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

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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.

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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

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