Prognostic Factors In Patients with Gastroenteropancreatic Neuroendocrine Neoplasms and Hepatic Metastases

Sara Massironi[1], Federica Cavalcoli[1, 2], Roberta Elisa Rossi[1, 2], Matilde Pia Spampatti[1, 2], Alessandra Zilli[1, 2], Giovanni Casazza[3], Dario Conte[1, 2], Clorinda Ciafardini[1], Maddalena Peracchi[2]

[1]Gastroenterology and Endoscopy Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[2]Department of Pathophysiology and Organ Transplantation, Università degli Studi di Milano, Milan, Italy

[3]Department of Biomedical and Clinical Sciences "L. Sacco", Università degli Studi di Milano, Milan,

ABSTRACT

Context Hepatic metastases represent the most relevant prognostic factor in gastroenteropancreatic neuroendocrine tumors and are associated with significantly reduced survival. **Objective** The aim of this single-institution retrospective series was to evaluate overall survival and progression-free survival from the diagnosis of liver metastases. **Patients** Among 230 consecutive patients diagnosed with gastroenteropancreatic neuroendocrine tumors, between 1995 and 2013, 93 had hepatic metastases: in 48 the primary tumor was pancreatic, in 45 gastrointestinal. **Results** Median overall survival was 96 months (95% CI, 48–168), 67% of the patients were progression-free at 5 years. Eleven patients underwent radical surgery, 49 had non-radical resection and medical therapy, 9 had partial resection with peptide receptor radionuclide therapy, 7 had medical treatment with radionuclide therapy; the remaining 17 patients received medical treatment only. Overall, 13 patients (14%) achieved complete remission, 22 (25%) partial remission, 25 (27%) disease stabilization, and 33 (35%) disease progression. The best overall survival (100% at 10 years) was observed in patients with radical resection. Age at diagnosis ($p<0.005$), low histological grade ($p<0.0001$), type of treatment ($p<0.001$), isolated liver involvement ($p<0.001$) and early chromogranin A decrease after treatment ($p<0.0001$) were positively associated with OS. At multivariate analysis, type of treatment ($p=0.0029$), low histological grade ($p<0.0001$) and early post-treatment chromogranin A decrease ($p=0.0078$), retained statistical significance, resulting independent predictors of overall survival. No specific factors were associated with progression-free surviva. **Conclusions** Our data has clearly defined the prognostic factors in a cohort of 93 patients with gastroenteropancreatic neuroendocrine tumors with liver metastasis

INTRODUCTION

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a heterogeneous group of neoplasms arising from the endocrine cells of the gastrointestinal tract, with an annual age-adjusted incidence of 5.25 cases per 100,000 people [1, 2, 3]. NETs are usually divided into functioning and non-functioning [4, 5]. According to the WHO 2010 classification, GEP-NETs are classified as well-differentiated grade 1 and 2 neuroendocrine tumors (NETs G1 and G2), and poorly differentiated grade 3 neuroendocrine carcinomas (NEC G3), according to their mitotic index and/or Ki-67 index (Ki-67%) [6].

The majority of NETs are metastatic at clinical diagnosis, with recent studies reporting 65–95% of distant metastases in GEP-NETs at diagnosis [7, 8] the liver being the most frequent site of spreading [9, 10].

The identification of metastatic disease represents the most important prognostic factor together with tumor grading and is associated with a significantly reduced survival compared to patients without liver metastases [11]. Experience indicates a 5-year overall survival of 56–83% for metastatic intestinal NETs and 40–60% for pancreatic NETs [9].

The optimal management of patients with NET hepatic metastases remains controversial. Surgical resection can be the best strategy, although feasible in only a minority of patients, due to frequency of bilobar disease [9, 12]. Liver transplantation is indicated in highly selected patients [13]. In patients with unresectable hepatic metastases, loco-regional therapies may control both disease progression and symptoms related to overproduction of biochemically active substances or tumor bulk [14, 15]. In this specific setting trans-catheter arterial embolization (TAE) and chemoembolization (TACE) have been proposed for neuroendocrine liver metastases, which are typically hypervascular deriving most of their blood supply (80-90%) from the hepatic artery [16]. TAE and TACE are usually safe and well tolerated therapeutic options

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Correspondence Sara Massironi
Gastroenterology and Endoscopy Unit
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
Via F. Sforza 35, 20122 Milan, Italy
Tel +39-02-55033445
Fax +39-02-50370410
E-mail sara.massironi@policlinico.mi.it

showing complete or partial response for symptoms, circulating biomarkers and imaging in 73–100%, 57–91%, and 33–35% of the patients, respectively [17, 18]. The mean survival time has been reported to be 24–32 months [17, 18].

Peptide receptor radionuclide therapy (PRRT) is an emerging therapy with increasing evidence of efficacy in metastatic disease. The two most commonly used radiopeptides for PRRT, ^{90}Y-octreotide and ^{177}Lu-octreotate, produce disease-control rates of 68–94% [19]. In addition to overt evidence of tumor shrinkage, biochemical and symptomatic responses are commonly observed and promising results have been observed in terms of both progression free-survival (PFS) and overall survival (OS) [20]. Recently similar results have been presented from the ongoing Netter-1 trial, the first phase III multicentric, randomized controlled trial evaluating ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Lutathera) in patients with inoperable midgut NETs with somatostatin receptor expression [21]. Indeed, the study showed a statistically significant increase in PFS and an objective response rate for Lutathera as compared to somatostatin analogues treatment.

In recent years, a number of novel targeted agents have emerged to provide new treatment options for patients with NETs. Everolimus [22], an inhibitor of mammalian target of rapamycin (mTOR), and Sunitinib [23] an oral tyrosine kinase inhibitor, which targets VEGFR-1, -2, and -3, are the most promising of such therapeutic options. Everolimus in the randomized RADIANT 3 trial [22], was demonstrated to improve the median progression-free survival from 4.6 months in the placebo arm to 11 months on the everolimus arm. Objective response rates on the everolimus arm were 5%. Sunitinib was compared to placebo in a multinational phase Ⅲ study of low and intermediate-grade pancreatic NETs [23]. Median progression free survival increased from 5.5 months on the placebo arm to 11.4 months on the sunitinib arm ($P< 0.001$). Response rates on the sunitinib arm were 9.3%.

For unresectable lesions the optimum selection of palliative treatment options (timing and method) is crucial to maintain or even improve quality of life and prolong survival.

Identifying prognostic factors for survival is essential in order to tailor the best therapeutic approach and evaluate therapeutic results [24], especially in such a heterogeneous setting as that of patients with neuroendocrine neoplasms. To date, several studies have evaluated the significance of prognostic factors in patients with GEP-NETs [8, 25, 26, 27, 28]. However only a few studies have focused on the prognostic factors in GEP-NETs with liver metastases [24, 29, 30].

Pathological grading and staging at diagnosis have been identified as the strongest prognostic features of GEP-NETs. Differentiation and proliferative index Ki-67% have emerged as the major determinants of prognosis in GEP-NETs [8, 26, 31, 32, 33, 34, 35, 36, 37], as the presence of lymph node metastases [8, 25, 38, 39] and of distant metastases [1]. Some epidemiological studies on GEP-NETs have reported on the increased age at diagnosis as a significant prognostic feature [37, 40], whilst the influence of gender on survival is still debated [1, 11, 37, 41]. Tumor size has been demonstrated to significantly correlate with clinical outcome and survival [8, 27].

Based on the above considerations, the primary aim of our present study was to evaluate both the overall survival (OS) and progression-free survival (PFS) of patients affected by GEP-NETs with liver metastases and to determine the main prognostic factors.

METHODS

From January 1995 to December 2013, among 230 patients affected by GEP-NETs and evaluated at the Neuroendocrine Tumor Research Centre, Gastroenterology and Endoscopy Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan, Italy, hepatic metastases were detected in 93 cases (40%), 41 females and 52 males with a median age of 60 ± SD 15.8 years. This subset represents the study group of the present retrospective series.

All the neoplasms were retrospectively classified on the basis of immuno-histochemical characteristics, according to the WHO 2010 classification [6], based on the Ki-67 index and were staged according to the tumor-node-metastasis (TNM) classification [42]. All the patients underwent a complete clinical, bio-chemical and imaging evaluation at diagnosis and during follow-up. Both plasma CgA levels and the circulating levels of specific hormones were evaluated at diagnosis, then after 3 months from the initial therapeutic regimen (in order to evaluate any early CgA response) and during follow-up. Follow-up imaging studies, including ultrasound examination, computed tomography (CT) and/or magnetic resonance imaging (MRI) were performed at diagnosis and during follow-up at regular intervals at 3 or 6 months. Functional somatostatin receptors imaging were performed initially and at 12-24 months during follow-up or when disease progression was suspected.

Characteristics of the 93 patients included are detailed in **Table 1**. Forty-five patients (48%) had gastrointestinal and 48 (52%) pancreatic NETs, fifty-three cases had a functioning tumor, while the remaining 40 (43%) had a non-functioning form in the pancreas (n=26), stomach (n=2), duodenum (n=1) ileum (n=6) and colon (n=3). Sixteen patients (17%) had a well-differentiated G1 neoplasm, the majority of patients 51 (55%) had a well-differentiated G2 neoplasm, and 26 (28%) presented with a poorly differentiated neuroendocrine carcinoma G3, as already reported [6]. In 77 cases (83%), metastases were already present at diagnosis, whereas in 16 patients (17%) hepatic metastases developed during follow-up. The patients were followed up for a median time of 36 months (range: 3–204 months). Metastases to the liver only were observed in 51 cases (55%), whereas the remaining 42

Table 1. Clinical and demographic characteristics of 93 patients with Gastroenteropancreatic neuroendocrine tumors and liver metastases.

Characteristics	Patients (# 93)
Age, years (Mean ± SD)	60 ± 15.8
Male/female (no. of patients)	52/41
Localization of the primary tumor (no. of patients)	
• Pancreas (no. of patients)	48
• Gut (no. of patients)	45
- Stomach/Duodenum	3/8
- Ileum/ Meckel's diverticulum	28/1
- Colon/Rectum	4/1
Functioning/non-functioning (no. of patients)	53/40
Grade (G1, G2, G3) (no. of patients)	16, 51, 26
Liver metastases at diagnosis (yes/no) (no. of patients)	77/16
Extrahepatic metastases (yes/no) (no. of patients)	42/51
Treatment (no. of patients)	
• RSR	11
• PR + MT	49
• PR+PRRT	9
• MT alone	17
• MT+ PRRT	7
Treatment outcome (no. of patients)*	
• Complete remission (CR)	13
• Partial remission (PR)	22
• Stable disease (SD)	25
• Progression disease (PD)	33
Overall survival, months [median (range)]	96 (3 – 204)
Disease-related deaths (no. of patients)	41

MT Medical treatment; MT+PRRT Medical treatment plus Peptide receptor radionuclide therapy; PR Partial resection; PR+PRRT Partial resection plus peptide receptor radionuclide therapy; RSR Radical surgical resection; no number, # number

*Treatment outcome was evaluated as radiologic response to treatment.

(45%) also had an extrahepatic localisation of the disease, involving the lung, the bone or the genitourinary tract.

Among the 26 patients with G3 neuroendocrine carcinoma (10 females, mean age 61.5 ± 13.9 years), twelve patients had a functioning tumor, while the remaining 14 had a non-functioning form. Distant metastases were present at diagnosis in 25 cases and an isolated liver involvement was observed in 19 cases. In this subgroup median follow up was 30 months (range 3-96 months).

In accordance with the available guidelines (European Neuroendocrine Tumor Society Guidelines, National Comprehensive Cancer Network Guidelines, North American Neuroendocrine Tumor Society Guidelines….) [9, 43, 44] the patients were offered 5 different treatment options: 1) radical surgical resection (RSR; 11 cases, 12%); 2) partial surgical resection, including loco-regional hepatic treatment and medical therapy (PR + MT; 49 cases, 51%); 3) partial surgical resection plus peptide receptor radionuclide therapy (PR+ PRRT; 9 cases, 10%); 4) medical therapy (MT, i.e. somatostatin analogues, interferon, chemotherapy, alone or in combination; 17 cases, 18%) and 5) MT + PRRT (7 cases, 8%). Symptomatic, bio-chemical (plasma CgA levels) and objective (i.e. reduction in tumor size) responses were evaluated according to the criteria released by the Italian Trials in Medical Oncology group (ITMO) [45] and classified as complete (CR), or partial (PR), when facing with a decrease >50%. The disease was considered: stable (SD) in the presence of a decrease <50% or an increase <25%, and progressive (PD) when the increase was higher than 25%. Complete remission (CR) was achieved in 13 patients (14%); 22 (24%) had a partial remission (RP), disease stabilization (SD) was observed in 25 cases (27%), whereas in the remaining 33 (35%) there was a disease progression.

Ethics

All the patients enrolled gave their informed consent to the study, which was approved by the ethics committee of the Institute. The study protocol conforms to the ethical guidelines of the "World Medical Association Declaration of Helsinki".

Statistics

Overall survival (OS) was calculated from the date of diagnosis of liver metastases up to his/her death or the end of data collection (i.e. December 2013). Progression-free survival (PFS) was defined as the time interval between the diagnosis of metastatic disease and (which coincided with time of enrolment in the study) and the time of disease progression or patient death, if occurring before documented radiological progression.

Continuous variables were reported as median (range); categorical variables were reported as counts (percentage). Overall and progression-free survival rates were estimated using the Kaplan-Meier method. The log-rank test was used to compare the survival curves, using the Sidak adjustment for post-hoc pairwise multiple comparison, as appropriate. The univariate and multivariate Cox regression models were used to analyze the possible association between the variables of interest (age, gender, Ki-67 index, primary tumor site, type of treatment, the presence of functioning neoplasm, the presence of metastases at diagnosis or their onset during follow-up, the presence of extra-hepatic metastases, early CgA response defined as a reduction >30% three months after treatment) and the risk of death. The best multivariate model was identified by using a stepwise selection method (entry criterion: $P<0.05$; removal criterion: $P>0.1$). For all the fitted Cox models, the proportional hazard assumption was checked and found to be met. The estimated hazard ratios (HR, as derived from the Cox models, were reported along with the pertinent 95% confidence intervals (CIs). A P value<0.05, two-sided, was considered statistically significant. The analyses were carried out by software i.e. SAS/STAT® release 9.4 (SAS Institute Inc., Cary, N.C., USA).

RESULTS

The median OS was 96 months (95% CI, 48–168). According to the Kaplan-Meier the estimate overall survival at 5 and 10 years from diagnosis of liver metastases was of 57% (95% CI: 45% to 67%) and 42% (95% CI: 29% to 55%), respectively. At the end of the study, 48 patients (52%) were still alive. Interestingly, of the 45 (48%)

deaths, 41 were disease-related. Overall survival did not significantly differ between male and female patients, gastrointestinal and pancreatic NETs, synchronous and metachronous metastases, functioning and non-functioning tumors, whereas overall survival according to grading, type of treatment, early CgA reduction and hepatic *vs*. extra-hepatic metastases are detailed in **Figure 1**. For the patients who had undergone RSR (including 2 patients who had received orthotropic liver transplantation, OLT), the survival rate at 5 and 10 years from the diagnosis of liver metastases, was 100%. For those patients treated with PR plus PRRT (n=9) the overall survival rate was 100% and 74% (95% CI, 29–93) at 5 and 10 years, respectively. The patients treated with PR plus MT (n=49) had an overall survival rate of 48% (95% CI, 31–64) and 31% (95% CI, 11–54) at 5 and 10 years, respectively. Finally, the patients who have received MT plus PRRT (n=7) had a survival rate of 48% (95% CI, 8–81) at 5 years while no patient was still alive after 10 years. In the subset treated with MT alone (n=17) the 5-year survival was 24% (95% CI, 7–45) and no one was still alive after 10 years. A significantly better OS was observed when PRRT was associated to MT compared to MT alone (log-rank test, p<0.0001). When considering the grade of disease, a better overall survival rates were observed in those patients with a low proliferative index (Ki-67<20%) (G1 and G2 *vs*.G3) (Log-rank test, P<0.001).

Complete remission (CR) was achieved in 13 patients (14%); 22 (24%) had a partial remission (RP), disease stabilization (SD) was observed in 25 cases (27%), whereas in the remaining 33 (35%) there was a disease progression.

Furthermore, those patients in whom an early decrease in CgA levels was observed (>30% of CgA decrease after treatment), showed a significantly longer survival compared to those without such a finding (log-rank test; P<0.0001).

The results of the Cox univariate and multivariate analyses exploring variables possibly associated with the risk of death are detailed in **Table 2**. Of interest, the Cox multivariate analysis highlighted that the type of treatment

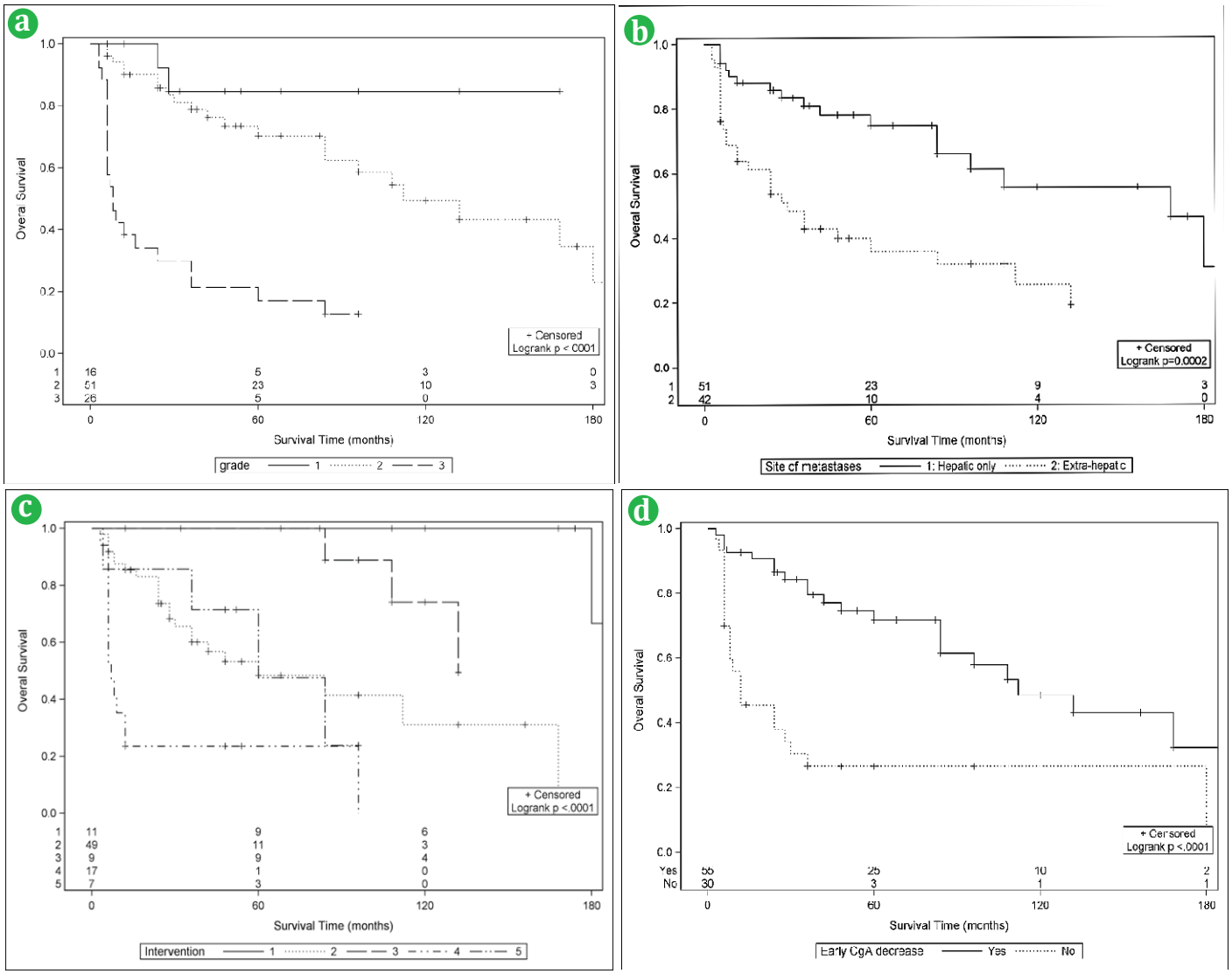

Figure 1. (a). Overall survival for advanced neuroendocrine neoplasm according to histological grade, **(b).** presence of hepatic metastases only vs. hepatic and extrahepatic disease, **(c).** type of treatment and **(d).** early Chromogranin A reduction after treatment.

* Type of intervention: 1) radical surgical resection; 2) partial surgical resection plus medical therapy; 3) partial surgical resection plus peptide receptor radionuclide 4) medical therapy and 5) medical therapy plus peptide receptor radionuclide therapy.

Table 2. Predictors of mortality for 93 patients with gastroenteropancreatic neuroendocrine neoplasms at univariate (left columns) and multivariate regression analysis (right columns).

	Univariate		Multivariate	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Grading (%)				
G1-G2	1	<0.0001	1	<0.0001
G3	5.82 (3.09 – 11.0)		5.49 (2.50 – 12.1)	
Site of NET				
Gastrointestinal	1	0.8981	-	
Pancreatic	1.04 (0.55 – 1.97)			
Syndrome				
Functioning	1	0.2262	-	
Non-functioning tumor	1.44 (0.80 – 2.60)			
Metastasis at enrolment				
Yes	1	0.5676	-	
No	1.27 (0.56 – 2.86)			
Site of metastases				
Hepatic only	1	0.0006	-	
Extra-hepatic	3.00 (1.60 – 5.62)			
Intervention				
PR + PRRT	1	0.0003	1	0.0018
PR+ MT	3.36 (0.97 – 11.6)		3.43 (0.92 – 12.9)	
MT + PRRT	3.70 (0.80 – 17.2)		1.75 (0.37 – 8.33)	
MT	12.8 (3.41 – 47.8)		13.2 (3.11 – 56.4)	
RSR*	-			
Age				
<65 years	1	0.0024	-	
≥65 years	2.57 (1.40 – 4.72)			
Gender				
Female	1	0.1194	-	
Male	1.63 (0.88 – 3.00)			
Early CgA reduction				
Present	1	<0.0001	1	0.0093
Absent	3.81 (2.04 – 7.11)		2.83 (1.29 – 6.21)	

MT Medical treatment; MT+PRRT Medical treatment plus Peptide receptor radionuclide therapy; PR Partial resection; PR+PRRT Partial resection plus peptide receptor radionuclide therapy; RSR Radical surgical resection

*Due to the low number of patients (11 patients with only 1 event at 180 months) the model could not provide a valid HR estimate for radical surgical resection (RSR).

received (p=0.0029), the histological grade [p<0.0001, hazard ratio (HR) of 3.5 for G2 tumors and of 15.2 for G3 carcinomas], and the early reduction of CgA levels (present *vs.* absent, p=0.0078, HR 7) retain statistical significance, thus resulting independent OS predictors.

Furthermore, the percentage of patients without progression of the disease at 5 years was 67%. As concerned PFS, the Kaplan-Meier curves (**Figure 2)** show that low-grade tumors had a trend towards a better PFS, as well as patients treated with radical surgery, even both these observations were not significant at log-rank test. In detail, out of the 11 patients operated with radical intent, 10 (91%) showed no evidence of recurrence (median PFS not reached), whereas in a single patient (9%) NET recurrence was observed after an interval of 170 months. Otherwise, in present study, at Cox analyses, no prognostic factors resulted to be significantly associated with PFS.

DISCUSSION

A proper identification of prognostic factors in patients with GEP-NETs is essential in order to improve their diagnostic and therapeutic management [24]. The present long-term study from a single Institution aimed at determining prognostic factors for OS and PFS in a large series of patients with GEP-NETs consecutively enrolled up, from the diagnosis of liver metastases. To date, only a few studies have focused on this particular set of patients [24, 29, 30], even if it is well known that liver metastases negatively affect tumor prognosis [46, 47, 48]. In our series, 93 patients out of 230 (39%) with GEP-NETs had liver involvement; 83% had liver metastases at diagnosis, while 17% presented liver involvement during follow-up, which is line with data previously reported [24, 29]. Overall survival after the diagnosis of liver metastases was found to be of 96 months (95% CI, 48–168). Panzuto *et al*. have observed similar results [29], reporting a median OS of 81 months (95% CI, 55–100) in patients with GEP-NETs and liver metastases. However, some previous studies reported a lower OS [24, 46], probably due to differences in the composition of the study groups (i.e. inclusion of patients with pulmonary and thymic NET) and in the availability of treatment options, mainly related to the study period.

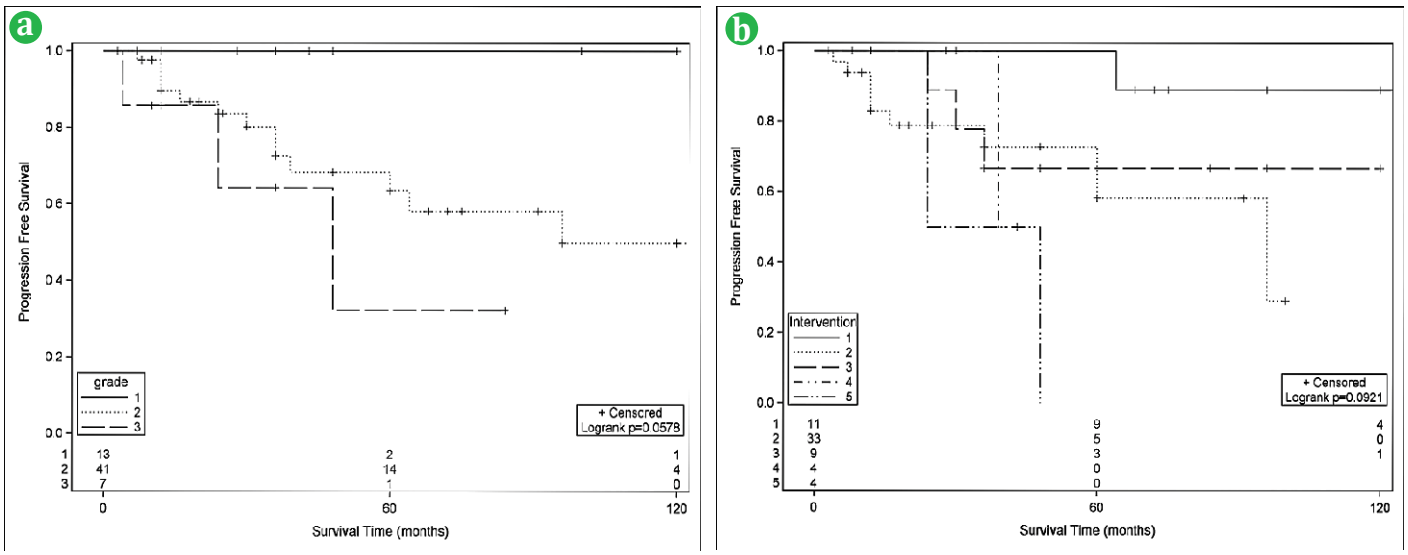

Figure 2. Progression free survival in **(a).** advanced neuroendocrine neoplasms according to tumor grade and **(b).** type of treatment.

* Type of intervention: 1) radical surgical resection; 2) partial surgical resection plus medical therapy; 3) partial surgical resection plus peptide receptor radionuclide therapy; 4) medical therapy and 5) medical therapy plus peptide receptor radionuclide therapy.

Moreover, the data from our series showed that the majority of deaths [41/48 (91%)] were disease-related, this being in accordance with previous papers that observed similar results in patients with metastatic GEP-NETs [24, 29], but different from that observed in patients without hepatic metastases [24].

In our series, the percentage of patients' disease progression free at 5 years was 67%, this being higher than rates previously reported [26, 49]. Such a difference may be explained taking in consideration the relatively low number of patients with poorly differentiated NET (G3) in the present study.

In the current series, the age at diagnosis, the histological grade, the type of treatment and the presence of extra-hepatic distant metastases have proved to be prognostic factors of OS for patients with GEP-NETs, after the diagnosis of metastatic disease. According to earlier studies [30, 37], advanced age at diagnosis (>65 years) has been found to be a risk factor for reduced survival in neuroendocrine tumors metastatic of the liver. It can be postulated that the presence of co-morbidities and reduced tolerance to treatments, which are both common in elder age, possibly reduce the number of applicable therapeutic options and their efficacy in older patients.

Histological grade based on Ki-67 value has already been confirmed as the strongest prognostic factor for GEP-NETs. An important finding of the present study, confirming previous evidence from Panzuto *et al*. [29], is the prognostic relevance of grading even in GEP-NETs with liver metastases.

The type of treatment has proved to be a variable strongly associated with survival. The overall survival of patients with both primary tumor and liver metastases radically resected was significantly better than that of patients who had not undergone RSR. Similar findings have been reported in the literature [50]. This finding may be due to an unavoidable selection bias, as the patients referred to radical surgery usually have a lower extent of the disease and a better performance status. In present study, the hepatic tumor burden (e.g. the size, number, and distribution of metastatic lesions in the liver) were not specifically evaluated. However, in GEP-NET, the extent and the pattern of metastatic disease represents a key-point for treatment selection [29], thus the lack specific analyses of the tumor burden may represents a source of bias. In our series, RSR was possible in only 11 patients (12%); this rate reflects those of other series, since only a small percentage of patients met the criteria for selection for radical surgery. All these 11 patients were alive 10 years after diagnosis of metastatic disease. In the present study, it was not possible to assess the effect on survival of the radical surgery only, due to the little number of deaths in this subgroup of patient. In our series, the patients treated with both PRRT and medical therapy showed a significantly longer overall survival compared with those who had undergone medical treatment only. Similarly, a trend toward higher overall survival, even if not statistically significant, was observed when PRRT was added to PR as compared to PR plus MT. Such data strongly confirm the benefits of PRRT on long-term survival, as recently reported, especially for well-differentiated tumors with progressive disease [51, 52] and it may be particularly relevant in our series in which well-differentiated tumors (G1 and G2) were more prevalent than poorly differentiated ones (G3).

In our series, the presence of extrahepatic metastatic disease has been found to be an important prognostic factor of survival for patients with metastatic GEP-NETs. The role of the presence of distant metastases also extrahepatic, particularly in the lung and bones, has been evaluated only in a few earlier studies [6, 26] confirming a critical role of distant non-hepatic metastases in GEP-NETs even in the presence of liver involvement. Panzuto *et al.* suggested that the presence of distant non-hepatic metastases might identify a subgroup of patients with a worse prognosis and shorter survival [26]. Thus, searching for extrahepatic

lesions during the initial staging of the disease as well as during follow-up appears clinically relevant.

Finally, the data from present series identified an early decrease of CgA levels after treatment as a favourable prognostic factor. These observations confirm previous results from our team [53] who reported that an early reduction of CgA levels within 3 months from treatment (either surgical or systemic) can anticipate favourable prognosis.

Although PFS is a key parameter for prognosis in GEP-NETs, the assessment of factors affecting PFS in GEP-NET with liver involvement is rare in the available literature. According to the present series, no prognostic factor has been found to be statistically significant for PFS. However, as from the Kaplan-Meier curve **(Figures 2a, 2b)**, a better PFS was observed in low grade tumors and, as expected in patients undergone radical surgery. The lack of factors that significantly influence PFS at Cox analysis could probably due to the relatively small number of patients analysed or the small number of events (progressions) observed.

This study shows some limitations, including its retrospective nature. Moreover, the study has been conducted over a 19-year time period. In recent years, new diagnostic techniques have emerged, leading to the diagnosis of metastatic disease from GEP-NETs at an earlier stage, often with a more limited liver burden of disease than in the past. Therapeutic strategies have also changed; in particular, PRRT has been introduced only in the last 10 years [51, 54]. Consequently, the patients diagnosed in 1995 may have had a diagnostic and therapeutic approach different from those diagnosed in recent years. Conversely, our series represents a "real-life" study conducted over a long period and with long follow-up. In addition, all the patients were followed-up at a single centre and had access to the same treatment options, thus limiting the treatment heterogeneity often observed in other studies. Most of the patients in the present study underwent a multi-step therapeutic approach. This should not be considered a confounding factor, since the multi-step association of different therapeutic strategies, when RSR is not feasible, is currently considered the best approach for these neoplasms.

CONCLUSION

In our GEP-NET series, OS and PFS have proved to be high even in the presence of liver metastases. Age, histological grade, type of treatment, early reduction of CgA after treatment and the presence of extrahepatic distant metastases were found to be prognostic factors for OS, after diagnosis of metastatic disease. At multivariate analysis, type of treatment, low histological grade and early post-treatment chromogranin A decrease, retained statistical significance, resulting independent predictors of OS.

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Conflict of Interest

The Authors declare no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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