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Assessing the role of primary tumour resection in patients with synchronous unresectable liver metastases from pancreatic neuroendocrine tumour of the body and tail. A propensity score survival evaluation

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Abstract

Background: The role of primary tumour surgery in pancreatic neuroendocrine tumours (PNETs) with unresectable liver metastases is controversial and international guidelines do not recommend surgery in such cases. Resectability of the primary tumour has never been considered in outcome comparisons between operated and non-operated patients.

Methods: From two institutional prospective databases of patients affected by PNET and unresectable liver metastases, 63 patients who underwent a left-pancreatectomy at diagnosis were identified and compared with a group of 30 patients with a potentially resectable but not-resected primary tumour located in the body or tail. The endpoint was overall survival (OS).

Results: The two groups significantly differed at baseline with regard to liver tumour burden Ki-67 labelling index, site of pancreas, results of the ^{18}FDG PET-CT and age. In the operated patients, surgical morbidity comprised 7 cases of pancreatic fistula. Postoperative mortality was nil. Median OS for patients undergoing left-pancreatectomy was 111 months vs 52 for the non operated patients ($p = 0.003$). At multivariate analysis after propensity score adjustment, no surgery as well as liver tumour burden>25% and higher Ki-67 index were associated with an increased risk of death during follow-up. In patients with unresectable primary tumour, OS was similar in comparison to that in the resectable but non-resected patients, and significantly worse than that in the resected patients ($p = 0.032$).

Conclusion: In PNETs located in the body or tail and diffuse liver metastases distal pancreatectomy may be justified in selected patients. Randomized studies may be safely proposed in future on this topic.

Keywords: Pancreatic neuroendocrine tumours; Synchronous liver metastases; Resection; Prognostic factors; Survival

Introduction

Pancreatic neuroendocrine tumours (PNETs) are rare neoplasms representing only about 1% of all pancreatic tumours by incidence, although their prevalence is close to 10%.[1,2] Liver metastases are found in more than 50% of patients affected by PNETs (in 80% of cases bilobar).[3] In some cases, these malignancies are not suitable for resection due to local vascular infiltration or liver metastases extending to both liver lobes, or because of extrahepatic metastases. Surgery has been proposed as the only potential curative treatment for metastatic PNETs, although few case

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series have been published.[3–5] Survival outcomes from liver resection for NET metastases since the year 2000 range from 74% to 100% at 5 years after surgery, with disease-free survival spanning from 29% to 96%.[6] At the time when liver metastases are bilobar and unresectable, survival probability decreases and survival percentages vary widely, depending on the treatment heterogeneity and time span of the reported series, from approximately 20%–40% at 5 years.[7] However, it is possible that good results for surgery represent selection bias. The Cochrane systematic reviews which were conducted did not identify any benefit of liver resection, either in terms of complete resection (R0 or R1) or cytoreduction (R2).[8,9] Moreover, regarding primary tumor surgery, the operated patients were always compared with non-operated patients without any distinction in this latter group between resectable and non resectable cases, where the resectability of the primary tumour represents the most relevant selection bias in choosing surgical candidates. In particular, for PNETs localized to the body and tail of the pancreas, resectability criteria are wider than for the head, indicating that an inoperable tumour invades the celiac axis or the retroperitoneum extensively. Distal pancreatectomy is associated with less morbidity and near-zero mortality in comparison with pancreaticoduodenectomy. For these reasons left-pancreatectomy represents the vast majority of cases of patients with PNETs and unresectable liver metastases among the published series.[10–12]

The role of primary tumor resection in the presence of widespread metastatic disease may allow better symptom control and may increase survival, improving the efficacy of further treatment by decreasing the overall tumor burden and limiting the disease to the liver.[13] Moreover it may stop seeding the liver with further disease.

The aim of the present study was to ascertain whether or not distal pancreatectomy in a PNET population with unresectable liver metastases is associated with better overall survival when compared with only those patients affected by a resectable primary PNET of the body-tail.

Patients and methods

From 1994 to 2013 the clinical records of 286 patients affected by primary PNET were prospectively collected through the institutional Tumour Registry at the European Institute of Oncology (IEO) in Milan and at the Sacro Cuore Hospital of Negrar, Italy. For the scope of this study, 208 patients with synchronous and unresectable PNET liver metastases were extracted. In these patients liver surgery and/or intraoperative thermal ablation was ruled out because in all cases a presumptive removal of all macroscopic disease with clear (negative) margins was not achievable, if the liver were to remain sufficiently functioning. Patients who were included, with a limited liver tumour burden (<25%), presented a bilobar distribution of small nodules showing PET with [^{68}Ga-DOTA]-D-Phe(1)-Tyr(3)-octreotide avidity. Among these patients, 124 had their primary tumor located in the body-tail of the pancreas. The patient flow diagram is shown in Fig. 1.

This prospective study made with data from the IEO and at the Sacro Cuore Hospital of Negrar tumour registries. In addition to the authorization given the guarantor of privacy in 2012, the Ethical Committees have renewed and extended the approval for the use of the data collected by the IEO and Sacro Cuore Hospital of Negrar tumour registries.

Indications for primary tumour surgery

Patients who underwent distal pancreatectomy (n = 63) were submitted to surgery after multidisciplinary discussion, in order to allow the treatment to be focused on liver metastases or to facilitate further systemic therapies (e.g. peptide receptor radionuclide therapy). In all these cases, distal pancreatectomy included an en bloc splenectomy.

All the pertinent imaging reports of patients not receiving primary tumour surgery were reviewed to assess whether or not the primary tumour was technically resectable at the time of diagnosis. Tumours were defined as non-resectable in the presence of extensive infiltration of the retroperitoneum, of the left kidney, infiltration of the stomach requiring a total gastrectomy or diaphragm involvement, or infiltration of the celiac axis.

For comparison with resected patients, we considered those patients with a primary tumour that presented the same above-mentioned resectability criteria, but who were not operated on either because they refused surgery or because they had started a systemic treatment (e.g. peptide receptor radionuclide therapy, chemotherapy, somatostatin analogues, interferon) (n = 30).

A survival analysis was performed also for patients affected by a technically non-resectable primary tumour (n = 31).

Histology assessment and staging

Histological differentiation grade, immunohistochemistry, mitotic index, and Ki-67 labelling index were assessed as suggested by Rindi et al.[14] Based on existing information, the WHO 2010 classification for histological typing of endocrine tumours was available for 80 patients based on mitotic count or Ki-67 index in NETs-G1 (with a mitotic count <2 per 10 high-power fields (HPF) and/or ≤2% Ki-67 index), and NETs-G2 (with a mitotic count 2–20 per 10 HPF and/or 3–20% Ki-67 index). All NECs are graded G3 (with a mitotic count >20 per 10 HPF and/or >20% Ki-67 index).[14] The Ki-67 labelling index was assessed on liver metastases or on the primary tumour. For patients in whom Ki-67 determination was conducted on primary tumour and liver metastases, where there was discordance the higher Ki-67 was considered for the analysis.

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