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Original research

Small intestinal neuroendocrine tumors with liver metastases and resection of the primary: Prognostic factors for decision making

Emilio Bertani [a, *], Massimo Falconi [b], Chiara Grana [c], Edoardo Botteri [d], Antonio Chiappa [e], Pasquale Misitano [f], Francesca Spada [g], Davide Ravizza [h], Barbara Bazolli [d], Nicola Fazio [g]

[a] Division of Hepatobiliopancreatic Surgery, European Institute of Oncology, University of Milano, Italy
[b] Division of Pancreatic Surgery, Ospedale San Raffaele IRCCS, Università Vita e Salute, Milano, Italy
[c] Division of Nuclear Medicine, European Institute of Oncology, Milano, Italy
[d] Division of Epidemiology and Biostatistics, European Institute of Oncology, Milano, Italy
[e] Division of Digestive Surgery, European Institute of Oncology, Milano, Italy
[f] Division of General Surgery, Cantù Hospital, Cantù, Italy
[g] Gastrointestinal and Neuroendocrine Cancer Medical Treatment Unit, European Institute of Oncology, Milano, Italy
[h] Division of Endoscopy, European Institute of Oncology, Milano, Italy

HIGHLIGHTS

- The role of surgery for metastatic intestinal neuroendocrine tumors is uncertain.
- Prognosis largely depends on liver tumor burden and extrahepatic metastases.
- A clear definition of radical liver surgery is needed for outcome comparisons.
- Debulking surgery in asymptomatic patients does not seem to have a merit.

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ABSTRACT

Introduction: Patients with small intestine neuroendocrine tumors present with liver metastases in 50–75% of cases at diagnosis. The aim of the present study was to assess prognostic factors in patients with liver metastases from intestinal neuroendocrine tumor after primary tumor surgical removal with or without liver surgery or radiofrequency ablation. The primary endpoint was disease-specific survival.
Methods: Data regarding seventy-eight consecutive patients with liver metastases who undergone primary tumor surgical removal between 1996 and 2011 were extracted from the institutional tumor registry and retrospectively analyzed.
Results: Liver tumor burden was <25% in 43 (55.1%) 25–50% in 30 (38.5%) and >50% in 5 (6.4%) patients. For the whole cohort of patients disease-specific survival at 3, 5 and 8 years was 93.2%, 83.6% and 77.3%, respectively. Fifteen patients who underwent radical liver surgery were all alive with a median survival of 106 months (range 18–152 months). In multivariate analysis the Ki-67 index in a continuous fashion significantly correlate with prognosis ($p = 0.021$). Liver tumor burden ($p = 0.036$) and extrahepatic involvement ($p = 0.03$), were the most powerful prognosticators for patients who underwent only debulking surgery.
Conclusion: The Ki-67 index, the liver tumor burden and the presence of extrahepatic metastases should be carefully considered in the selection criteria for liver debulking in asymptomatic patients.

1. Introduction

The incidence and prevalence of neuroendocrine tumors (NETs) has increased substantially, ranging from 2.5 to 5 cases per 100.000 [1]. Concerning small intestinal NETs (SI-NETs) it has been reported that the incidence has increased more than threefold in the last 30

Abbreviations: SI-NETs, small intestinal neuroendocrine tumor(s); PET, positron emission tomography; WHO, World Health Organization; OS, overall survival; DSS, disease-specific survival; SSA, somatostatin analogs; ENETS, European Neuroendocrine Tumors Society; NANETS, North American Neuroendocrine Tumors Society; GEP-NET, gastroenteropancreatic neuroendocrine tumor.

* Corresponding author. Department of General and Laparoscopic Surgery, European Institute of Oncology, Via G. Ripamonti, 435, 20141 Milano, Italy.
E-mail address: emilio.bertani@ieo.it (E. Bertani).

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years to become the most common small bowel neoplasm [2]. SI-NETs are commonly diagnosed at stage IV, with metastases frequently found in the liver (50–75% of cases) [2,3].

In the setting of metastatic disease many authors advocate the resection of the primary small bowel tumor in order to prevent subsequent complications of malnutrition, bowel obstruction and infarction [4–8]. For the aforementioned reasons, even with the lack of randomised trials, the most recent European Neuroendocrine Tumor Society (ENETS) and North American Neuroendocrine Tumor Society (NANETS) guidelines recommend removing the primary small bowel tumor [9,10]. For liver metastases, cytoreductive surgery was also recommended, and in selected patients liver transplantation has been demonstrated to be a viable option [11–14]. However, despite these recommendations, the real impact of liver resection/radiofrequency thermal ablation (RFA) on prognosis has been recently questioned [15]. Nonetheless, stage IV disease seems to represent a very heterogeneous group of patients where prognosis is likely to be influenced by several factors. Some are related to the treatment delivered, such as the possible impact of the primary tumor removal and of liver-directed therapies (i.e. surgery or RFA). Other factors to be considered are tumor biology and spread (i.e. the Ki-67 proliferative index), the presence of extrahepatic disease and the liver tumor burden. All these factors render comparisons of the present literature inconsistent. This inconsistency is also due to the heterogeneous selection criteria for surgical candidates and the definition of radical surgery [11–17].

The aim of the present study was to assess whether debulking/non-radical liver surgery/RFA could play a part and to ascertain which factors to take into consideration for decision making with patients affected by stage IV SI-NET with liver metastases who have had the primary tumor removed, particularly when radical liver surgery seems no longer achievable.

2. Materials and methods

2.1. Patients inclusion criteria

All the consecutive patients who presented at the European Institute of Oncology (IEO), Milan, with a histologically confirmed diagnosis of SI-NET with liver metastases from 1996 to 2011 were identified from the institutional tumor registry. For the purpose of the study only patients who underwent surgical resection of the primary tumor at diagnosis with or without liver resection were selected. Patients who did not undergo surgery of the primary tumor or patients who underwent resection of the primary tumor because of small bowel obstruction were excluded from the study to make the patients population more homogeneous.

Indication for liver surgery and/or intraoperative thermal ablation was only made when a presumptive removal of all macroscopic disease with clear (negative) margins was achievable leaving a sufficient functioning liver, or was conducted for palliative purposes in patients with functioning tumors. Intraoperative thermal ablation was associated with liver resection, when deemed necessary, to avoid extensive hepatectomies for deep liver metastases <4 cm in diameter. In all the cases selected for the present study, liver surgery or intraoperative thermal ablation were carried out synchronously with the primary tumor resection. If extrahepatic disease was present, liver resection was indicated for i) resectable/ablatable pulmonary metastases; ii) resectable/ablatable isolated extrahepatic sites—e.g., ovary, lung; iii) local direct extension of liver metastases to the diaphragm and/or the adrenal gland that can be resected; iv) symptom palliation in patients with functioning tumors. Contraindications to liver resection included uncontrolled extrahepatic disease such as 1) widespread pulmonary disease; 2) diffuse peritoneal disease; 3) extensive nodal disease, such as retroperitoneal, mediastinal or portal nodes; 4) central nervous system metastases. However, despite similar clinical presentations, some patients underwent surgery and/or RFA depending on resource availability and clinical expertise at the time of operation.

2.2. Definition of liver tumor burden, radical surgery and histology

The extent of hepatic metastases was defined by the radiologist based on conventional imaging procedures including computed tomography (CT) and/or magnetic resonance (MRI) in all patients. Liver tumor burden was categorized into one of three categories based on the volume of the liver replaced by the tumor and evaluated as <25%, from 25 to 50%, and >50% of liver involvement after three-dimensional reconstruction before surgery. Liver resection was categorized as radical when all the sites of liver metastases detectable by preoperative morphological and functional imaging or by intraoperative ultrasound were resected. All the cases who underwent intraoperative RFA with or without liver resection were categorized as non-radical. Those patients undergoing primary tumor resection without any liver directed treatment, as well as those undergoing non-radical liver resection were included in debulking surgery group.

Histological tumor differentiation, immunohistochemistry, mitotic index, and Ki-67 labeling index on the primary tumor were assessed and tumors were re-classified according to the WHO 2010 classification [18].

2.3. Statistical methods

The Chi-square test, the Chi-square test for trend and the Fisher exact test were used, as appropriate, to compare distributions of categorical and ordinal variables. The primary endpoints were cancer-related survival and overall survival, calculated respectively from the date of diagnosis to the date of death from cancer and to the date of death from any cause. In the case of no events, observations were censored at the last visit date for overall survival and the last visit date or date of death from causes other than cancer for cancer-related survival. Survival curves were generated using the Kaplan-Maier method. The Wilcoxon test and the Wilcoxon test for trend were used to assess survival differences for nominal and ordinal variables, respectively. A multivariable Cox proportional hazards regression model was used to assess the independent prognostic value of the variables that were significantly associated with survival ($P < 0.05$) at the univariate analysis. Only variables which maintained the statistical significance in the multivariable model were reported in the final multivariable model. All analyses were carried out with the SAS software (SAS Institute, Cary, NC) and the R (http://cran.r-project.org/) software. All the reported *P*-values were two sided.

3. Results

3.1. Patients characteristics

From 1996 to 2011 136 patients affected by SI-NETs were identified. Out of the 136 patients, 26 were excluded because they did not have distant metastases, 9 were excluded because they had synchronous extrahepatic metastases alone, 13 were excluded because their primary tumor was not resected at diagnosis, and finally 10 patients were excluded because they presented small bowel obstruction at diagnosis (Fig. 1). Therefore, for the body of the analysis 78 patients were included, all of whom with primary tumor resected at the diagnosis, receiving (29 cases) or not (49 cases) a liver-directed therapy of the liver metastases.

Of the 78 included patients, 46 (59%) were males. The median