Available online at www.sciencedirect.com

ScienceDirect

EJSO 43 (2017) 380–387

EJSO the Journal of Cancer Surgery

www.ejso.com

# Primary tumour resection may improve survival in functional well-differentiated neuroendocrine tumours metastatic to the liver

D. Citterio [a,c], S. Pusceddu [a,c], A. Facciorusso [a], J. Coppa [a], M. Milione [a], R. Buzzoni [a], M. Bongini [a], F. deBraud [a,b], V. Mazzaferro [a,b,*]

[a] *Comprehensive ENETS Center, Medical and Surgical Oncology and Pathology, Istituto Nazionale Tumori (National Cancer Institute) IRCCS Foundation, via Venezian 1, 20133 Milan, Italy*

[b] *University of Milan, Italy*

Accepted 18 October 2016

Available online 24 November 2016

## Abstract

*Background*: Functional well-differentiated neuroendocrine tumours (NET) with liver metastases represent a therapeutic challenge with few alternative options in guidelines. In these patients, the role of surgical resection of the primary tumour is controversial.

*Patients and methods*: From a regional registry collecting somatostatin analogue (SSA)-treated tumours from 1979 to 2005, a series of 139 patients presenting with symptomatic, liver-metastatic, well-differentiated NET (G1–G2, mitoses: ≤20, Ki-67: ≤20%) was prospectively collected and retrospectively analysed. Surgery on either the primary tumour or liver metastases was chosen: 1) when low perioperative risk was predictable; 2) in presence of an impending risk of obstruction, bleeding, or perforation; or 3) if liver metastases were suitable of curative or subtotal (>90%) tumour removal. Impact of the most relevant clinico-pathological parameters on survival was studied.

*Results*: Median follow-up was 127 months and median survival was 94 months, with 138 vs. 37 months in resected vs. non-resected primary NET ($p < 0.001$), respectively. In the univariate analysis, prolonged survival was significantly associated with primary tumour resection ($p < 0.001$), resection of liver metastases ($p = 0.002$), site of primary (carcinoid vs. pancreatic, $p = 0.018$), basal chromogranin-A (CgA) <200 ng/mL ($p = 0.001$), and absence of diarrhea ($p = 0.012$). Multivariate analysis showed that primary tumour resection was an independent positive prognostic factor (HR = 3.17; 95% CI: 1.77–5.69, $p < 0.001$), whereas diarrhea, basal CgA ≥200 ng/mL, and high tumour load were independent negative prognostic factors. Also, in 103 patients with non-resectable liver metastases, primary tumour resection was significantly associated with prolonged survival (median 137 vs. 32 months, $p < 0.0001$).

*Conclusions*: Primary tumour resection may improve survival in functional well-differentiated NET with liver metastases.



*Keywords:* Carcinoid tumour; Neuroendocrine tumours; Liver metastases; Prognosis; Somatostatin analogues; Surgical treatment

## Introduction

Among the heterogeneous group of neuroendocrine tumours (NETs), those classified as well-differentiated[1] are considered indolent malignancies, and liver metastases are often present at initial diagnosis. Within this group of tumours, functional neuroendocrine tumours (fNETs) represent a therapeutic challenge compared to non-functional NETs because of the adjunctive component represented by the deteriorated quality of life.[2,3]

*Abbreviations:* NET, neuroendocrine tumour; pNET, pancreatic neuroendocrine tumour; fNET, functional neuroendocrine tumours; OS, overall survival; CI, confidence interval; SSA, somatostatin analogues; CgA, chromogranin-A; WHO, World Health Organization; HPF, high power field.

* Corresponding author. Department of Surgery, Istituto Nazionale Tumori IRCCS, via Venezian 1, 2013 Milano, Italy. Fax: +39 02 2390 3259.

*E-mail address:* vincenzo.mazzaferro@istitutotumori.mi.it (V. Mazzaferro).

[c] These authors contributed equally to the work and therefore share first authorship.

http://dx.doi.org/10.1016/j.ejso.2016.10.031

0748-7983/

The benefit of primary NET removal in the presence of unresectable liver metastases is controversial: studies have shown that this practice could increase disease control,[4–8] but data on the possible amelioration of survival are scanty and affected by selection bias. Current international guidelines recommend surgical excision of the primary tumour site in patients with G1–G2 NETs carrying distant metastases only if limited complication risks and intent-to-cure in offering treatments are provided.[9,10] The utility of primary tumour resection is even more questionable for fNET because of the marginal benefit in the palliative setting of symptom control[6,11–13] and for pancreatic neuroendocrine tumours (pNET), considering the risk of postoperative complications.[14,15]

In this study, we planned an academic, non-sponsored investigation aimed at analysing the effect of primary tumour resection and other clinico-pathological variables on the outcome of a consistent and homogeneous group of patients presenting with liver metastases and functional syndrome from histologically proven, well-differentiated NETs. The opportunity for such a prospective consecutive series collection was offered by the implementation in our centre more than 15 years ago of a centralized registry for somatostatin analogue (SSA) receivers.

## Patients and methods

### *Data source*

This is a retrospective analysis of a prospectively collected series of patients treated with SSA of any kind, presenting with various grades of carcinoid syndrome and liver metastases from well-differentiated NETs. Overall patient survival in those undergoing resection of the primary tumour was the primary endpoint of the analysis, together with other conventional prognosticators of outcome.

Of 1532 patients presenting with a diagnosis of NET from 1979 to 2005 at the Istituto Nazionale Tumori (National Cancer Institute) of Milan, a prospective cohort of 139 patients with liver metastases and functioning, well-differentiated NETs (fNETs) was followed according to the requirements for the prescription of SSA in our region. Ethical approval for the study was obtained from the Institutional Review Board.

### *Eligibility criteria and study procedures*

To be included in the analysis, patients had to meet the following eligibility criteria: 1) histology-confirmed diagnosis of well-differentiated NET; 2) presence of liver metastases; 3) $\leq$20 mitoses/10 high power field (HPF) and Ki-67 labelling index $\leq$20% at either the primary or metastatic sites (i.e. tumour at low/intermediate level of differentiation); 4) hormone-secreting status associated with a distinct clinical syndrome (functioning NETs); 5) performance status (PS) 0–1 at presentation, according to the Eastern Cooperative Oncology Group.

The NET diagnosis was confirmed by the general haematoxylin and eosin (H&E) histology and by immunohistochemistry in all cases. Slices were reviewed for mitotic count and grading assessment in agreement with the World Health Organization (WHO) 2010 classification update; therefore, NETs G1 had a mitotic count $\leq$2/10 HPF and/or $\leq$2% Ki-67 index while NETs G2 had a mitotic count 2–10/10 HPF and/or 3–20% Ki-67 index.

Since 2000, multidisciplinary discussions with up-to-date radiological workup and pathology have been in place in our institution. In this setting and even before implementation of the NET board, surgical intervention on either primary or secondary tumour locations, if deemed feasible, was considered as the first-line option. In general, surgical intervention was decided when: 1) minimal perioperative risk and reasonably uneventful primary tumour removal was predictable or, on the other hand, when there was an impending risk of intestinal obstruction, bleeding, or perforation; 2) liver metastases were suitable for surgical resection through single or multi-stage operations or when at least 90% of the tumour load in the liver was considered removable, with the aim to relieve symptoms and achieve palliation, with or without combined intra-arterial embolo-therapies.

The extension of the hepatic tumour load was defined by three-dimensional reconstruction computed tomography scan or magnetic resonance imaging (MRI) together with intraoperative ultrasound when appropriate. Liver tumour burden was categorized into three categories on the basis of the extent of hepatic (H) replacement: $\leq$25% of the liver parenchyma (H1), 26–50% (H2), and $>$50% (H3). Metastatic liver spread thought to be not amenable to potentially curative removal was offered loco-regional treatments (radiofrequency ablation or chemoembolization). The diagnosis of functioning NETs was established on the basis of clinical symptoms and laboratory tests. Various hormone secretion markers were collected according to diagnosis of VIPoma, gastrinoma, insulinoma, glucagonoma, and somatostatinoma, whereas chromogranin-A (CgA) at presentation was determined in 82% of the patients.

Performance status and carcinoid syndrome were clinically determined through physical examination and a patient interview that had to assess at least one of the following: flushing, diarrhea, carcinoid heart disease, or intermittent bronchoconstriction. As previously mentioned, all patients were registered for being treated with SSA including octreotide either in slow-release formulation or long-acting release or, more recently, lanreotide (Autogel). All patients were followed up in a dedicated NET outpatient clinic and censored for survival at each visit until death.

### *Data analysis*

Overall survival (OS) from the date of first referral was estimated through the Kaplan–Meier method and compared between groups by a log-rank test. The nature of the implemented registry did not allow a detailed analysis on disease

progression and quality of life, with particular reference to symptom control. In fact, survival was the sole endpoint progressively collected with solid data.

The inferential analysis for OS in either group was conducted using the Cox univariate and multivariate regression model to estimate hazard ratios (HR) and 95% confidence interval (CI). Statistically significant variables from the univariate Cox analysis were considered for the multivariate models.

The following variables were analysed: gender, age (below vs. above the median), histology and grading, site of primary tumour, resection of the primary tumour, resection of liver metastases, main component of the functional clinical syndrome (diarrhea or flushing), burden of liver disease (H1 vs. H2 vs. H3), and CgA serum level (below vs. above the median). The survival benefit of primary tumour resection was studied overall and in the subgroup of patients with resectable vs. non-resectable liver metastases. The threshold level for qualifying a comparison as significant was set at $p \leq 0.05$.

Statistical analysis was performed using SPSS Statistics software version 21.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 12.5 (MedCalc Software, Ostend, Belgium).

## Results

### *Patients and groups*

A total of 139 patients met the eligibility criteria and were considered for the analysis. Baseline characteristics of the collected cohort are reported in Table 1.

The median age was 56 years (95% CI: 51–55 years, range 13–78 years), and females were slightly predominant (52%). The pancreatic NET represented 26% of the series (36 patients), whereas the predominant primary tumour site was the jejunum-ileum in 66 cases (47%); the primary tumour site was unknown in 19 patients (14%). The main symptoms associated with the carcinoid syndrome were flushing (75%), diarrhea (61%), and carcinoid heart disease (7%) with two or more symptoms being present in 53 cases (38%). The CgA levels at presentation were ≥200 ng/mL in approximately half of the patients (49%). All patients received SSA as a cornerstone of treatment, either alone (n = 95; 68%), in combination with chemotherapy (n = 30; 22%), or, more recently, with everolimus (n = 14; 10%). In addition, 93 patients (67%) underwent primary tumour resection and 36 (26%) underwent resection of liver metastases (32 out of 38 after resection of the primary tumour). In 25 patients (18%), trans-arterial chemoembolization or radiofrequency ablation was added to the systemic and/or surgical treatment of liver metastases.

### *Outcomes and subgroups analysis*

The outline of the distribution of patients, according to the treatments applied together with the main outcome observed during follow-up, is summarized in Fig. 1.

Table 1
Baseline characteristics of 139 patients presenting with carcinoid syndrome (functioning NET) and liver metastases, treated with first line somatostatin analogs.

| Patient characteristics | n (%) |
|---|---|
| Age | |
| ≥55 | 63 (45) |
| <55 | 76 (55) |
| Sex | |
| Male | 67 (48) |
| Female | 72 (52) |
| Primary tumour site | |
| Ileum | 66 (47) |
| Pancreas | 36 (26) |
| Lung | 13 (9) |
| Stomach | 5 (4) |
| Unknown | 19 (14) |
| Embrionic origin classification | |
| Foregut | 54 (39) |
| Midgut | 66 (47) |
| Unknown | 19 (14) |
| Hepatic tumour load | |
| <25% of liver volume (H1) | 36 (26) |
| 25–50% of liver volume (H2) | 50 (36) |
| >50% of liver volume (H3) | 25 (18) |
| Not assessed | 28 (20) |
| Liver-directed locoregional therapies | |
| No | 114 (82) |
| Yes | 25 (18) |
| Symptoms | |
| Flushing | 104 (75) |
| Diarrhea | 85 (61) |
| Carcinoid heart disease | 10 (7) |
| Two or more symptoms | 53 (38) |
| Chromogranin-A at presentation | |
| <200 ng/mL | 47 (34) |
| ≥200 ng/mL | 68 (49) |
| Not known | 24 (17) |
| Primary tumour surgical resection | |
| No | 46 (33) |
| Yes | 93 (67) |
| Liver metastases surgical resection | |
| No | 103 (74) |
| Yes | 36 (26) |

After a median follow-up of 127 months (95% CI: 93–142), 74 deaths were occurred out of 139 patients and the median OS of the entire cohort was 94 months (95% CI: 75–137).

When different treatment groups based on surgical intervention were scrutinized (Fig. 2), a significant difference in median OS among patients who underwent primary tumour resection and those who did not was noticed, and it was 138 months (95% CI: 94–208) vs. 37 months (95% CI: 27–80), respectively ($p < 0.001$).

The survival advantage favouring those patients in whom primary tumour was removed appeared to be also maintained in those patients with liver metastases thought to be too advanced for any surgical attempt. In fact, as shown in Figs. 1 and 3a, median OS was 137 months (95% CI: 70–208) in patients with primary tumour resection and 32 months (95% CI: 26–63) in patients without

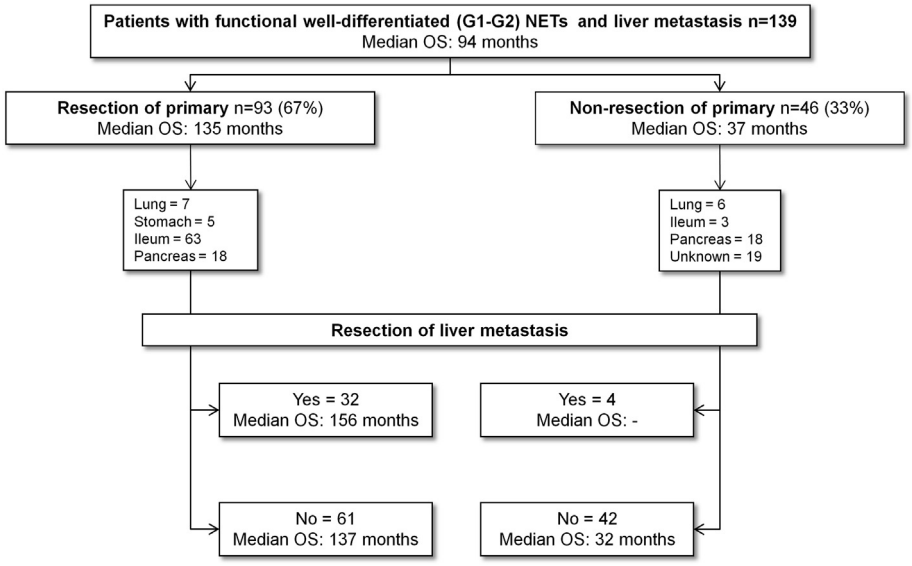


Figure 1. Study outline. Patients' distribution according to surgical treatment applied and main outcomes observed during follow-up.

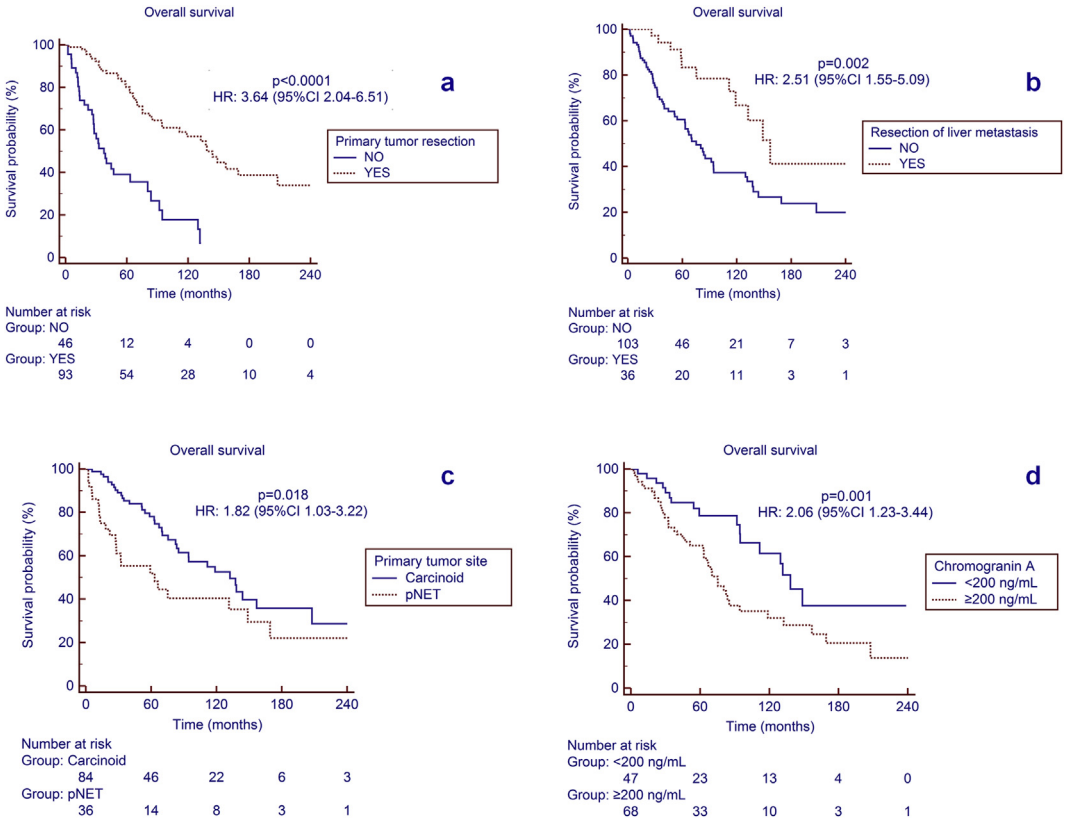


Figure 2. Survival curves of 139 patients with functional NET and liver metastases according to primary tumour resection (a), resection of liver metastases (b), primary tumour site (c) and chromogranin-A serum levels (d).

primary tumour resection ($p < 0.001$). Resection of the primary tumour also conferred a significant benefit to patients with liver metastases from well-differentiated pancreatic primaries (Fig. 3b), who had a HR of 4.7 (95% CI: 1.98–11.39) and a median survival of 169 months (95% CI: 75–306) with respect to those patients with non-resectable pNET (median OS 18 months; 95% CI: 12–28; $p < 0.0001$).

The observed long median follow-up allowed differential calculation of the actuarial survivals at 20 years of the population under study, according to the main events characterizing their tumour presentation and therapy

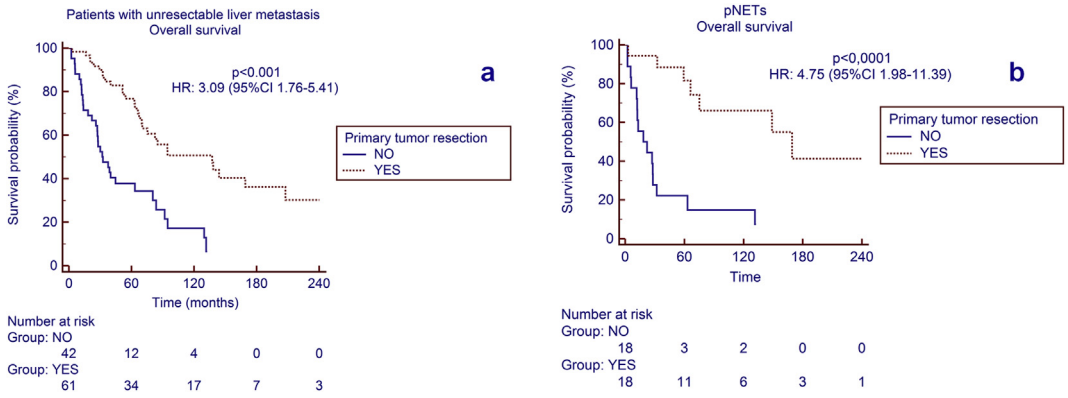


Figure 3. Effect of primary tumour resection in high-risk categories of well-differentiated functioning NETs: patients with non-resectable liver metastases (a) and patients with pancreatic NETs (b).

(Table 2 and Fig. 2). At such long follow-up intervals, primary tumour resection emerged as a significantly positive prognosticator for survival at univariate analysis (HR 3.64; 95% CI: 2.04−6.51), as well as carcinoid vs. pancreatic tumour (HR 1.82; 95% CI: 1.03−3.22), CgA serum level at presentation <200 ng/mL (HR 2.06; 95% CI: 1.23−3.44), resection of liver metastases (HR 2.51; 95% CI: 1.55−5.09), and the absence of diarrhea (HR 1.91; 95% CI: 1.20−3.03).

### *Prognostic factors*

Univariate and multivariate analysis of the variables with a significant impact on long-term survival are summarized in Table 2.

Again, in the multivariate analysis, primary tumour resection showed to be an independent positive prognostic factor (HR 3.17; 95% CI: 1.77−5.69; p < 0.001), as well as the absence of diarrhea (HR 0.49; 95% CI: 0.27−0.88; p = 0.016) and CgA serum level <200 ng/mL at presentation (HR 0.49; 95% CI: 0.26−0.82, p = 0.009), whereas resection of liver metastases was only borderline significant in affecting survival (p = 0.054).

Apart from primary tumour resection, all other factors affecting prognosis were influenced by the intra-hepatic metastatic NET load, particularly for the tumour invading more than 50% of the liver volume showing the highest negative impact on survival (HR 2.41; 95% CI: 1.05−5.54, p = 0.03).

## Discussion

Surgical resection of the primary tumour site in patients with metastatic well-differentiated NETs is a controversial practice, especially in patients at advanced stages, in whom hormone secretion from the liver metastases are by far the

Table 2
Prognostic impact of different variables at univariate and multivariate analysis in 139 patients with well-differentiated functioning NET and liver metastases.

| Predictor | Category | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | Hazard ratio (95% CI) | p value | Hazard ratio (95% CI) | p value |
| Age | ≥55 | 1,37 (0,86−2,19) | 0,206 | | |
| | <55 | 1 | | | |
| Sex | Male | 1,23 (0,78−1,93) | 0,376 | | |
| | Female | 1 | | | |
| Primary tumour site | pNET[a] | 1,82 (1,03−3,22) | **0,018** | 1,17 (0,52−2,61) | 0.703 |
| | Carcinoid | 1 | | 1 | |
| Primary tumour resection | No | 3,64 (2,04−6,51) | **<0.001** | 3,17 (1,77−5,69) | **<0,001** |
| | Yes | 1 | | 1 | |
| Liver metastases resection | No | 2,51 (1,55−5,09) | **0,002** | 2,08 (0,99−4,39) | 0,054 |
| | Yes | 1 | | 1 | |
| Flushing | No | 1,46 (0,84−2,54) | 0,129 | | |
| | Yes | 1 | | | |
| Diarrhea | Yes | 1,91 (1,20−3,03) | **0,012** | 0,49 (0,27−0,88) | **0,016** |
| | No | 1 | | 1 | |
| Chromogranin-A | ≥200 ng/mL | 2,06 (1,23−3,44) | **0,001** | 0,46 (0,26−0,82) | **0,009** |
| | <200 ng/mL | 1 | | 1 | |
| Hepatic tumour load | >50% (H3) | 2,21 (1,08−4,51) | **0,04** | 2,41 (1,05−5,54) | **0,03** |
| | 25−50% (H2) | 1,76 (0,92−3,37) | | 2,4 (1,13−5,09) | |
| | <25% (H1) | 1 | | 1 | |

Bold indicates p values less than 0.05.
[a] pNET indicates pancreatic neuroendocrine tumours.

most responsible factor affecting performance status and quality of life.[16–18] A study from United States reported a progression-free survival of 56 months after primary tumour resection in patients with non-resectable liver metastases from NET compared with 25 months observed when the primary tumour was not resected, with median survivals of 159 vs. 47 months, respectively.[13] Furthermore, in the UKINETS study, resection of the primary tumour was one of the independent predictors of prolonged survival in midgut tumours with liver metastases.[12] A positive impact on prognosis after resection of the primary tumour has also been reported for pancreatic NETs.[5,19]

No solid evidence in favour of primary NET resection has ever been produced from prospective series,[7,11] and at least in theory, the removal of minor cancer deposits at the primary tumour location is likely not to benefit patients in whom liver metastases represent the prevalent and most dreadful condition affecting survival. As a consequence, current guidelines recommend resection of a primary tumour of the jejunum-ileum in the presence of liver metastases mainly for symptomatic reasons or to facilitate liver-directed therapies,[9] although resection of a primary pancreatic NET is even more questionable and not recommended.[20]

An additional limitation in assessing the role of therapeutic interventions on these patients is represented by the long natural history of cancer growth observed in well-differentiated NET with liver metastasis, in which a median survival of up to 60 months is reported.[21,22] The observation that long-time intervals up to 10 years are needed for observing possible advantages in patient survival with respect to historic controls[23] was confirmed in the present series of 139 patients registered with functioning, metastatic, and well-differentiated NET on which unprecedented survival curves up to 20 years were calculated.

In the selected, unfavourable population of metastatic NET, the gain in survival obtained by surgical removal of the primary tumour, regardless of the location, was significant and apparently independent from other factors affecting patient outcome such as primary tumour site, liver metastasis resection, CgA level, and hepatic tumour load (Table 2). The observed median survival of the patients treated along the years with SSA and other medical therapies was in fact 37 months (95% CI 27–80) – therefore in line with other series,[21,22] whereas patients in whom medical treatment was complemented with resection of the primary NET tumour, a median survival of 138 months (95% CI 94–208), with a HR of 3.17 (95% CI 1.77–5.69), was observed. Notably, the positive prognostic effect of surgical eradication of the primary NET tumour was maintained across the subgroup of patients that did not undergo resection of liver metastasis (median survival of 137 vs. 32 months, Fig. 3a).

Unfortunately, no solid data could be derived in respect to quality of life and the progression rate of symptomatic patients with liver metastasis undergoing or not undergoing primary tumour resection, because our source of data was only a SSA-delivered registry. However, the crude evidence of prolongation of survival in the present series could not be observed if there was not some slowdown in disease progression and tumour growth produced by resecting the primary NET location, even though the contribution of tumour burden and biology factors (i.e., intensity of diarrhea, Cg-A serum level, pancreatic location, well-differentiated grade in all cases) certainly played a significant role, as shown in the multivariate analysis.

In addition, as noted in Fig. 1, resection of the primary tumour was more frequently performed in patients with intestinal rather than pancreatic primaries, in accordance with more frequent non-resectability conditions of pNET, also considering that patients submitted to surgery may also present more favourable clinical conditions than those not eligible for such operations.

Although the influence of these selection biases certainly affected our analysis, this is to our knowledge the largest series of metastatic functioning well-differentiated NET published in the literature and the first report to demonstrate in such selected subgroups of NET a clear positive impact of primary tumour resection on survival.

Interventional strategies on liver metastasis may have played an additional role in controlling symptoms, slowing disease progression, and ultimately prolonging survival. Although the results of these therapies are mainly reported in uncontrolled studies,[24–28] there is a general consensus on their repeated use during the course of the disease, particularly in the early phase following SSA therapy, to prevent carcinoid crisis in functionally active NET. In our series, mainly collected during the last two decades of the 1990s, embolo-therapies represented a marginal strategy for treating NET and were equally applied to surgical and non-surgical patients. Certainly, the differential contribution of modern embolo-therapies in controlling tumour symptoms and liver metastasis with respect to surgical removal of the primary tumour location should be investigated in prospective series of histology-proven well-differentiated NET.

In recent years, the multiple tyrosine kinase inhibitor sunitinib and the mTOR inhibitor everolimus have been approved for therapy in different NETs after positive phase III trials,[29,30] and telotristat etiprate has been shown to be effective in controlling refractory carcinoid syndrome.[31] These new therapies may change the scenario for the medical management of advanced NETs and offer better chances of disease control in combination with SSA that was the sole therapy available for the presented cohort during most part of the study, being only 14 (10%) the patients that received everolimus.

NET prognostic studies are frequently hampered by retrospective design, and our investigation makes no exception. Such limitation tempers the enthusiasm on the conclusion emerging from our data that primary NET resection may benefit patients with metastatic functioning G1–G2 NET, whether or not liver-directed therapies were added.

Although non-conclusive, the signals emerging from the presented analysis support the current effort to implement a prospective randomized study, comparing in these patients primary tumour resection combined with the best medical and interventional treatment vs. medical and interventional treatment alone.

## Conflict of interest statement

The authors have no conflicts of interest directly relevant to this study.

## Role of the funding source

No specific funding was assigned to this study.

## Acknowledgements

The authors thank Matteo Casu for assistance in data management for this study.

## References

1. Bosman FT. *WHO classification of tumor of the digestive system*. Lyon: IARC Press; 2010.
2. Pearman TP, Beaumont JL, Cella D, Neary MP, Yao J. Health-related quality of life in patients with neuroendocrine tumors: an investigation of treatment type, disease status, and symptom burden. *Support Care Cancer* 2016;**24**:3695–703.
3. Zerbi A, Falconi M, Rindi G, et al. AISP-Network Study Group. Clinicopathological features of pancreatic endocrine tumors: a prospective multicenter study in Italy of 297 sporadic cases. *Am J Gastroenterol* 2010;**105**:1421–9.
4. Schindl M, Kaczirek K, Passler C, et al. Treatment of small intestinal neuroendocrine tumors: is an extended multimodal approach justified? *World J Surg* 2002;**26**:976–84.
5. Capurso G, Bettini R, Rinzivillo M, Boninsegna L, Delle Fave G, Falconi M. Role of resection of the primary pancreatic neuroendocrine tumour only in patients with unresectable metastatic liver disease: a systematic review. *Neuroendocrinology* 2011;**93**:223–9.
6. Capurso G, Rinzivillo M, Bettini R, Boninsegna L, Delle Fave G, Falconi M. Systematic review of resection of primary midgut carcinoid tumour in patients with unresectable liver metastases. *Br J Surg* 2012;**99**:1480–6.
7. Bettini R, Mantovani W, Boninsegna L, et al. Primary tumour resection in metastatic nonfunctioning pancreatic endocrine carcinomas. *Dig Liver Dis* 2009;**41**:49–55.
8. Eriksson B, Kloppel G, Krenning E, et al. Frascati Consensus Conference participants. Consensus guidelines for the management of patients with digestive neuroendocrine tumors—well-differentiated jejunal-ileal tumor/carcinoma. *Neuroendocrinology* 2008;**87**:8–19.
9. Niederle B, Pape UF, Costa F, et al. Vienna Consensus Conference Participants. ENETS consensus guidelines update for neuroendocrine neoplasms of the jejunum and ileum. *Neuroendocrinology* 2016;**103**:125–38.
10. Boudreaux JP, Klimstra DS, Hassan MM, et al. North American Neuroendocrine Tumor Society (NANETS). The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. *Pancreas* 2010;**39**:753–66.
11. Strosberg J, Gardner N, Kvols L. Survival and prognostic factor analysis of 146 metastatic neuroendocrine tumors of the mid-gut. *Neuroendocrinology* 2009;**89**:471–6.
12. Ahmed A, Turner G, King B, et al. Midgut neuroendocrine tumours with liver metastases: results of the UKINETS study. *Endocr Relat Cancer* 2009;**16**:885–94.
13. Givi B, Pommier SJ, Thompson AK, Diggs BS, Pommier RF. Operative resection of primary carcinoid neoplasms in patients with liver metastases yields significantly better survival. *Surgery* 2006;**140**:891–7. [discussion 897—898].
14. Birnbaum DJ, Turrini O, Vigano L, et al. Surgical management of advanced pancreatic neuroendocrine tumors: short-term and long-term results from an international multi-institutional study. *Ann Surg Oncol* 2015;**22**:1000–7.
15. Gaujoux S, Gonen M, Tang L, et al. Synchronous resection of primary and liver metastases for neuroendocrine tumors. *Ann Surg Oncol* 2012;**19**:4270–7.
16. Pavel M, O'Toole D, Costa F, et al. Vienna Consensus Conference Participants. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology* 2016;**103**:172–85.
17. Frilling A, Modlin IM, Kidd M, et al. Working Group on Neuroendocrine Liver Metastases. Recommendations for management of patients with neuroendocrine liver metastases. *Lancet Oncol* 2014;**15**:e8–e21.
18. Jann H, Roll S, Couvelard A, et al. Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis classification determines clinical outcome. *Cancer* 2011;**117**:3332–41.
19. Bertani E, Fazio N, Botteri E, et al. Resection of the primary pancreatic neuroendocrine tumor in patients with unresectable liver metastases: possible indications for a multimodal approach. *Surgery* 2014;**155**:607–14.
20. Falconi M, Eriksson B, Kaltsas G, et al. Vienna Consensus Conference Participants. ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. *Neuroendocrinology* 2016;**103**:153–71.
21. Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am* 2011;**40**:1–18. [vii].
22. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008;**26**:3063–72.
23. Mazzaferro V, Sposito C, Coppa J, et al. The long-term benefit of liver transplantation for hepatic metastases from neuroendocrine tumors. *Am J Transplant* 2016 May 1. http://dx.doi.org/10.1111/ajt.13831 [Epub ahead of print].
24. de Baere T, Deschamps F, Tselikas L, et al. GEP-NETS update: interventional radiology: role in the treatment of liver metastases from GEP-NETs. *Eur J Endocrinol* 2015;**172**:R151–66.
25. Fiore F, Del Prete M, Franco R, et al. Transarterial embolization (TAE) is equally effective and slightly safer than transarterial chemoembolization (TACE) to manage liver metastases in neuroendocrine tumors. *Endocrine* 2014;**47**:177–82.
26. Maire F, Lombard-Bohas C, O'Toole D, et al. Hepatic arterial embolization versus chemoembolization in the treatment of liver metastases from well-differentiated midgut endocrine tumors: a prospective randomized study. *Neuroendocrinology* 2012;**96**:294–300.
27. Engelman ES, Leon-Ferre R, Naraev BG, et al. Comparison of transarterial liver-directed therapies for low-grade metastatic neuroendocrine tumors in a single institution. *Pancreas* 2014;**43**:219–25.
28. Benson 3rd AB, Geschwind JF, Mulcahy MF, et al. Radioembolisation for liver metastases: results from a prospective 151 patient multi-institutional phase II study. *Eur J Cancer* 2013;**49**:3122–30.
29. Raymond E, Dahan L, Raoul J, et al. Sunitinib Malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011;**364**:501–13.

30. Yao JC, Fazio N, Singh S, et al. RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet* 2016;**387**:968–77.

31. Kulke MH, Horsch D, Caplin M, et al. Abstracts from the European Cancer Congress 2015 37LBA telotristat etiprate is effective in treating patients with carcinoid syndrome that is inadequately controlled by somatostatin analog therapy (the phase 3 TELESTAR clinical trial). *Eur J Cancer* 2015;**51**:S728.