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# Postrecurrence Survival After Liver Transplantation for Liver Metastases From Neuroendocrine Tumors

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**ABBREVIATIONS**

CgA, Chromogranin A

CNI, Calcineurin Inhibitors

CT, Computed Tomography

GEP, Gastro-Entero-Pancreatic

HCC, Hepatocellular Carcinoma

IQR, Interquartile Range

LT, Liver Transplant

mTOR, Mammalian Target Of Rapamycin

NET, Neuroendocrine Tumor

PET-$Ga^{68}$, Positron Emission Tomography $Gallium^{68}$

PRRT, Peptide Receptor Radionuclide Therapy

RECIST, Response Evaluation Criteria in Solid Tumors

SSA, Somatostatin Analogues

TTR, Time-To-Recurrence

UP, Untreatable Progression

## ABSTRACT

### Background

Liver metastases from neuroendocrine tumors (NETs) is an accepted indication for liver transplantation (LT). Despite strict patient selection, post-LT recurrence is observed in 30-50% of cases. Postrecurrence survival is poorly investigated as well as factors influencing postrecurrence outcomes.

### Methods

Consecutive patients treated at a single Institution for post-LT recurrence of NET between Jan 1st, 2004 and Dec 31th, 2018 were included. Baseline patients' characteristics, data on the primary tumor, pretransplant therapies, posttransplant recurrence and treatments and long-term outcomes were prospectively collected and retrospectively analyzed.

### Results

Thirty-two patients presented with post-LT NET recurrence occurring 82.9 months (IQR 29.4-119.1) from LT, and the most common sites were abdominal lymph nodes (59.4%), peritoneum (6.3%) and lungs (6.3%). Fourteen patients (43.8%) underwent surgery with radical intent. Five- and 10-years survival after recurrence were 76.3% and 45.5%, respectively. Only time from LT to recurrence had a significant impact on post recurrence survival, being 5-years OS 89.5% versus 0% for patients recurring > 24 months after LT versus ≤ 24 months, respectively (p=.001). Moreover, for patients with Mib-1 > 2% at recurrence, 5-years OS was 87.5% versus 0% for those undergoing surgery versus loco-regional or systemic treatments (p=0.011).

### Conclusions

The presented results, although based on a retrospective and relatively small series, show that excellent long-term survival is observed after post-LT NET recurrence, particularly in those patients recurring long after LT (> 24 months). An aggressive surgical treatment might result in a new chance of cure for a selected subgroup of patients.

## Introduction

Neuroendocrine tumors (NETs) represent rare heterogeneous neoplasms and comprise approximately 2% of all malignant tumors of the gastro-entero-pancreatic (GEP) system,[1] although their incidence has increased over the last decades.[2]

The majority of NETs are metastatic at clinical diagnosis and the liver is the most frequent site of metastases.[3,4] Surgical resection of the primary tumor and metastases remains, when possible, the only curative treatment in patients with GEP-NETs.[5] However, surgical resection with curative intent is feasible only in a small proportion of cases.[6] In carefully selected patients with liver-only metastases, liver transplantation (LT) may be evaluated,[3] representing a potential chance of radical cure if proper patient selection is provided.[7] The results of LT for NETs are quite heterogeneous, also in experienced Centers, with an overall survival at 5 years ranging from 40% to 90%,[7-10] and the most favorable outcomes are observed when strict selection criteria are applied. Conversely, poor survival outcomes are reported for patients undergoing LT with extensive metastatic liver involvement or uncontrolled disease.[10-12] Such results are mainly related to post-LT recurrences, even in well-differentiated metastatic NETs,[13] and the progression of recurrent or residual tumor are thought to be exacerbated by immunosuppressive therapy. Overall, posttransplant recurrence is observed in 30-50% of cases at 5 years after LT for NET,[7] but management is highly individualized and little is known on postrecurrence survival since data on tumor recurrence after LT in national and international registries are mainly focused on LT for hepatocellular carcinoma (HCC).[14,15] A long-lasting post-LT follow-up is mandatory for these patients, however there are no approved follow-up strategies for the detection or prevention of tumor recurrence after LT, also taken into account that specific prognostic factors of tumor recurrence are not well-defined and data on the effect of immunosuppressive therapy after LT for NETs are scanty.

Given the lack of solid evidence and dedicated guidelines focused on NET recurrence after LT, particularly in terms of management of disease recurrence, aims of present study are 2-fold: to

identify factors influencing postrecurrence survival and to define the best treatment strategy according to disease presentation.

**Materials and Methods**

This is a retrospective analysis of a prospectively and consecutively collected series of patients treated at a single Institution (Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy) for post-LT recurrence of NET occurred between Jan 1st,2004 and Dec 31th, 2018. The study was approved by the Institutional ethical and scientific review board, and was conducted in accordance with Helsinki Declaration as revised in 2013. Patients had undergone LT for liver metastases from NET according to previously published inclusion criteria,[8] which were briefly: 1) confirmed histology of low-grade (G1-G2) NET; 2) primary tumor drained by the portal system and removed through a separate curative resection prior to LT consideration; 3) metastatic diffusion to <50% of the total liver volume; 4) stable disease/response to therapies for at least 6 months prior to LT consideration; 5) Age < 60 years (relative criteria). All transplants had been performed with full grafts from brain dead deceased donors. At laparotomy extrahepatic spread was always ruled out before proceeding with total hepatectomy, and lymphadenectomy including stations 12b, 12p 12a, 8 and 9 was performed. Then , LT according to standard techniques with piggy-back caval anastomosis and no extracorporeal circulation was performed.

Baseline patients' characteristics as well as data on the primary tumor (ie, site, grading, functioning versus nonfunctioning neoplasm, pathology variables including the T and N status), LT (ie, timing, complications including rejection, type and levels of immunosuppression), pretransplant therapies (ie, type of surgery, loco-regional treatments, somatostatin analogues-SSAs, peptide receptor radionuclide therapy-PRRT, chemotherapy), posttransplant recurrence (ie, time from LT, site and kind of the recurrence, single versus multiple), treatments and long-term outcomes were prospectively collected and retrospectively analyzed.

*Inclusion criteria*

To be included in the analysis the following criteria had to be met: 1. Previous LT for NET liver metastases as primary indication with curative intent 2. Confirmed NET recurrence after LT 3. Complete clinical, radiological and pathological data on prerecurrence clinical history 4. At least 6 months of follow-up after NET recurrence.

At suspicion of recurrence, patients underwent a thorough staging including at least total body contrast-enhanced computed tomography (CT) scan, somatostatin receptor scintigraphy (Octreoscan) or Positron Emission Tomography Gallium$^{68}$ (PET-Ga$^{68}$), full clinical examination, and laboratory tests including serum Chromogranin A (CgA). When feasible, pathology confirmation was pursued either through a percutaneous or endoscopic ultrasound (EUS)-guided biopsy of the suspected lesion(s) (ie, in case of liver or lymph nodes recurrence, respectively). To be included in the present analysis, NET recurrence had to be defined as a histologically confirmed lesion (either at diagnosis or after surgery for recurrence). In case of impossibility to obtain histological confirmation, NET recurrence was confirmed in presence of an enlarging lesion with parallel sustained increase of CgA or as a metabolically active lesion at Octreoscan or PET- Ga$^{68}$.

*Treatments at recurrence*

The treatment strategy was thoroughly discussed within the multidisciplinary NET board in a case-by-case manner. In all the cases the following principles were applied when NET recurrence was confirmed: 1. In case of functional tumors SSAs were started 2. Immunosuppression with calcineurin inhibitors (CNI) was minimized and mammalian target of rapamycin (mTOR) inhibitors were started 3. A minimal observation period of 3 months, to assess for the diseases' biological aggressiveness, was undertaken.

In case of stable or slow-progressing disease after this observation period, surgical removal with radical intent was indicated whenever feasible. Alternatively, should the patients' condition be suboptimal or the disease presentation not amenable to surgical removal, loco-regional treatments (ie, transarterial chemoembolization, external-beam radiotherapy) versus systemic treatments

(maintenance of SSAs, PRRT or chemotherapy) were indicated in case of single site versus multiple site presentations, respectively. Tumor response was evaluated after each treatment and every 3 months with chest-abdominal CT scan and CgA serum level determination; response assessment was performed according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

*Statistical Analysis*

The primary aim of the study was to evaluate postrecurrence survival, and to identify pre- and post-LT factors related to postrecurrence survival. Secondary aim was to identify the most appropriate treatment strategy according to disease presentation and tumor biology.

Categorical variables were reported as the number of cases and percentage, continuous variables were expressed as median and interquartile range (IQR). Differences between median Ki-67 monoclonal antibody staining (MIB-1%) at different time points were calculated with the Wilcoxon test for independent samples. Spearman's test was used to assess for correlations between continuous variables (Spearman's ρ).

Survival was computed as the interval between date of NET recurrence after LT and date of death for any reason, with censoring at the date of last follow-up in alive patients. Time-to-recurrence (TTR) was defined as time from LT to first appearance of NET recurrence at any site during the follow-up period: the date of recurrence was thus assessed retrospectively in some cases as the date of first radiological appearance of new lesions, rather than at subsequent histological or surgical confirmation. Untreatable progression (UP) was defined as progression with no chance of any surgical, loco-regional or systemic treatment as per multidisciplinary decision. Time to UP was computed as the interval between date of NET recurrence after LT and date of UP, with censoring at the date of death or last follow-up in patients with no UP. Survival curves were obtained with the Kaplan-Meier method and compared by means of log-rank test. Median follow-up time was calculated with the reverse Kaplan–Meier method.

All analyses were 2-tailed and the threshold of statistical significance was set at $p < 0.05$. Statistical analysis was performed using SPSS Statistics software version 26.0 (IBM Corp., Armonk, NY, USA).

**Results**

During the study period, 53 patients underwent LT for NET liver metastases: the 5- and 10-years overall survival (OS) were 92% and 84%, while the 5- and 10-years disease-free survival were 69% and 45%. Of these patients, 32 presented post-LT NET recurrence and were treated at our Institution: their disease presentation, pretransplant and posttransplant oncological treatments performed before recurrence are depicted in Table 1.

Primary tumors were mainly intestinal (20 patients, 62.5%), T stage was T3-T4 in 24 cases (75.0%), grading was G1-G2 in all patients according to the WHO 2010 classification system and median MIB-1 % of the primary tumor was 1.75 (1-2); most patients (28, 87.5%) were metastatic at the first diagnosis. During waiting time all patients underwent loco-regional or systemic treatments, and 30 patients showed a stable disease or partial response (93.8%). At enlisting, 25 of the 32 patients fulfilled the Milan criteria for LT of metastatic NETs (78.1%).[8,16]

Median time from diagnosis of NET to LT was 22.6 months (14.1-72.4). At LT, 21 patients (65.6%) were found with lymph node metastases at the hepatic hilum. Median MIB-1 % of liver metastases at LT was 3.25 (2-8), significantly higher than that of the primary tumor ($p<0.0001$) with a median percentage variation of 87.5% (30-237.5%). A moderate correlation was found between time from diagnosis of the primary to LT and % variation in MIB-1 % ($\rho$ =-0.354; $p=0.047$).

After LT, 26 patients (81.3%) were started on tacrolimus immunosuppression, whereas 6 (18.7%) on ciclosporin.

*Characteristics of recurrence*

Patients characteristics at recurrence are described in Table 2.

NET recurrence occurred at a median time from LT of 82.9 months (IQR 32.5-118.8), and median age at recurrence was 55 years (IQR 48.5-60.3). In 26 cases (81.2%) recurrence occurred at a single site, while in 6 cases (18.8%) at multiple sites. The most common localizations in case of single site recurrence were distant lymph nodes in 13 patients (40.6%, of which 11 abdominal lymph nodes and 2 thoracic lymph nodes), followed by loco-regional lymph nodes in 6 patients (18.8%), peritoneum in 2 cases (6.3%) and lungs in 2 cases (6.3%). Twelve patients (37.5%) showed increased CgA levels at the time of recurrence. MIB-1 % at recurrence was available in 21 patients: the median value was 9 (2-18), significantly higher than that of the metastases at LT (p=0.016), with a median percentage variation of 108.3% (IQR 0-350%), similar to percentage variation of MIB-1 between primary tumor and LT (p=0.701). Variations of MIB-1 values at different time points are shown in Figure 1. No significant correlation was found between time from LT to recurrence and % variation in MIB1% (ρ=-0.155, p=0.502).

Finally, no correlation was found between time from diagnosis of NET to LT and time from LT to recurrence (ρ=-0.114, p=0.536).

*Treatments at recurrence*

At recurrence 20 patients (62.5%) received SSAs because bearing functional tumors. Moreover, 14 patients (43.8%) underwent surgery with radical intent: 3 over 6 patients with loco-regional lymph nodes metastases (50%), 5 over 13 patients with distant lymph nodes metastases (38.5%), 3 over 4 patients with lung or peritoneal metastases (75%) and 3 over 9 patients with other or multiple metastatic sites (33.3%). Surgery resulted in a complete removal of all metastatic sites (complete response at radiological follow-up 3 months after surgery) in 13 patients (92.8%), while in 1 patient a progressive disease was detected.

Of the remaining 18 patients who were deemed nonresectable, 1 received chemotherapy (3.1%), 2 received PRRT (6.2%) and 15 (46.9%) were maintained on SSAs when indicated.

*Long-term outcomes*

Median follow-up after recurrence was 73.7 months: at the end of follow-up 11 patients (34.4%) had died, of whom 7 because of progression of NET recurrence and 4 for other causes; after different kinds of intervention 4 patients (12.5%) were alive and free of disease, and 17 were alive with active disease. Figure 2 depicts the flowchart of disease presentations, treatments for recurrence and status at last follow-up of these patients.

Five and 10-years OS from LT were 90.6% and 79.6%, respectively. Median, 5- and 10-years OS from recurrence were 81 months, 76.3% and 45.5%, respectively. At the end of follow-up 11 patients reached UP, and 9 of them subsequently died. The rate of UP at 5 years was 57.2%.

*Prognostic factors*

All the pre- and post-LT patient-related and tumor-related characteristics summarized in Table 1 and Table 2 were tested at univariate analysis for their possible influence on postrecurrence survival: only time from LT to recurrence had a significant impact on postrecurrence survival, being 5-years OS 89.5% versus 0% for patients recurring > 24 months after LT versus ≤ 24 months, respectively (p=0.001). No differences in terms of patients' characteristics were found according to the timing of post-LT recurrence, but patients recurring ≤ 24 months tended to present higher MIB1% at LT as shown in Table S1 http://links.lww.com/TP/C217 . Moreover, surgical treatment of recurrence appeared to be associated with a better survival, being 5-years OS of patients undergoing surgery 90.9% versus 64.5% for patients undergoing systemic or loco-regional treatments (p=0.062). This tendency was further confirmed when results were stratified by Mib-1 % at recurrence (21 patients): for patients with Mib-1 > 2%, 5-years OS was 87.5% versus 0% for those undergoing surgery versus loco-regional or systemic treatments (p=0.011); for patients with Mib-1 ≤ 2%, 5-years OS was 100% versus 75% for those undergoing surgery versus loco-regional or systemic treatments (p=0.225). Figure 3 depicts the Kaplan-Meier survival curves. CgA at recurrence was lower in patients undergoing surgery versus non surgical treatment (85.1 versus

132.5, p=0.038), while the other characteristics of recurrence were similar between the 2 groups as shown in Table S2 http://links.lww.com/TP/C217 .

**Discussion**

According to the present series, excellent long term survival is observed even after post-LT NET recurrence. Data on tumor recurrence after LT are scanty in the neuroendocrine setting and, to the best of our knowledge, this is the first study specifically focused on NET recurrence after LT.

The recurrence-free survival after LT at 5 years has been reported to vary from 20% to 80%,[7,10,12,17,18] mirroring the high heterogeneity of transplant candidacy criteria. There are no prospective randomized trials showing the superiority of LT over resection or nonsurgical treatment, however a survival benefit of nearly 3.5 years (38.4 months) at 10 years has been shown in favor of LT in the only comparative study published up to date.[8] In the current series, 5-years and 10-years survival from LT were excellent (ie, 90.6% and 79.6%, respectively), thus confirming the survival benefit derived from LT even in patients who experienced post-LT recurrence. Moreover, the observed postrecurrence survivals at 5-years and 10 years of 76.5% and 45.5%, respectively appear as particularly interesting when put in the context of other oncological indications to LT: it resembles to that of selected patients bearing colorectal liver metastases (5-year OS 57%),[19] while it largely exceeds that of patients recurring after LT for HCC in whom an OS as low as 10.5 months has been repeatedly reported.[15,20,21]

In the current series, NET recurrence occurred at a median time from LT of approximately 7 years, which is a longer period when compared to HCC recurrence, which occurs at a median time of 18-20 months[15,20-22]: this data highlights the need for a strict life-long follow-up after LT in this subgroup of patients. Up to date, standardized follow-up protocols are lacking and data about the factors that are most likely to affect outcomes remain an unmet need.[3] Lymph nodes in the abdominal region were the most common metastatic site at recurrence. However, loco-regional lymph-nodal recurrence - defined as recurrence occurring on lymphatic stations originally draining the primary tumor, and potential expression of residual disease after LT - was relatively rare,

occurring only in 6 patients. Most patients, indeed, showed recurrence either at distant lymph-nodal stations, at distant organs or at multiple sites: a recurrence pattern that is the expression of a systemic rather than a local disease. It is conceivable that the long time-to-recurrence and the favorable postrecurrence survival observed in this study might be partially explained by the stringent pre-LT inclusion criteria adopted for most of the patients in the present series, resulting in the selection of tumors with more favorable biology. Therefore, the external validity of these results should be interpreted with caution particularly when considering LT for NET liver metastases as a salvage or palliative procedure.

Time from LT to recurrence was the only factor significantly affecting postrecurrence survival, while no pretransplant factors nor other postrecurrence variables appeared to be related with long-term OS. From a theoretical point of view, patients can experience 2 types of recurrences. Early recurrences may be the linked to remaining (previously undetected) extrahepatic tumoral deposits left at the time of transplantation, or derive from the post-LT engraftment of circulating tumoral clones. Conversely, late recurrences might be related to the engraftment of less aggressive and probably less numerous circulating cells.[14,23] As repeatedly reported in LT for HCC, these 2 types of recurrences have different expected outcomes, being late recurrences generally more indolent.[15] In our series, 5-years postrecurrence survival was 89.5% for patients recurring more than 24 months after LT and 0% for patients recurring less than 24 months after LT (p=.001). From a risk-benefit standpoint this data should be kept in mind when offering a surgical treatment for post-LT NET recurrence, since more side-effects can be accepted when decent chances of cure or at least of prolonged survival can be foreseen.

Surgical resection also appeared to have an influence on survival, being 5-year OS 90.9% for operated patients versus 64.5% for patients treated by nonsurgical means (p=0.062). This tendency was further confirmed when results were stratified by Mib-1 % at recurrence (evaluable on 21 patients): the effectiveness of surgical removal achieved statistical significance only for those patients with a Mib-1 > 2%, being 5-years OS 87.5% versus 0% for those undergoing surgery

versus loco-regional or systemic treatments (p=0.011). It could be speculated that especially in those patients with more aggressive tumors, a radical surgical treatment allows the disease to restart from scratch; treatment possibilities in case of a new recurrence are, therefore, similar to those of disease-free patients (surgery again, medical treatment, PRRT), with potentially similar responses and results in terms of survival. By pursuing such an aggressive approach, UP – defined as progression with no chance of any surgical, locoregional or systemic treatment as per multidisciplinary decision- was reached only in 11 out of 32 patients with a rate of UP at 5 years contained at 57.2%.

Although one might speculate that immunosuppressive therapy can affect the natural biology of the tumor, leading to more aggressiveness for recurrent tumors compared to the primary tumor and less typical sites,[24] these hypotheses have not been fully confirmed in our study. In particular, we confirmed a significant change in the proliferation index from the resection of the primary (median MIB-1 1.75%) to liver metastases at LT (median MIB-1 3.25%, p<0.0001) to tumor recurrence (median MIB-1 9%, p=0.016). However, the percentage increase of MIB-1 between primary tumor and LT (+87.5%) was similar to the percentage increase between LT and recurrence (+108.3%, p=0.701), even in the context of a significantly longer period of time (LT to recurrence 82.9 months, primary to LT 22.6 months). Therefore tumor characteristics (in terms of proliferation index) and tumor behavior (in terms of patients' long term survival) do not seem to be significantly affected by post-LT immunosuppression. MIB-1 might be heterogeneous within the primary tumor, within liver metastases as well as between the primary tumor and its metastatic recurrences[25]: in the current study, when MIB-1 heterogeneity was present in surgical specimens, the highest MIB-1 was reported with no risk of underestimating tumor grade; this was not possible when only biopsies of recurrence were available.

The present study has, indeed, some limitations including its retrospective nature and the relatively small sample size which impeded the evaluation of independent predictors of survival through multivariable analysis. However this is, to our knowledge, the first study entirely focused on NET

recurrence after LT, and reflects the single-center experience of a liver transplant center with long expertise in the neuroendocrine field. Our results might be partially explained by the homogeneity of the case series in terms of transplant criteria and postrecurrence management, even in the context of a very long time-span. It is conceivable that a multicenter study would probably have reduced the risk of type II error, but the heterogeneity of transplant criteria and patient management would have probably prevented from any meaningful conclusion.

In conclusion, in cases of recurrent NET after LT, treatment options are limited, dedicated guidelines are lacking, and the management should be multidisciplinary and highly individualized. According to our preliminary results, when recurrence appears late after transplant (at least after 2 years), patients might expect excellent postrecurrence survival, comparable to that of metastatic NET at first diagnosis. Moreover, although post-LT recurrence is in most cases a systemic disease, the subgroup of patients with a more aggressive recurrence (in terms of Mib-1 > 2%) might particularly benefit from surgical resection with a radical intent. For those with lower proliferative index at recurrence the survival benefit of surgery is less evident, therefore an aggressive surgical treatment might potentially be postponed at the first appearance of progression.

Taken into account the lack of both clear-cut prognostic factors of tumor recurrence and dedicated guidelines, further prospective studies are urgently needed to draw more robust conclusions.

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**Figure Legends**

**Figure 1.** Mib-1 values (%) of the 32 patients at the time of primary tumor removal, time of LT and time of recurrence.

Colored lines: values for single patients. Bars: median and IQR ranges.

**Figure 2.** Flowchart of treatments performed according to disease presentations, and main outcomes of 32 patients who presented with NET recurrence after liver transplant.

**Figure 3.** Kaplan-Meier survival curves.

**a)** Overall survival from liver transplant

**b)** Overall survival after NET recurrence

**c)** Overall survival after NET recurrence according to time from LT to recurrence

**d)** Overall survival after NET recurrence according to main treatment performed for NET recurrence

**Table 1.** Pretransplant and posttransplant characteristics of the study population

| Characteristic (32 patients) | N (%) or median (IQR) |
|---|---|
| Gender (female) | 15 (46.9%) |
| Age at LT (years) | 49.5 (40.0-57.0) |
| Site of primary tumor | |
| - Ileum/cecum | 20 (62.5%) |
| - Pancreas | 11 (34.4%) |
| - Unknown | 1 (3.1%) |
| Type of primary tumor | |
| - Functioning | 17 (53.1%) |
| - Not functioning | 15 (46.9%) |
| Carcinoid syndrome (yes) | 11 (34.4%) |
| T stage of primary tumor, | |
| - T1/T2 | 8 (25.0%) |
| - T3 | 21 (65.6%) |
| - T4 | 3 (9.4%) |
| Mib-1 % of primary tumor | 2 (1.0-2.8) |
| WHO grading of primary tumor | |
| - G1 | 25 (78.1%) |
| - G2 | 7 (21.9%) |
| N stage of primary tumor | |
| - N0 | 5 (15.6%) |
| - N1 | 27 (84.4%) |
| N site of primary tumor | |
| - Locoregional | 14 (43.8%) |
| - Mesenteric artery | 15 (46.9%) |
| - Splenic artery/Celiac | 1 (3.1%) |
| - Portal vein | 2 (6.3%) |
| Synchronous liver metastases (yes) | 28 (87.5%) |
| Serum chromogranin-A (ng/mL) | 222.5 (60.0-320.8) |
| Pre-LT liver treatment(s) | |
| - Somatostatin analogues | 30 (93.8%) |
| - Liver resection | 8 (25.0%) |
| - Locoregional treatment | 18 (56.3%) |
| - Chemotherapy | 6 (18.7 %) |
| - PRRT | 1 (3.1%) |
| Number of pre-LT LRTs | 2 (1-3) |
| Response to pre-LT treatments | |
| - SD | 24 (75.0%) |
| - PR | 6 (18.8%) |
| - PD | 2(6.2%) |
| Fulfilling Milan criteria for LT (yes)[8,12] | 25 (78.1%) |
| Time from diagnosis of NET to LT (months) | 22.6 (14.1-72.4) |
| - ≤ 24 months | 17 (53.1%) |
| - > 24 months | 15 (46.9%) |
| Metastatic lymph nodes at LT (yes) | 21 (65.6%) |
| Mib-1 % Liver Metastases at LT | 3.3 (2.0-8.0) |
| Acute graft rejection epysodes | 4 (12.5%) |
| Immunosuppressive treatment | |
| - Tacrolimus monotherapy | 26 (81.3%) |

| | |
|---|---|
| - Ciclosporine monotherapy | 6 (18.7%) |
| Abbreviations: IQR, Interquartile Range; LT Liver Transplantation; LRT, Locoregional Treatment; SD, Stable Disease; PR, Partial Response; PD, Progression of Disease | |

**Table 2.** Characteristics of recurrence and treatments

| **Characteristics (32 patients)** | **N (%) or median (IQR)** |
|---|---|
| Age at recurrence, years | 55.0 (48.5-60.3) |
| Time from LT to recurrence | 82.9 (32.5-118.8) |
| - < 24 months | 7 (21.9%) |
| - ≥ 24 months | 25 (78.1%) |
| Serum CgA (ng/mL) at recurrence | 111.9 (56.0-145.4) |
| Mib-1 % of recurrence (21 pts) | |
| - Mib-1 ≤ 2 % | 7 (33.3%) |
| - Mib-1 2-20% | 10 (47.6%) |
| - Mib-1 >20% | 4 (19.1%) |
| Site of recurrence | |
| - Single | 26 (81.2%) |
| - Multiple | 6 (18.8%) |
| Single site recurrence locations (26 pts) | |
| - Abdominal lymph nodes | 17 (65.4%) |
| *- Locoregional*[a] | *6 (23.1%)* |
| *- Distant* | *11 (42.3%)* |
| - Thoracic lymph nodes | 2 (7.7%) |
| - Peritoneum | 2 (7.7%) |
| - Lung | 2 (7.7%) |
| - Bone | 1 (3.8%) |
| - Other (brain, breast) | 2 (7.7%) |
| Multiple site recurrence locations (6 pts) | |
| - Abdominal lymph nodes | 3 (50.0%) |
| - Thoracic lymph nodes | 2 (33.3%) |
| - Peritoneum | 3 (50.0%) |
| - Liver | 1 (16.7%) |
| - Lung | 1 (16.7%) |
| - Bone | 2 (33.3%) |
| Treatment (total) | |
| - Somatostatin analogues | 20 (62.5%) |
| - Chemotherapy | 4 (1.5%) |
| - PRRT | 2 (6.2%) |
| - Surgery | 14 (43.7%) |
| - Radiotherapy | 1 (3.1%) |
| - Follow up (no treatment) | 3 (9.4%) |
| Predominant[b] treatment | |
| -Somatostatin analogues | 11 (34.4%) |
| -Chemotherapy | 3 (9.4%) |
| -PRRT | 2 (6.2%) |
| -Surgery | 14 (43.8%) |
| -Follow up | 2 (6.2%) |
| Outcome of predominant treatment | |
| -Complete response | 12 (37.5%) |
| -Partial response | 4 (12.5%) |
| -Stable disesase | 13 (40.6%) |
| -Progressive disease | 3 (9.4%) |

Abbreviations: IQR, Interquartile Range; LT, Liver Transplantation; CgA, Chromogranin A; PRRT, Peptide Receptor Radionuclide Therapy; SSA, Somatostin Analogues.
[a]Locoregional lymph nodes refers to recurrence occurring on lymphatic stations originally draining the primary tumor (ie, mesenteric lymph nodes for ileal NET).

[b]Predominant treatment refers to the most aggressive treatment each patient received for recurrence (ie, surgery is the predominant treatment in a patient who received both surgery and SSA).

Figure 1

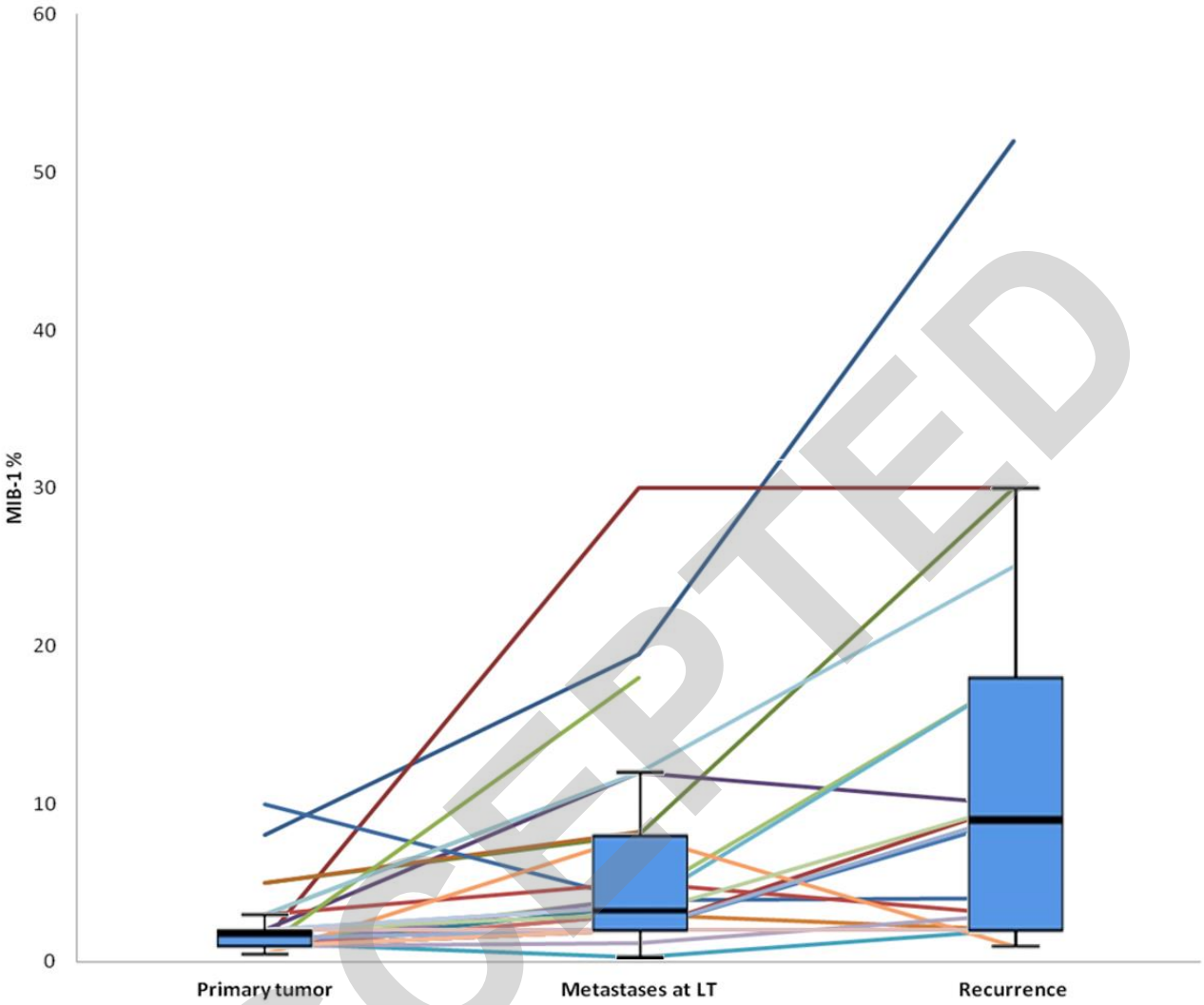

Figure 2

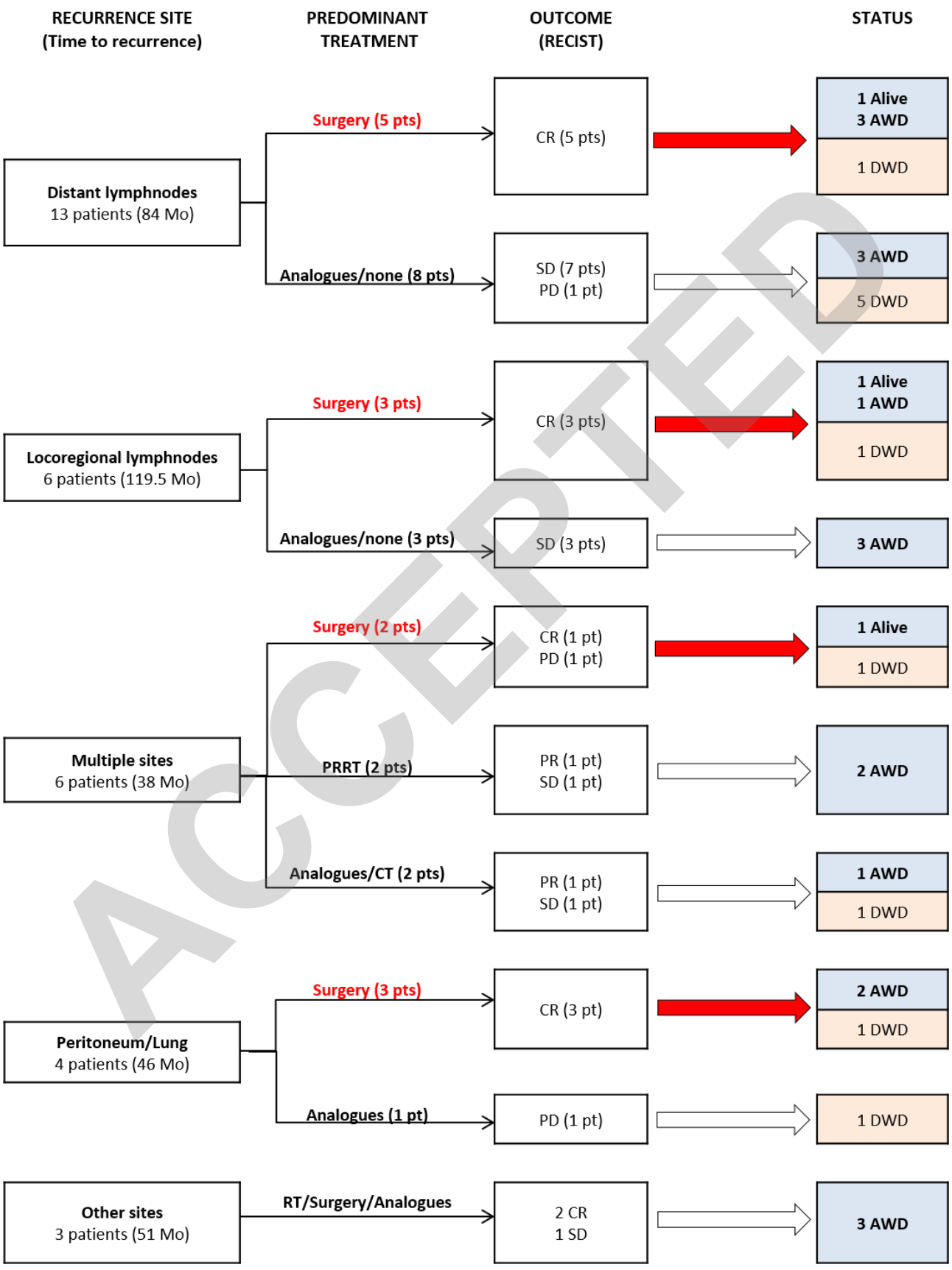

Figure 3