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Results after surgical treatment of liver metastases in patients with high-grade gastroenteropancreatic neuroendocrine carcinomas

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Abstract

Background: Gastroenteropancreatic neuroendocrine carcinomas (GEP-NEC) are generally characterized by synchronous metastases, high aggressiveness and a dismal prognosis. Current international guidelines do not recommend surgical treatment of liver metastases, however the existing data are scarce. The aim of this study was to evaluate the results of curatively intended resection/radiofrequency ablation (RFA) of liver metastases in patients with metastatic GEP-NEC.

Methods: 32 patients with a diagnosis of high-grade gastroenteropancreatic neuroendocrine neoplasm (Ki-67 $>$ 20%) and with intended curative resection/RFA of liver metastases, were identified among 840 patients from two Nordic GEP-NEC registries. Tumor morphology (well vs poor differentiation) was reassessed. Overall survival (OS) and progression-free survival (PFS) was assessed by Kaplan–Meier analyses for the entire cohort and for subgroups.

Results: Median OS after resection/RFA of liver metastases was 35.9 months (95%-CI: 20.6–51.3) with a five-year OS of 43%. The median PFS was 8.4 months (95%-CI: 3.9–13). Four patients (13%) were disease-free after 5 years. Two patients had well-differentiated morphology (NET G3) and 20 patients (63%) had Ki-67 $\geq$ 55%. A Ki-67 $<$ 55% and receiving adjuvant chemotherapy were statistically significant factors of improved OS after liver resection/RFA.

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Conclusion: This study shows a long median and long term survival after liver surgery/RFA for these selected metastatic GEP-NEC patients, particularly for the group with a Ki-67 in the relatively lower G3 range. Our findings indicate a possible role for surgical treatment of liver metastases in the management of this patient population.

Keywords: Neuroendocrine carcinoma; Metastases; Liver; Surgery; Survival

Introduction

Neuroendocrine carcinoma (NEC) is broadly defined as a poorly differentiated neuroendocrine neoplasm (NEN) with Ki-67 > 20% or mitotic rate>20/10 high-power fields.[1] In contrast to well differentiated NENs (WHO G1–G2), NECs (WHO G3) are highly aggressive with a propensity for early metastases and a dismal prognosis.[2–6] At the time of diagnosis 57–88% of patients with gastroenteropancreatic NECs (GEP-NEC) have distant disease with the liver as the main metastatic site.[2,5–7] Patients with localized GEP-NECs have a median survival of 16 months, while for the group with metastases median survival is only 5 months.[6] Current guidelines recommend platinum-based chemotherapy as first-line treatment in the metastatic setting.[8–10] However, median survival is only 11–13 months and three-year survival 5–10% for these chemotherapy treated patients.[5,7,11]

Due to the highly aggressive behavior and high risk of metastatic disease, the benefit of surgical treatment for GEP-NEC patients has been questioned. International guidelines currently recommend surgery for NENs G1/G2 with resectable liver metastases and in selected cases as debulking surgery, while for GEP-NECs (WHO G3), surgery in the metastatic setting is not recommended.[12–14] Published data to support these recommendations regarding GEP-NECs are scarce. Two studies evaluating the role of surgical resection of liver metastases in NEN patients, found a median survival of 6–15 months for the minor fraction of patients with poorly differentiated NENs.[15,16] Two case reports describe long-term survival in GEP-NEC patients after locoregional treatment of their liver metastases.[17,18]

Thus the possible benefit of liver surgery in metastatic GEP-NECs is unsettled. With our study we aim to further evaluate the possible role of surgical treatment of liver metastases in this patient population.

Patients and methods

Patients with high-grade gastroenteropancreatic neuroendocrine neoplasm (WHO G3) with surgical treatment of liver metastases were identified from two combined medical/surgical Nordic NEC registries. One registry is a retrospective GEP-NEC database consisting of 485 patients diagnosed between 2000 and 2012. The second registry is a prospective GEP-NEC database of 355 patients, collected from January 2013 to September 2015. Twelve Nordic tertiary care institutions have submitted data. Informed consent has been obtained from all patients, and the study has been approved by the medical ethics committees of all participating countries. The inclusion criteria for the present study were: Histopathological confirmed diagnosis of a high-grade neuroendocrine neoplasm (NEN) with Ki-67 > 20%, a gastroenteropancreatic primary or an unknown primary with predominantly abdominal tumor burden, either synchronous or metachronous liver metastases, surgical resection and/or RFA of metastatic disease in the liver with a curative intent. RFA was accepted as a treatment modality as published data support a role for this approach when treating selected patients with limited size liver metastases from colorectal cancer with a curative intent.[19] Tumor morphology was classified as small-cell or non-small cell. A central review to assess histological differentiation (well differentiated morphology vs poorly differentiated morphology) was performed by four experienced neuroendocrine pathologists (LT, AP, JYS, BF). If the Ki-67 value was reported from both the primary tumor and metastases, the higher value was adopted. A cut-off value of 55% for Ki-67 was used when performing statistical analyses.[11] We chose to use progression-free survival instead of disease-free survival as some of our patients never became disease free. The patient who died within 30 days of surgery was excluded from the subgroup analysis comparing patients that did and did not receive adjuvant chemotherapy. This was in order to avoid potential bias as this patient died before chemotherapy could be given. Previously described prognostic markers in GEP-NEC patients were applied for subgroup analyses.[11,15] Number of metastases is an important prognostic marker after hepatic surgery for metastatic colorectal cancer, and was therefore included in the analyses.[20,21]

Statistical analyses

OS was defined as the time from surgical treatment of liver metastases to last follow-up or death. PFS was defined as the time from surgical treatment of liver metastases until progression or recurrence of the disease. Descriptive methods were used to characterize the patient population. The survival was assessed by Kaplan–Meier analyses for the entire patient population and for subgroups (one criteria at a time). We compared the subgroups by logrank and

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