Surgical treatment of pNET – Experience of a “high-volume” center

Florian Bösch, Katharina Hofmann, Michaela Coenen, Sebastian Pratschke, Michael Thomas, Thomas Knösel, Christiane J. Brun, Markus Guba, Jens Werner, Martin K. Angele

Department of General, Visceral, and Transplant Surgery, Ludwig-Maximilians-University Munich, Munich, Germany
Department of Medical Informatics, Biometry and Epidemiology, IBE, Chair for Public Health and Health Services Research, Research Unit for Biopsychosocial Health, Ludwig-Maximilians-Universität (LMU) München, Munich, Germany
Institute of Pathology, Ludwig-Maximilians-Universität (LMU) München, Munich, Germany
Department of General, Visceral, and Cancer Surgery, University of Cologne, Cologne, Germany

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ABSTRACT

Background: Neuroendocrine tumors of the pancreas (pNETs) are a rare disease. Grading according to the Ki67-index is the most validated risk factor. Nevertheless, controversies exist concerning other prognostic factors. The aim of this study was to evaluate published risk factors.

Methods: Patients with pancreatic NETs who underwent surgery at our department from 2000 to 2014 were analyzed. The patient and tumor characteristics were evaluated. Kaplan-Meier analyses, univariate calculations as well as multivariate analyses were performed.

Results: In total, 98 patients underwent surgery due to a pNET. The final study population consisted of 88 patients. Univariate analysis demonstrated that overall survival is influenced by tumor grading, local resection margin and presence of distant metastases. However, in the multivariate analysis, only grading and the resection margin had prognostic significance. The size of the primary tumor directly correlated with the probability of metastases. Multivisceral operations had no influence on morbidity or mortality.

Conclusions: Resection of pNETs is the only curative treatment and is safe. Since the incidence of pNETs is low, treatment should be performed at a high-volume center.

1. Introduction

Neuroendocrine tumors of the pancreas (pNETs) are rare neoplasms. Nevertheless, these tumors will increasingly demand our attention due to an aging population and a higher likelihood of subclinical tumor detection [1]. pNETs arise from the enterochromaffin cells in the pancreas. Hormone-active and inactive pNETs exist, which primarily metastasize to the liver. The clinical course of pNETs is highly variable, and even in advanced stages patients can survive for years. Consequently, there is some uncertainty regarding how to address small incidentalomas when the overall live expectancy is limited [1–3].

The predominant prognostic marker is tumor grading determined either by the Ki-67 or mitotic index. Highly and intermediately differentiated tumors have a more benign course than poorly differentiated tumors. The slow disease progression of highly differentiated tumors may warrant surgical treatment not only with curative intent but also in a palliative setting. Pancreas resection is the treatment of choice for tumors restricted to the pancreas [4]. Liver metastases should be resected for highly and intermediately differentiated tumors. In patients with non-resectable liver metastases of well-differentiated tumors palliative resection (debulking) is recommended when the tumor burden can be reduced by > 90% [5,6]. Liver transplantation may be considered in selected patients with non-resectable liver metastases of highly differentiated tumors without extrahepatic disease [7,8].

Conservative treatment with receptor radionuclides and biotherapy with somatostatin analogs is effective and may favorably affect the clinical course when surgery is not applicable. Unlike adenocarcinoma of the pancreas, for which the spontaneous clinical course and conservative treatment are dismal and surgery is the only chance of a cure, surgical treatment for pNETs has to compare favorably with conservative treatment options [9]. Therefore, we need to critically appraise surgical outcomes, including the morbidity and mortality associated with these procedures.

Here, we analyzed the impact of established prognostic markers on the outcomes of pNETs after surgical resection in one of the largest cohorts reported to date.
2. Materials and methods

We included 98 consecutive patients undergoing surgical treatment for pNETs at our institution between 4/2000 and 12/2014. Demographic, disease-specific, perioperative and outcome data were extracted from our prospective NET database. Incomplete datasets were analyzed as appropriate. Tumor grading was based on either the Ki-67 index or the mitotic count of the pathological specimens. Postoperative complications were described according to the Clavien-Dindo classification [10]. Tumor debulking was defined as primary tumor resection in the case of non-resectable liver metastases. This surgical approach strived for extrahepatic tumor clearance, thus allowing liver directed therapy.

For the survival data, the mean survival times with their 95% confidence intervals (95% CIs) and Kaplan-Meier curves were plotted for the entire sample and compared in subpopulations stratified by gender, grading, and metastases using log-rank-tests.

Univariate analyses were conducted using the Chi-square test for categorical parameters (e.g., grading and the presence of distant metastases) and the Mann-Whitney U test for interval-scaled (non-normally distributed) parameters (e.g., survival time); p-values less than 0.05 were considered significant.

Cox proportional hazard regression analyses were conducted on the model overall and for 5-year and progression-free survival and selected covariates. For effect size, the hazard ratio \( \text{Exp}(B) \) with its 95% CIs and p-values were reported [11].

SPSS version 22.0 for Windows (Armonk, NY, USA: IBM Corp.) was used for the data analyses.

3. Results

3.1. Demographic data and clinical presentation

Ninety-eight records with pNETs were identified in our NET database within the observation period. Ten records were excluded from the analysis due to inconsistent or missing data (Fig. 1). The mean age was 59 years (min: 28; max: 83). The sex distribution was almost equal (43 females (48.9%) and 45 males (51.1%)).

The tumors were nonfunctioning in 66 patients (75.0%). Twelve patients (13.6%) had an insulinoma, 4 had either a gastrinoma or a glucagonoma (4.5% each) and one each had either a somatostatinoma or a vasoactive intestinal peptide tumor (VIPoma) (1.1%). Typical symptoms of a functional pNET, such as flushing or diarrhea, were apparent in only 10 cases (12.7%), and 17 patients (21.8%) had a history of pain prior to surgery. The majority of tumors (n = 69; 87.3%) were completely asymptomatic.

The tumors were classified according to the ENETS and the UICC classification system [1–3,12]. The majority of 33 patients (37.9%) were UICC stage I, stage II consisted of 24 patients (27.6%) and stage III of 4 patients (4.6%). Distant metastases had 26 patients (29.9%), subsequently they were classified as stage IV. The distributions of ENETS stages I (23 patients, 26.1%) and II (21 patients, 23.9%) were almost equal. Eighteen patients (20.5%) had ENETS stage III tumors, and 26 patients (29.5%) had stage IV tumors.

Seven of the 85 patients (8.2%) had more than one tumor. The mean tumor size was 2.9 cm. Positive lymph nodes were present in 33% (n = 29), and 29.5% (n = 26) had distant metastases. Complete reporting of angioinvasion was found for 67 patients (76.1%), and of lymphatic vessel invasion for 55 patients (62.5%). Angioinvasion had 14.9% (n = 10) of the patients, and lymphatic invasion had 30.9% (n = 17).

3.2. Histopathology and staging

Pancreatic surgical resection consisted of distal pancreatoduodenectomy (n = 43; 48.9%), pancreatic head resection (n = 28; 31.8%), enucleation (n = 7; 8%), segmental resection of the body (n = 5; 5.7%) and total pancreatectomy (n = 5; 5.7%). Indication for total pancreatectomy should be a rare indication for patients with pNET and critically scrutinized in every case. Nonetheless, indication for pancreatectomy was given in 5 patients due to the extent of the primary tumor. These patients suffered from tumor related endocrine symptoms. Two patients had multiple pNETs (15 and 27 tumors) exceeding 2 cm.

An extended multivisceral operation, including additional liver or colon resection, was performed on 19.3% of the patients, and tumor debulking was performed on 23.9%.

3.4. Overall survival and prognostic factors

The mean overall survival was 49.18 months [95% CI: 41.5; 56.8]. The overall survival rate was 70.5%, and the 5-year survival rate was 77.3%.

UICC stage I or II patients had a mean overall survival of 92.4 months [95% CI: 75.1; 109.6 months] or 110.2 months [95% CI: 86.4; 134 months], respectively. UICC stage III patients had a mean overall survival of 108 months [95% CI: 94.6; 121.3 months]. Stage IV patients had a mean overall survival of 67.7 months [95% CI: 44.3; 91 months].

ENETS stage I patients had a median overall survival rate of 80.4 months [95% CI: 61.2; 99.6 months], whereas stage II patients attained a higher median overall survival rate of 128.9 months [95% CI: 105.7; 152.1 months]. Stage III patients had a mean overall survival of 104.3 months [95% CI: 80.8; 127.8 months] and stage IV patients had a mean overall survival of 67.7 months [95% CI: 44.3; 91 months]. The overall survival did not differ between the patients with stage I or II compared to those with stage III or IV. No difference in the overall and 5-year survival was observed for the female or male patients.

The extent of the primary tumor (denoted as T1–T4) was not a relevant prognostic factor for overall survival. Nonetheless, the size of the primary tumor was important for assessment of the risk of lymph node or distant metastases. Only 3.4% of the patients with T1 tumors had lymph node metastases, whereas such metastases were present in 57.1% of the patients with T4 tumors (p < 0.001) (Fig. 2). A significant association was also found between the tumor extent and the presence of distant metastases, with the probability of distant metastases increased more than three-fold in the T3 tumors compared to the T1 tumors (p < 0.05) (Fig. 3).

The absence of lymph node metastases has been shown to be associated with better survival [13]. However, patients with negative lymph nodes did not have better survival rates (p > 0.05). Thus, whether the lymph node ratio could predict overall survival was tested. However, no