Surgical management of pancreatic neuroendocrine tumors
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CHAPTER 9

Nomogram to predict recurrent disease in non-functional pancreatic neuroendocrine tumors.

Identify the high risk patient

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ABSTRACT

Background: Reliable prognostic factors for recurrence of non-functional pancreatic neuroendocrine tumors (NF-pNET) are unknown because of its rarity. Aim of this study was to predict recurrent disease in patients with grade 1 or 2 NF-pNET after curative resection in order to identify patients who might benefit from adjuvant treatment or intense follow-up.

Methods: Retrospectively all patients with resected NF-pNET from 1997-2013 of two academic institutions were included. Patients with distant metastases or hereditary syndromes were excluded. Recurrent disease was defined as local tumor recurrence, lymph node- or distant metastases. Independent predictors for recurrent disease after curative resection were identified with a multivariable Cox regression. With the independent predictors, a nomogram was made to predict recurrent disease within 5-years after curative resection. The nomogram was internally validated.

Results: ninety-seven patients with grade 1-2 NF-pNET were included and median follow-up was 57 months (IQR 35-82). Twenty-three (24%) patients developed recurrent disease and 7 patients died due to tumor progression. Overall 5-year disease specific survival was 96%. Independent predictors for recurrent disease were tumor size>2cm, positive lymph nodes in resected specimen and perineural invasion. Patients with a nomogram score ≥14 were high risk patients for recurrent disease with a c-statistic of 0.79(CI95% 0.70-0.88) and Hosmer–Lemeshow test of 6.45(p=0.694).

Conclusions: We established a novel nomogram to predict recurrent disease after curative resection in grade 1 and 2 NF-pNET. This practical prognostic model may help to identify high risk patients for tumor recurrence. Clinical trials should be initiated to investigate whether these high risk patients might benefit from adjuvant therapy.
INTRODUCTION

In patients with curative resected non-functional pancreatic neuroendocrine tumor (NF-pNET), the overall prognosis is favourable. The main focus during follow-up is to detect recurrent disease. Reliable recurrence rates are difficult to deduce from the literature, because of the rarity of the disease and because the group of patients with resected pNETs is heterogeneous. Most studies include patients with hereditary syndromes, hormonal overproduction, incidentally detected pNET and patients with metastases or debulking resections. All these different pNET patients have different patterns of tumor recurrence and survival. In patients with resectable NF-pNET, grade 3 NF-pNET or the presence of metastases at diagnosis are associated with a poor prognosis. Other factors than tumor grade such as age and tumor size influence survival. Tumor size might even be so influential, that recommendations are made for non-operative management in selective small (≤2cm) NF-pNET.

In comparison with other forms of cancer including pancreatic cancer, adjuvant treatment after surgical resection is not yet recommended in patients with NF-pNET. In metastatic patients, different treatment options are available in order to reduce tumor load, to inhibit tumor growth or to alleviate the symptoms. These different treatment options, such as chemotherapy, long-acting somatostatin analogues, mTOR or tyrosine kinase inhibitors and peptide receptor radionuclide therapy (PRRT), may be an option as adjuvant treatment in patient with risk factors for recurrent disease after curative resection. However, it is unclear which combination of risk factors for recurrent disease matters most in patients with grade 1 or 2 NF-pNET.

The aim of this study was to analyse the long-term outcome in a very selective group of patients with NF-pNET without hereditary syndromes, grade 3 tumors or distant metastasis at time of diagnosis. First, the 5 and 10-year disease specific survival after pancreatic resection for NF-pNET was calculated. Secondly, significant predictors for recurrent disease in patients with grade 1 or 2 NF-pNET were analyzed. With these predictors, a nomogram was developed to calculate the recurrent risk of the individual patient and to identify the high risk patient for recurrent disease after curative resection.

METHODS

Retrospectively all NF-pNET with a curative resection from 1997 to 2013 of two academic institutions were included. Both institutions were high volume centers for pancreatic surgery and specialized in the treatment of neuroendocrine tumors. The institutions were the Erasmus Medical Centre in Rotterdam and the Academic Medical Centre in Amsterdam, both in The Netherlands. Patients were included in the database if patients had pathology proven pNET. Patients with an ampullary NET or duodenal NET were excluded from the study. The pathology reports of all pancreas resections in the selected period were reviewed.
for the diagnosis of pNET. Inclusion criteria for this study were adults with a curative resected grade 1 or 2 NF-pNET without metastasis at the time of diagnosis. All patients with locally advanced disease or distant metastases, successfully treated or not, were excluded. Patients with hereditary syndromes, such as Multiple Endocrine Neoplasia type 1 (MEN-1) or Von Hippel-Lindau syndrome (VHL), even if diagnosed after resection of the pNET, were also excluded. Patients with grade 3 NF-pNET were excluded for survival analysis.

NF-pNET was defined as a pNET without clinical syndrome based on excessive hormone secretion or symptoms associated with hormone overproduction. The medical records, radiological imaging reports and operation reports were reviewed for the demographics and clinical data including, age of surgery, body mass index (BMI), sex, tumor size (based on preoperative radiological imaging), tumor location and type of surgery. Radiological imaging consisted of abdominal CT scan and, if necessary, endoscopic ultrasonography and octreotide scintigraphy (Octreoscan).

Depending on tumor location, pancreatoduodenectomy or distal pancreatectomy was performed. Tumor enucleation or central pancreatectomy was performed in patients with small pNET which were adequately distanced from the pancreatic duct. Lymphadenectomy was not routinely performed in patients with tumor enucleation. Resection margins are classified according the Royal College of Pathologists. Completely excised tumors are classified as R0, tumors with microscopic margin involvement <1mm are classified as R1. Pathology was performed according to the local protocols.

Major complications were defined as pancreatic fistula grade B/C, delayed gastric emptying grade B/C or post-operative bleeding grade B/C, scored according to the ISGPF classifications. The pathology reports were carefully reassessed for lymph node involvement, vascular or perineural invasion. Mitotic count and histological grade were based on the World Health Organisation (WHO) classification of 2010 in grade 1 to 3. The pathology slides were reassessed if the tumor grade was incomplete or missing.

Recurrent disease was defined as local recurrence in the pancreas, new localization in lymph nodes or the onset of distant metastases. Besides routine control of physical symptoms, the follow-up program consisted of physical examination, laboratory tests and radiological imaging every 6 months or every year, depending on the test results. The survival was last updated at July 2014. Disease specific survival was defined as the percentage of patients still alive and not has died due to NF-pNET. Recurrent free survival was defined as the percentage of patients without recurrent disease after resection.

Statistical analysis
Statistical analyses were performed using IBM SPSS statistics 20 and R for windows version 3.0.2 (cran-Rproject.org). Based on the outcome, the data was described with mean and standard deviation (SD) or median and interquartile range (IQR). In categorical data, the number
and proportion (%) are displayed. Kaplan-Meier curves were used to determine the median time for recurrent disease and survival. To identify predictors for recurrent disease, a univariable and multivariable Cox proportional hazard model for 5-year recurrence was used. The assumption of proportional hazard regression was tested by visually inspecting the log minus log plots. No violations were detected for any of the variables included in the model. The results were presented with the Hazard Ratio (HR) and the 95% confidence interval (CI95). A nomogram was made, based on the significant predictors from the backward multivariable analysis. Based on the nomogram scores, high risk patients for 5-year recurrent disease were identified. The value of a high risk patient was calculated as the cut-off value whereby 50% of the patients had developed recurrent disease within 5 years using Kaplan-Meier analysis. Model performance was assessed by measuring discrimination and calibration. Discrimination is the ability to separate the persons who will have a recurrence from the persons who will not have a recurrence, while calibration is the ability to correctly quantify the observed absolute risk. The discriminative ability of the model was examined by calculating Harrel’s c-statistic 24 with 95% CI and the calibration of the model was assessed by calculating the goodness of fit Hosmer–Lemeshow Chi-square test. Moreover we examined the discrimination of the WHO grade model 23 and compared the c-statistics of the two models using a z-test. The c-statistic may vary from 0.5 to 1.0. A discriminative value of 0.5 was considered as good as chance and a value above 0.9 was excellent. If the calibration was not significantly different, the prediction of the model was comparable with the actual outcome. A 2 sided p-value < 0.05 was considered significant. The study has been approved by the Medical Ethics Review Committee.
RESULTS

Overall, 122 resected patients were screened for inclusion; nine patients with synchronous metastases at the time of the operation and were excluded. In total, 8 patients had a grade 3 tumor with a median Ki67 index of 35% (IQR: 26-50). All 8 patients developed recurrent disease within 5 years with a median of 11 months (IQR 4.0-17.9) and the median disease specific survival was 23 months (IQR 16.8-29.2). The 8 patients with grade 3 tumor were excluded since it is known that these tumors are highly aggressive. Also 5 patients with MEN-1 syndrome and 1 patient with VHL were excluded. In total, 99 patients were finally included. Patients’ characteristics are listed in table 1.

<table>
<thead>
<tr>
<th>n = 99 patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)(^1)</td>
<td>56.2 (10.9)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>44 (44)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>25.0 (4.0)</td>
</tr>
<tr>
<td>ASA classification(^2), n (%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>23 (23)</td>
</tr>
<tr>
<td>II</td>
<td>70 (71)</td>
</tr>
<tr>
<td>III</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Tumor location, n (%)</td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>50 (51)</td>
</tr>
<tr>
<td>Corpus</td>
<td>19 (19)</td>
</tr>
<tr>
<td>Tail</td>
<td>30 (30)</td>
</tr>
</tbody>
</table>

\(^1\) Standard deviation, \(^2\)Body mass index, \(^3\)Society of Anaesthesiologists classification

Table 1 Characteristics of patients with a resected non-functional pancreatic neuroendocrine tumor

Oncological outcome after resection

A pancreateoduodenectomy was performed in 42 (43%), left pancreatectomy in 33 (33%), tumor enucleation in 14 (14%), central pancreatectomy in 9 (9%) and total pancreatectomy in 1 (1%) patient. Total pancreatectomy was carried out because of the suspicion of IPMN and positive resection margins peri-operative. The postoperative pathology result was an NF-pNET. In-hospital mortality after pancreatic resection was 2% (2/107), both due to complications after pancreateoduodenectomy. The postoperative outcome is listed in table 2.
Long-term Follow-up
Since two patients died postoperatively, 97 patients were suitable for long-term survival analysis. Median follow-up time was 57 months (IQR 35-82), 23 (24%) patients developed recurrent disease and 13 patients (13%) died, including 7 patients due to tumor progression.

The 5-year disease specific survival of the 97 patients was 96% and the overall 5-year survival was 91%. The 10-year disease specific survival was 82% and the overall 10-year survival was 65%. The 10-year disease specific survival (A) and 10-year recurrent free survival (B) were shown in figure 1.

Independent predictors for recurrent disease
In the univariable Cox regression including 97 patients for analysis, tumor size > 2cm, positive lymph nodes in resected specimen, R1 resection margin, tumor grade II, perineural and vascular invasion were risk factors for recurrent disease after curative resection, as listed in table 3. With a backwards selection, only tumor size >2cm, positive lymph nodes and perineural invasion were significant predictors for recurrent disease in the multivariable analysis.
Table 3: Risk factors for recurrent disease in patients with non-functional pancreatic neuroendocrine tumors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariable Cox regression</th>
<th>Multivariable Cox regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>HR = 1.08, CI 0.48-2.44, P = 0.86</td>
<td></td>
</tr>
<tr>
<td>Age &gt; 55 yr</td>
<td>HR = 0.96, CI 0.42-2.22, P = 0.93</td>
<td></td>
</tr>
<tr>
<td>Tumor location pancreatic head</td>
<td>HR = 1.85, CI 0.80-4.28, P = 0.15</td>
<td></td>
</tr>
<tr>
<td>BMI &gt; 26</td>
<td>HR = 0.40, CI 0.15-1.06, P = 0.07</td>
<td></td>
</tr>
<tr>
<td>ASA classification III-IV</td>
<td>HR = 0.04, CI 0.0-40.0, P = 0.37</td>
<td></td>
</tr>
<tr>
<td>Negative somatostatin scintigraphy</td>
<td>HR = 1.5, CI 0.41-5.48, P = 0.54</td>
<td></td>
</tr>
<tr>
<td>Tumor size &gt; 2 cm</td>
<td>HR = 11.79, CI 1.59-87.48, P = 0.016</td>
<td>HR = 10.5, CI 1.4-81.0, P = 0.024</td>
</tr>
<tr>
<td>Positive lymph nodes in resected specimen</td>
<td>HR = 4.67, CI 1.9-11.30, P = 0.001</td>
<td>HR = 2.9, CI 1.2-6.8, P = 0.014</td>
</tr>
<tr>
<td>R1 resection margin</td>
<td>HR = 2.5, CI 1.08-5.97, P = 0.032</td>
<td></td>
</tr>
<tr>
<td>Major complications</td>
<td>HR = 0.53, CI 0.20-1.42, P = 0.21</td>
<td></td>
</tr>
<tr>
<td>Tumor grade 2</td>
<td>HR = 4.46, CI 1.8-10.87, P = 0.001</td>
<td></td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>HR = 4.47, CI 1.8-10.92, P = 0.001</td>
<td>HR = 5.3, CI 2.0-13.6, P = 0.001</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>HR = 3.4, CI 1.5-7.7, P = 0.003</td>
<td></td>
</tr>
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</table>

1 Body mass index; 2 Society of Anaesthesiologists classification; 3 only patients in analysis if a somatostatin scintigraphy was performed (n = 68); 4 Patients with tumor enucleation were excluded from this analysis since no lymphadenectomy was carried out; 5 Hazard Ratio; 6 Confidence interval; * P < 0.05
No | Yes
---|---
Positive lymph nodes | 0 | 3

No | Yes
---|---
Perineural invasion | 0 | 5

No | Yes
---|---
Tumor size >2cm | 0 | 11

Total points

| 0 | 3 | 5 | 8 | 11 | 14 | 16 | 19 |

Probability %

| 4 | 9 | 15 | 38 | 49 | 62 | 82 | 99 |

Figure 2. Nomogram to predict recurrent disease within 5 years after curative resection. Each predictor has its own number of points. If a predictor is present, the patient will receive the corresponding points. These points can be added up to a total number of points. The number of total points can be translated into the probability of recurrent disease within 5 years after curative resection.

**Nomogram and high risk patients**

Based on the hazard ratios of the significant predictors from the multivariable backwards Cox Regression, a nomogram was made, see figure 2. The nomogram predict the probability to develop recurrent disease within 5 years after curative resection in patients with a grade 1 or 2 NF-pNET. Compared to patients without recurrent disease, the nomogram scores were significant increased in patients with recurrent disease (p <0.001), see figure 3. Based on the nomogram, high risk patients for recurrent disease can be identified. In the patients with a nomogram score ≥ 14, 50% have developed recurrent disease within 5 years (median 34 months (CI95% 18-50)). Therefore, patients with a nomogram score ≥ 14 are identified as high risk patients for recurrent disease within 5 years, see figure 3.
Discrimination and calibration of the Nomogram

The discrimination of the nomogram was 0.79 (CI95%: 0.70-0.88) and the Hosmer Lemeshow chi-square test was 6.45 (p=0.694). Therefore, the ability of the nomogram to separate patients who will develop recurrent disease was good. In practice, the WHO grading is used to predict recurrent disease. In our study-population, the discrimination of the WHO grading was lower compared to our nomogram with a c-statistic of 0.689 (CI95%: 0.590-0.788), however this was not significant (p-value=0.066). The Hosmer Lemeshow chi-square test was not available, since there were only two variable, grade 1 and grade 2.

DISCUSSION

The 5 and 10-year disease specific survival after pancreatic resection for NF-pNET without hereditary syndromes or distant metastases at time of surgery was resp. 96% and 82%. Predictors for recurrent disease in patients with a grade 1 or 2 NF-pNET were tumor size > 2cm, positive lymph nodes and perineural invasion. These factors are translated in a nomogram to predict recurrent disease within 5 years after curative resection. Patients with a nomogram score ≥14 are high risk patients for recurrent disease.

Based on our cohort, the nomogram was better in the prediction of recurrent disease within 5-years compared to tumor grade of the WHO classification with a c-statistic of resp. 0.788 and 0.689 (P: 0.066). High risk patients may benefit from adjuvant treatment after their curative resection. However, until now adjuvant treatment is no standard care and there is no evidence that adjuvant treatment reduces the risk of recurrent disease. Based on the treatment...
in patients with advanced pNET, different treatment options are available for adjuvant treatment such as chemotherapy, long-acting somatostatin analogues, mTOR or tyrosine kinase inhibitors and PRRT.

Most studies on risk factors for recurrent disease after resection of pNET included patients with distant metastases, functional and non-functional tumors or patients with MEN1 syndrome. By including all these patients, the results may be clouded or misleading since the recurrent and survival rate is different for these patients. In this study, we included a very selective group of NF-pNET and analyzed risk factors for recurrent disease. Patients with independent predictors for recurrent disease may benefit from a stricter follow-up program. Instead of a surveillance program with radiological imaging and biochemical markers (such as chromogranin A) on a yearly basis, patients with independent predictors for recurrent disease might benefit from follow-up every 6 months with biochemical markers and radiological imaging. It is beyond this article to discuss the different options of radiological imaging and the ideal follow-up program.

There are some limitations to this study. First the extended inclusion period. In the beginning of the study, the follow-up program was not standardized for every patient. For example, in patients with elevated chromogranin A, radiological imaging was more frequently performed. On the other hand, in patients with a grade 1 tumor without positive lymph nodes, a less strict follow-up program was followed. This may bias the time to detect recurrent disease. However, until now there is no exact follow-up program in the guidelines. Another limitation is the diversity in race in our study; almost all the included patients were Caucasians. Other studies have found differences between different races and survival. Since almost all the patients were of the same race, it was not possible to include this variable in the analysis. Thirdly, the accuracy of the specimen handling and pathology reports might result in bias. According La Rosa et al, also nuclear atypia, necrosis and cytokeratin 19 expression were significant predictors for overall disease-specific survival. These factors were not fully known in all our patients and therefore not included in the cox regression analysis. In our nomogram, only grade 1 and 2 NF-pNET were included because a grade 3 tumor was an already known risk factor for a poor prognosis and by including these patients, the prediction model would be skewed. Also in daily practice, the treatment of grade 3 NF-pNET is different compared to grade 1 and 2 tumors. Since the limited data, it is still unclear if resectable grade 3 NF-pNET may benefit from surgical resection of the primary tumor. Finally, our nomogram needs to be externally validated in order to investigate whether the nomogram is useful in another population.

For further studies, an uniform description is preferred as regards to the results. In survival analysis, an accurate distinction should be made between functioning and non-functioning pNET and patients with hereditary syndromes should be separately analyzed. Even in this patient group with often small numbers, it is important to provide accurate and detailed data.
Our future goal in the treatment of NF-pNET may be the adjuvant treatment of high risk patients with NF-pNET. International randomized trials are needed to investigate if these high risk patients may benefit from adjuvant treatment after curative resection.

In conclusion

Although tumor grade is important for prognosis, also tumor size >2cm, positive lymph nodes and perineural invasion are independent predictors for tumor recurrence. Surgical resection is required in order to be fully informed on these predictors and the pathologist needs to describe all these factors as well in the pathology report. The nomogram predicts recurrent disease after curative resection in grade 1 and 2 NF-pNET based on these risk factors. Patients with a nomogram score ≥ 14 are identified as high risk patients and these patients may benefit from adjuvant therapy or intensive follow-up.

Declaration of interest and Funding

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REFERENCES


