.4%, 3/14) and ileal resection (14.3%, 2/14). In one case, an ileal resection and liver transplantation were performed in two different surgeries. Extra-hepatic metastases were present in 30.8% of patients (8/26), with the most secondary cases occurring in the lymph nodes (62.5%, 5/8) and bone (37.5%, 3/8).

Characteristics of hepatic metastases. Hepatic metastases were synchronous in the 53.8% of cases and metachronous in the 46.2% of cases. Metachronous hepatic secondaries were diagnosed in 80% of cases within 4 years from the primary tumor resection, at a median time interval of 13 months (range, 6-40 months).

The median number of hepatic metastases was 3 [interquartile range (IQR), 2-6], ranging between 1-23. The hepatic

Table I. Description of the population (n=26).

Characteristic	No. of patients (%)
Age at diagnosis, years[a]	58.04±13.05
Length of follow-up, months[b]	24 (13-58)
Gender, male	12 (46.2)
Symptoms associated with carcinoid syndrome	4 (15.4)
Presence of synchronous liver metastases	14 (53.8)
Presence of extra-hepatic metastases[c]	8 (30.8)
Lymph nodes	5 (62.5)
Bones	3 (37.5)
Lungs	2 (25.0)
Brain	1 (12.5)
Mediastinum	1 (12.5)
Surgical treatment for primary tumor in cases with synchronous liver metastasis (n=14)	
Gastrectomy	3 (21.4)
Ileal resection	3 (21.4)
Right hemicolectomy	3 (21.4)
Resection of the rectum	1 (7.1)
Partial pancreatectomy	5 (35.7)
Surgical treatment of liver metastases[d]	
Hepatic resections	22 (84.6)
Partial right hepatectomy	1 (4.5)
Partial left hepatectomy	0 (0.0)
Single hepatic segmentectomy	1 (4.5)
Multiple hepatic segmentectomies	1 (4.5)
Wedge excision	20 (90.9)
Orthotopic liver transplantation	4 (15.4)
Number of hepatic wedge resections[b]	3 (2-6)
Maximum tumor diameter, cm[e]	6 (3-8)
Post-surgical complications	3 (11.5)
Localization of the primary tumor	
Stomach	4 (15.4)
Esophagus	1 (3.8)
Duodenum	2 (7.7)
Ileum	6 (23.1)
Pancreas	8 (30.8)
Colon	3 (11.5)
Lung	1 (3.8)
Unknown primary	1 (3.8)

[a]Data are presented as mean ± standard deviation. [b]Data are presented as median (IQR). [c]In 3 cases there were multiple locations of extra-hepatic metastases. [d]In 1 case of partial hepatectomy, a resection wedge was also performed. [e]Data are presented as median (IQR). IQR, interquartile range.

metastases were localized in a single hepatic segment in the 15.4% of cases (4/26), in >1 segment within the same hepatic lobe in the 30.8% of cases (8/26), and diffused to both lobes in the 53.8% of cases (14/26). The final group mentioned includes all four patients that underwent OLT.

Surgical treatment of hepatic metastases. The majority of patients (84.6%, 22/26) underwent a hepatic resection, which, in the majority of cases, was a wedge metastasectomy (90%, 20/22) (Table I). In 50% of cases, >3 resections were performed. The mean diameter of the greatest resected metastasis was 6 cm (IQR, 3-8 cm).

Complete hepatic disease resection was reached in the 84.6% of patients (22/26), whereas residual hepatic disease was classified as microscopic in 3 cases (11.5%) and macroscopic in one single case (3.8%). For patients that received typical (lobectomy, segmentectomy or pluri-segmentectomy) and atypical hepatic resections (wedge resection or metastasectomy), complete hepatic disease resection was reached in 66.7% (2/3) and 84.2% (16/19) of cases, respectively. No residual disease was left in all four transplanted patients. For patients with hepatic complete disease resections, the 5-year OS rate was 58.4% (95% CI, 38.0-90.0%), while the 5-year OS rate for patients with microscopic or macroscopic hepatic residual disease the was 0% (P=0.0003).

The mean length of surgery was 4.94±0.83 h, the mean recovery length was 10.60±4.67 days, and 71% of patients required a recovery in the intensive care unit in the immediate post-operative time. Post-operative complications affected 11.5% of patients (3/26), including intra-abdominal bleeding, intra-abdominal sero-hematic collections, pleural effusion and pancreatic fistula, which for only 1/3 cases required a surgical re-intervention. Another patient should be included among surgical complications, a woman that experienced a dramatic post-operative diffuse hepatic necrosis required an urgent rescue OLT; however, this case has been considered among the 4 cases of OLT and resulted in no complications following transplantation. In only 1 case of OLT (right lobe living related liver transplantation, already presented as a case report), liver failure was registered at the 1 year follow-up, due to intrahepatic multiple arterio-portal fistulas (26). The patient later succumbed while waiting for a rescue re-transplantation, and at the time of liver failure this patient was free of disease.

No significant differences were identified between patients that received hepatic resections and those that underwent OLTs (Table II). Furthermore, considering the differences between people that survived and passed away, only an increased prevalence of extra-hepatic metastases were observed in patients that had passed away compared with patients that remained alive at 5 years subsequent to surgery (P=0.064).

The OS rate at 5 years was 47.2% (95% CI, 28.8-77.1%) (Fig. 1A). Fig. 1B shows the OS rates of patients with and without extra-hepatic metastases at 5 years [25.0% (95% CI, 7.5-83.0%) and 54.8% (95% CI, 31.1-96.7%), respectively], which were found to be significantly different (P=0.012).

In Fig. 1C and D, the OS rates were compared between patients that received OLTs and hepatic resections, with hepatic resections subdivided into synchronous and metachronous ones in Fig. 1C, and no significant differences were observed in either case. In Fig. 1D the OS rates of patients that underwent hepatic resections and OLTs were 44.9% (95% CI, 26.0-77.7%) and 50% (95% CI, 12.5-100.0%) at 5 years, respectively (P=0.651).

Table II. Description of the population in patients treated with hepatic resection (n=22) or OLT (n=4).

Characteristic	Hepatic resections, no. of patients (%)	OLT, no. of patients (%)	P-value
Age at diagnosis, years[a]	59.73±12.78	48.75±11.84	0.161
Length of follow-up, months[b]	26 (10-58)	16 (14-33)	0.670
Gender, male	12 (54.5)	0 (0.0)	0.100
Symptoms associated with carcinoid syndrome	2 (9.1)	2 (50.0)	0.099
Presence of synchronous liver metastases	12 (54.5)	2 (50.0)	0.867
Presence of extra-hepatic metastases[c]	6 (27.3)	2 (50.0)	0.563
Lymph nodes	4 (66.7)	1 (50.0)	1.000
Bones	2 (33.4)	1 (50.0)	0.673
Lungs	2 (33.4)	0 (0.0)	0.346
Brain	1 (16.7)	0 (0.0)	0.537
Mediastinum	1 (16.7)	0 (0.0)	0.537
Post-surgical complications	2 (9.1)	1 (25.0)	0.408
Localization of the primary tumor			
Stomach	4 (18.2)	0 (0.0)	0.354
Esophagus	1 (4.5)	0 (0.0)	0.664
Duodenum	2 (9.1)	0 (0.0)	0.530
Ileum	3 (13.6)	3 (75.0)	<0.050
Pancreas	7 (31.8)	1 (25.0)	0.786
Colon	3 (13.6)	0 (0.0)	0.432
Lung	1 (4.5)	0 (0.0)	0.664
Unknown primary	1 (4.5)	0 (0.0)	0.664

[a]Data are presented as mean ± standard deviation. [b]Data are presented as median (interquartile range). [c]In 3 cases there were multiple locations of extra-hepatic metastases. OLT, orthotopic liver transplantation.

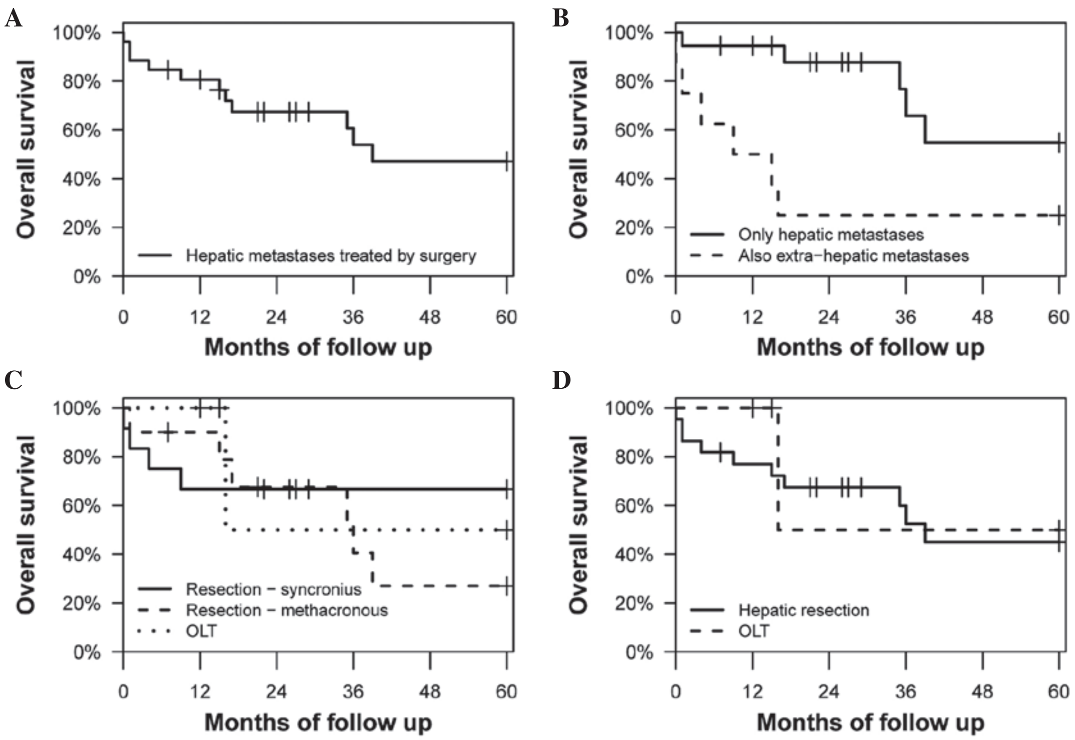

Figure 1. Kaplan-Meier curves depicting: (A) Overall survival rate of all the 26 cases analyzed; (B) overall survival of patients with liver metastases alone and patients with liver metastasis and extra-hepatic metastases; (C) patients with synchronous or metachronous liver metastases and different surgical treatment; (D) differences between patients with hepatic resection and OLT. OLT, orthotopic liver transplantation.

Table III. Description of the population in patients with metachronous (n=12) or synchronous (n=14) liver metastases.

Characteristic	Metachronous metastases, no. of patients (%)	Synchronous metastases, no. of patients (%)	P-value
Age at diagnosis, years[a]	60.50±11.56	53.07±15.43	0.174
Length of follow-up, months[b]	28 (15-46)	24 (10-56)	0.758
Gender, male	7 (58.3)	5 (35.7)	0.249
Symptoms associated with carcinoid syndrome	0 (0.0)	4 (28.6)	0.100
Presence of extra-hepatic metastases[c]	4 (33.3)	4 (28.6)	0.793
Lymph nodes	2 (50.0)	3 (75.0)	1.000
Bones	1 (25.0)	2 (50.0)	0.465
Lungs	0 (0.0)	2 (50.0)	0.102
Brain	1 (25.0)	0 (0.0)	0.285
Mediastinum	1 (25.0)	0 (0.0)	0.285
Surgical treatment of liver metastases[d]			
Hepatic resections	10 (83.3)	12 (85.7)	0.867
Partial right hepatectomy	1 (10.0)	0 (0.0)	0.262
Partial left hepatectomy	0 (0.0)	0 (0.0)	1.000
Single hepatic segmentectomy	1 (10.0)	0 (0.0)	0.262
Multiple hepatic segmentectomies	0 (0.0)	1 (8.3)	0.350
Wedge excision	9 (90.0)	11 (91.7)	0.892
Orthotopic liver transplantation	2 (16.7)	2 (14.3)	0.867
Maximum tumor diameter, cm[e]	6 (4-8)	6 (3-8)	1.000
Post-surgical complications	0 (0.0)	3 (21.4)	0.225
Localization of the primary tumor			
Stomach	2 (16.7)	2 (14.3)	0.867
Esophagus	0 (0.0)	1 (7.1)	0.345
Duodenum	1 (8.3)	1 (7.1)	0.910
Ileum	2 (16.7)	4 (28.6)	0.473
Pancreas	4 (33.3)	4 (28.6)	0.973
Colon	1 (8.3)	2 (14.3)	0.636
Lung	1 (8.3)	0 (0.0)	0.271
Unknown primary	1 (8.3)	0 (0.0)	0.271

[a]Data are presented as mean ± standard deviation. [b]Data are presented as median (IQR). [c]In 3 cases there were multiple locations of extra-hepatic metastases. [d]In 1 case of partial hepatectomy, a wedge resection was also performed. [e]Data are presented as median (IQR). IQR, interquartile range.

Table III evaluates the differences between patients with synchronous and metachronous hepatic metastases, and Table IV compares the patients with or without extra-hepatic metastases. Also in these cases, no significant differences have been highlighted. Recurrences affected 57.7% of the patients studied. In particular, among patients with a recurrence, 66.7% experienced a hepatic recurrence and a single case was successfully re-resected, whereas 33.3% of the patients had an extra-hepatic recurrence for which a palliative systemic treatment was undertaken.

Discussion

Hepatic metastases were synchronous in 53.8% of cases and metachronous in 46.2% of cases. The median number of resected hepatic metastases was 3. Complete resection of hepatic disease was achieved in 84.6% of cases. Recurrences were observed in 57.7% of patients, of which 66.7% were intra-hepatic and 33.3% extra-hepatic. Post-operative complications affected 11.5% of patients, but required re-intervention in a single case. The OS rates of patients that underwent hepatic resections and OLTs were 44.9% (95% CI, 26.0-77.7%) and 50.0% (95% CI, 12.5-100.0%) at 5 years following surgery, respectively.

There is currently no accordance regarding the best therapeutic management of patients with non-resectable liver metastases from NETs; however, numerous non-surgical treatments have been developed in order to provide a chance of survival. The treatments that may be employed, which are currently considered as palliative options, include biotherapy with somatostatin analogs, peptide-mediated radioreceptor therapy, transarterial chemoembolisation, selective

Table IV. Differences between patients with hepatic metastases only (n=18) and patients with hepatic and extra-hepatic metastases (n=8).

Characteristic	Hepatic metastases only, no. of patients (%)	Hepatic and extra-hepatic metastases, no. of patients (%)	P-value
Age at diagnosis, years[a]	56.39±15.2	56.75±11.91	0.949
Length of follow-up, months[b]	28 (18-58)	12 (3-28)	0.071
Gender, male	8 (44.4)	4 (50.0)	0.793
Symptoms associated with carcinoid syndrome	2 (11.1)	2 (25.0)	0.365
Post-surgical complications	2 (11.1)	1 (12.5)	0.919
Presence of synchronous liver metastases	10 (55.6)	4 (50.0)	0.793
Surgical treatment of liver metastases[c]			
Hepatic resections	16 (88.9)	6 (75.0)	0.365
Partial right hepatectomy	0 (0.0)	1 (16.7)	0.095
Partial left hepatectomy	0 (0.0)	0 (0.0)	1.000
Single hepatic segmentectomy	1 (6.2)	0 (0.0)	0.531
Multiple hepatic segmentectomies	1 (6.2)	0 (0.0)	0.531
Wedge excision	14 (87.5)	6 (100.0)	0.364
Orthotopic liver transplantation	2 (11.1)	2 (25.0)	0.365
Maximum tumor diameter, cm[d]	6 (2-10)	6 (4-7)	1.000
Localization of the primary tumor			
Stomach	3 (16.7)	1 (12.5)	0.786
Esophagus	0 (0.0)	1 (12.5)	0.126
Duodenum	2 (11.1)	0 (0.0)	0.326
Ileum	4 (22.2)	2 (25.0)	0.877
Pancreas	6 (33.3)	2 (25.0)	0.671
Colon	2 (11.1)	1 (12.5)	0.919
Lung	1 (5.6)	0 (0.0)	0.497
Unknown primary	0 (0.0)	1 (12.5)	0.126

[a]Data are presented as mean ± standard deviation. [b]Data are presented as median (IQR). [c]In 1 case of partial hepatectomy, a wedge resection was also performed. [d]Data are presented as median (IQR). IQR, interquartile range.

intra-arterial radiotherapy and novel molecular target-directed therapy (6,27,28).

Currently, for cases of resectable liver metastases from NETs, the current literature demonstrates surgery to be the most efficient approach (4,17,18,23,24,29-32). In addition, a potentially curative resection of liver secondaries may be undertaken in 13.7-24.5% of patients with metastatic NETs (33-35). However, although cytoreductive procedures are recognized to have a crucial role among patients with hormonal symptoms, who can consequently have a great benefit from the reduction of secreting mass and a relief from symptoms, the role of such aggressive surgery in case of asymptomatic disease remains a subject of debate. In fact, the majority of patients with liver metastases from NETs recur after hepatic resection, with recurrence rates up to 70-94% at 5 years (7,23,25,36-39), and the role of repeated operations remains ill-defined (37).

The survival impact of hepatic resection is challenging to assess for several reasons. First, the patient selection criteria for hepatic surgery differed across centers, and the completeness of the resection was not determined clearly in several studies. Second, numerous studies reporting the outcome of surgical management of liver metastases from NETs focused solely on resection rather than combined approaches, such as resection and ablation, and the results of liver resection or other therapies were often not determined separately. Third, as prospective randomized data of surgical resection in metastatic neuroendocrine tumors are lacking, recommendations have to rely on recently published retrospective series. Fourth, the majority of studies provide an analysis of pooled data from a mixed group of NETs, which are of foregut, midgut and hindgut origin.

In the literature, the 5-year OS rate of patients that have received surgery for hepatic metastases from NETs ranges between 67-93% (29); for cases of surgery with palliative intent, the rate is 64%, and for cases that received conservative non-surgical treatments the rate varies between 18-52% (29). The 5-year OS rates of the population examined in the present study were 44.9 and 50.0% for hepatic resections and OLTs, respectively, and therefore lower compared with the data presented in the previous literature (29). However, this finding is probably a consequence of the option for patients that are affected by metachronous metastases to receive palliative resections at the Santa Maria della Misericordia' and 'Ospedali Riuniti Umberto I, GM Lancisi, G Salesi' university hospitals. Furthermore, taking into consideration only patients affected by synchronous metastases, the 5-year OS rate was >60%. Moreover, if the rescue OLT is excluded, the 5-year OS rate of transplanted patients was 100%. Finally, the present study showed that, for the differences between hepatic resections and OLT, the results of the surgeries were encouraging and comparable in terms of survival to those of Coppa *et al* (35). In addition, in a recent publication in Europe, the 5-year OS following OLT was found to be 52% (40), which is in accordance with the present results. In the same study, which focused on OLT for liver metastases of NET, the authors found certain predictors of poor outcome, including hepatomegaly, age >45 years and any amount of resection concurrent with OLT (40). By considering these poor outcome predictors as exclusion criteria, it was possible to achieve a 5-year OS of 60-80% (40). However, with these strict criteria certain patients that could benefit from OLT would be excluded (40). Furthermore, in other studies, lengthening the diagnosis-to-OLT time interval had a positive effect or had a no negative effect on the outcome of OLT (40,41). In addition, contradictory statements remain to exist on the indications of OLT with regards to the diagnosis-to-OLT interval in liver metastases of NETs (40,41).

In accordance with the natural history and high recurrence rates of the disease, hepatic metastases from NETs could indicate that subclinical disease is already present, and therefore, in the opinion of certain authors, aggressive liver resection cannot be considered curative (15,37,42). In a study conducted by Saxena *et al* (30), the majority of patients with hepatic metastases from NETs experienced treatment failure after receiving a liver resection. In particular, 57 patients (79%) developed disease progression at a median time of 23 months, and the liver accounted for the most common site for the progression of disease (69%) (30). In another multi-institutional study on 339 patients, Mayo *et al* (37) demonstrated that the majority of liver metastases from NETs originated as carcinoid tumors (53%) and, at 5 years subsequent to surgery, the recurrence rate was 94%. In the same study, according with the multivariate analysis, synchronous disease, non-functional NET hormonal status and extrahepatic disease were the most important predictive factors for worse survival (37).

The current literature suggests that surgical resection of hepatic neuroendocrine neoplasms may be associated with favorable outcomes; however, clinical and oncological variables to distinguish the patient cohorts that would benefit most from such aggressive therapy have not been clearly identified. Patients with an increased number of hepatic tumors tend to be managed without surgical resection and patients with synchronous disease are more likely to be treated without surgery (29).

In a previous meta-analysis, an increase in the 5-year OS rate was also observed in patients affected by hepatic metastases from NETs that underwent hepatic surgery (29); however, randomized clinical trials are necessary to more adequately evaluate the effect of surgery on survival of this group of patients.

Liver metastases are frequently encountered in patients with gastrointestinal NETs and are an important factor in the prognosis of the patient. For patients with resectable hepatic disease, the majority of the authors recommend the use of liver resection, as this treatment most likely offers the best long-term outcome. However, the number of patients that can be considered as candidates for hepatic resection is very restricted, and the recurrence of disease following surgery is a common occurrence.

Since no randomized clinical trial has provided meaningful information regarding the sustained advantages of hepatic resection, no certain conclusion on the impact of this aggressive approach can be achieved. Therefore, further studies comparing liver resection alone or in combination with other therapy are recommended to be undertaken. In addition, an accurate evaluation of novel clinical and biological parameters may be useful to improve the identification of patients that may better benefit from hepatic surgical therapy.

OLT appears to be safe and effective in the treatment of selected patients and demonstrates a survival that is comparable with patients treated by hepatic resection; however, additional randomized clinical trials are also required on this subject.

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