Natural course of small, asymptomatic neuroendocrine pancreatic tumours in multiple endocrine neoplasia type 1: an endoscopic ultrasound imaging study

P H Kann¹, E Balakina¹, ⁵, D Ivan¹, D K Bartsch², S Meyer¹, K-J Klose³, Th Behr⁴ and P Langer²

¹Division of Endocrinology and Diabetology, ²Department of Surgery, Philipp’s University, D-35033 Marburg, Germany
³Departments of Radiology and ⁴Nuclear Medicine, Philipp’s University, Marburg, Germany,
⁵I M Sechenov Moscow Medical Academy, Moscow, Russia

(Requests for offprints should be addressed to P H Kann; Email: Kannp@med.uni-marburg.de)

P H Kann and E Balakina contributed equally to this paper

Abstract

Endoscopic ultrasound (EUS) enables detection and localization of pancreatic neuroendocrine tumours. Even small tumours down to a diameter of 1–2 mm can be visualized. Since such small tumours usually cannot be detected by computed tomography (ct), magnetic resonance imaging (mri) and somatostatin receptor scintigraphy (srs), and experience with EUS imaging is limited, there is no clear evidence for clinical management in multiple endocrine neoplasia type 1 (MEN1). Knowledge about the natural course of growth and metastatic distribution is mandatory to come to appropriate clinical decisions and guidelines. This prospective study was aimed to assess the natural course of small (<15 mm) neuroendocrine pancreatic tumours without clinical symptoms due to endocrine activity or mechanical problems and without clear indication for surgical therapy in MEN1 by EUS.

A total of 82 asymptomatic tumours <15 mm (5.9 ± 3.2 mm diameter at baseline) in 20 patients with MEN1-disease (8 female/12 male, 43 ± 13 years) were studied over a period of 20 ± 12 months (33.8 patient years, 106.7 tumour years) by EUS. Change in largest diameter of each tumour and annual tumour incidence rate in the patients’ cohort were calculated.

Increase of largest tumour diameter was found to be 1.3 ± 3.2% per month, annual tumour incidence rate 0.62 new tumours per patient year. In one patient, rapid progressive pancreatic manifestation of MEN1 was observed. There was no evidence in ct and/or srs and/or mri for metastatic disease in all patients. Only 4/84 (4.8%) pancreatic tumours could be visualized by computed tomography, 5/79 (6.3%) by somatostatin receptor imaging and 4/39 (10.3%) by magnetic resonance imaging.

Small asymptomatic neuroendocrine pancreatic tumours in MEN1 usually seem to grow slowly. Annual tumour incidence rate is low. However, faster growing tumours and patients with rapidly progressive disease can be observed. Risk for obvious metastatic disease from asymptomatic neuroendocrine pancreatic tumours <15 mm in MEN1 seems to be low.

Endocrine-Related Cancer (2006) 13 1195–1202

Introduction

In addition, EUS enables to visualize small neuroendocrine tumours down to a diameter of 1–2 mm can be visualized (Kann et al. 2001, 2003, Wamsteker et al. 2003, Hellman et al. 2005, Thomas-Marques et al. 2006). Therefore, its use in endocrinology for imaging of the endocrine pancreas and also the adrenal glands is becoming more frequent (Kann et al. 1998a, 1998b, 1999, 2000, 2004, Kann 2005). However, compared with pancreatic adenocarcinomas, neuroendocrine tumours of the pancreas are rare. Only small series or single cases have been published (Bolondi et al. 1990, Lightdale et al. 1991, Zimmer et al. 1994, Meyenberger et al. 1995, Scheffold et al. 1995, Kann et al. 2001, 2003).

Occurrence of neuroendocrine gastroenteropancreatic tumours is a feature of MEN1-disease, reports on their prevalence usually refer to surgery (Carty et al. 1998) and histopathological studies (Le Bodic et al. 1996). Recommended imaging procedures are abdominal sonography, ct, mri and srs (Chanson et al. 1997, Owen et al. 2001). However, very small tumours cannot be detected by these means.

Detection of small pancreatic tumours in MEN1-patients by EUS imaging (Langer et al. 2004) raises new questions. Experiences with EUS in MEN1 are limited. Thus, there is no knowledge on clinical relevance and no clear evidence for clinical management of small neuroendocrine pancreatic tumours only detected by EUS, however negative by ct, mri and srs.

Knowledge about natural course of growth, proliferation and metastatic distribution is mandatory to come to appropriate clinical decisions and guidelines (Mignon 2000).

This study was aimed to assess the natural course by EUS imaging of small (< 15 mm) neuroendocrine pancreatic tumours without clinical symptoms due to endocrine activity or mechanical problems such as obstruction of biliary and/or pancreatic ducts, and no clear indication for surgical therapy to provide information on the clinical relevance of these small tumours. Besides change in tumour diameter, annual incidence rate of neuroendocrine pancreatic tumours as detected by EUS should be calculated in these patients. Further, risk for obvious metastatic disease should be considered.

The purpose of this study was thus to provide information about the spontaneous follow-up of small neuroendocrine pancreatic tumours in MEN1. Knowing this, it can be possible to distinguish patients with the ‘usual course’ from patients with rapid progressive disease.

This study was approved by the local ethical committee and conducted as a prospective study. From two patients (patients no. 1 and 2) also results from EUS examinations performed before starting the prospective study were included, since these examinations were performed according to the same protocol by the same examiner. Informed consent was obtained from each patient.

Materials and methods
Twenty patients with MEN1-disease (8 female/12 male, 43 ± 13 years: patient characteristics given in Tables 1 and 2) with a total of 84 asymptomatic, endocrine inactive tumours < 15 mm in largest diameter in were studied. In total, this analysis refers to 33.8 patient years and 106.7 tumour years respectively.

In 61 of these tumours, change in largest tumour diameter could be calculated since at least two EUS ultrasound examinations were performed, and these tumours could clearly be reidentified during follow-up. Ten of these 61 tumours were newly detected during follow-up, not at the first examination, however included into the calculation of growth velocity since they were measured at least twice.

Concerning the remaining 23 tumours, six were newly detected in follow-up and only examined once, one additional tumour was detected once and could not clearly be reidentified at the following examinations. Thus, in these tumours calculation of change in largest tumour diameter was not possible. One patient (patient no. 18) with rapidly progressive disease could not be included into the calculation of growth velocity. At the time of inclusion into the study, he had two tumours, after 12 months, four tumours were found, and after 29 months, a total of nine pancreatic tumours were detected. It was not possible to discriminate clearly between newly detected and formerly described tumours. Two tumours in patient no. 11 were excluded from analysis since they were larger than 15 mm (20.2 mm/20.5 mm). This patient was treated by surgery after 5 months of follow-up. This is the only patient where the tumours were confirmed by histology to be neuroendocrine tumours in this study yet.

The mean observation time of patients was 20 ± 12 months (range 5–45 months, median observation time 20 months). The mean observation time of the tumours that were taken to calculate growth velocity (n = 61) was 19 ± 12 months (range 5–45 months, median observation time 20 months).

EUS was performed by one single experienced investigator (phk) using a Pentax FG 32 UA endosonoscope with a longitudinal 7.5 MHz sector array in combination with a Hitachi EUB 525 ultrasound computer. Premedication was performed with 30 mg
pentazocine, 10–30 mg diazepam and 0.25–0.5 mg atropine. Examination time was approximately 45 min.

Neuroendocrine pancreatic tumours were defined by EUS imaging according to the recently published criteria obtained from patients where the EUS findings were confirmed by postoperative histology (Kann et al. 2001, 2003). In summary, neuroendocrine pancreatic tumours usually appear hypoechoic compared with normal pancreatic tissue or, more rarely, isoechoic with a small hypoechoic bordering (halo).

EUS imaging was performed at least twice, up to eight (mean ± s.d., 3.2 ± 1.5) times, time interval between the EUS examination – by study protocol to be performed every 6 months – was 9.8 ± 5.1 months. This deviation from the study protocol was due to the retrospective inclusion of examinations in patients no. 1 and 2 and also due to clinical and logistic needs and problems. Patients from all regions in Germany were included in this study.

Referring to RECIST criteria (Therasse et al. 2000) and a recent study confirming reliability of this approach for EUS imaging (Kann et al. 2006), largest diameter of each tumour that could be detected was determined by EUS at baseline and in follow-up. The slope of the regression line (change from baseline (\%)/time (months)) of each single tumour referring to all measurements available for each particular tumour was taken as change in largest tumour diameter.

Annual tumour incidence rate was calculated as cumulative number of newly detected tumours in all

### Table 1 clinical characteristics of 20 patient with MEN1-disease

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Gender/age</th>
<th>Pituitary tumour</th>
<th>Primary hyperparathyroidism</th>
<th>Neuroendocrine pancreatic tumour(s) confirmed by previous pancreatic surgery</th>
<th>Genetical diagnosis MEN1</th>
<th>Number of pancreatic tumours detected by endosonography (first examination)</th>
<th>Number of pancreatic tumours detected by endosonography (last examination)</th>
<th>Observation period (months)</th>
<th>Number of pancreatic tumours detected by ct (last examination)</th>
<th>Number of pancreatic tumours detected by mri (last examination)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>f/42</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>m/36</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>m/21</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>m/54</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>m/55</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>m/30</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>m/0</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>m/0</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>m/0</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>m/0</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>m/0</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>m/0</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>m/0</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>m/0</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>m/0</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>16</td>
<td>m/0</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>17</td>
<td>m/0</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>m/0</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>19</td>
<td>m/0</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>m/0</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>2</td>
<td>2</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

f, female; m, male; y, yes; n, no; n/d, not done.

Table 2 genetical diagnosis of 20 patient with MEN1-disease

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>c.155-3TCC &gt; TTC missense</td>
</tr>
<tr>
<td>2</td>
<td>No mutation detected</td>
</tr>
<tr>
<td>3</td>
<td>67 Ins AGCCC</td>
</tr>
<tr>
<td>4</td>
<td>No mutation detected</td>
</tr>
<tr>
<td>5</td>
<td>E116X</td>
</tr>
<tr>
<td>6</td>
<td>427 Del 6 bp 1390 (GTCCCA)</td>
</tr>
<tr>
<td>7</td>
<td>Q554X</td>
</tr>
<tr>
<td>8</td>
<td>splice Intron 4 C894 G → A</td>
</tr>
<tr>
<td>9</td>
<td>No mutation detected</td>
</tr>
<tr>
<td>10</td>
<td>466 14 bp Del</td>
</tr>
<tr>
<td>11</td>
<td>c.894-9G &gt; A splice-site</td>
</tr>
<tr>
<td>12</td>
<td>E116X</td>
</tr>
<tr>
<td>13</td>
<td>K119X</td>
</tr>
<tr>
<td>14</td>
<td>514 Ins C</td>
</tr>
<tr>
<td>15</td>
<td>C488G → stop</td>
</tr>
<tr>
<td>16</td>
<td>E116X</td>
</tr>
<tr>
<td>17</td>
<td>K120X</td>
</tr>
<tr>
<td>18</td>
<td>No mutation detected</td>
</tr>
<tr>
<td>19</td>
<td>L168P</td>
</tr>
<tr>
<td>20</td>
<td>L168P</td>
</tr>
</tbody>
</table>
patients divided by the cumulative observation period of all patients included in this study.

Besides in one patient (patient no. 11, mentioned above), all the tumours investigated in this study were not yet confirmed by histology. Even if the diagnosis of MEN1-disease makes in very likely to consider pancreatic lesions as described above as neuroendocrine tumours, it cannot completely be ruled out that also different pancreatic processes might have been detected by EUS imaging in these patients (Kann et al. 2003).

In all patients, EUS findings were compared with ct (systematically performed in every patient) and/or srs and/or mri (as available) not only concerning the pancreas, but also whether there might be evidence for metastatic disease in the abdomen, especially in the liver (systematic EUS imaging of the liver was not performed in this study).

Therapeutic means that might influence tumour behaviour such as somatostatine analogues, α-interferon, radioligand therapy, irradiation, embolization and cytotstatic therapy were defined exclusion criteria.

Results

At the time of first detection, mean tumour size was $5.9 \pm 3.2$ mm (range 1.5–14.5 mm, $n=73$; patient no. 18 – who developed seven new tumour during a period of 29 months – was excluded from this analysis since the time of first detection could not clearly be defined as explained above; two tumours larger than 15 mm [patient no. 11] were also not included in this calculation).

Change in largest tumour diameter was found to be $1.3 \pm 3.2\%$ per month and ranged from $-7.8$ to $+10.6\%$ per month ($n=61$; Fig. 1).

Annual tumour incidence rate was calculated 0.62 new tumours/patient year ($n=20$ patients; this calculation included patient no. 18).

The large majority of the tumours analysed in this study was not detected by any other imaging procedure:

- ct: 4/84 (4.8%) detected
- srs: 5/79 (6.3%) detected
- mri: 4/39 (10.3%) detected

In all the patients, there was no evidence for metastatic disease by ct and/or srs and/or mri during the study.

One patient (no. 18, already mentioned above with the increasing number of pancreatic tumours from 2 to 9 over a period of 29 months) had previous resection of a gastrinoma in the duodenal wall and of one solitary metastasis in the liver (detected by ct, mri, srs; confirmed by histology; 2.5 cm in diameter in liver segment 4) before the start of the study.

Discussion

In general, neuroendocrine tumours of the pancreas are rare. If they cause typical symptoms, such as recurring and multiple peptic ulcers, severe diarrhoea or fasting hypoglycaemia due to endocrine activity, there is a clear indication for surgical treatment (Kann et al. 2001).

Large clinically hormone inactive neuroendocrine pancreatic tumours may cause abdominal discomfort, pain, symptoms of intestinal and biliary obstruction, nausea and other unspecific epigastric symptoms and thus be a target of surgical intervention, also to come to an histological diagnosis (Omaitis et al. 2003).

There is a very low probability for incidental detection of small, endocrine inactive, asymptomatic neuroendocrine tumours of the pancreas in the general population since EUS imaging of the pancreas is not used in a widespread matter, and these tumours usually do not seem to be detectable by other methods of imaging. If a small pancreatic tumour is detected incidentally, this – if operability and resectability is given – will usually be considered as an indication for surgery since the most probable histological correlate for such a pancreatic tumour will be an adenocarcinoma, and the patient might benefit from early surgical treatment.

The situation is completely different in patients with known MEN1-disease. They have a very large $a$ priori probability for neuroendocrine pancreatic tumours. Each pancreatic lesion detected in these patients is much more likely to be a neuroendocrine tumour than anything else. Neuroendocrine pancreatic and duodenal tumours are an important factor determining mortality in these patients. These tumours may be clinically insignificant with a benign course, others however are very malignant (Bartsch et al. 2000, Lairmore et al. 2000). Such malignant neuroendocrine pancreatic tumours occur in about 30% of patients (Bartsch et al. 2000, Dotzenrath et al. 2001).

Management of neuroendocrine pancreatic and duodenal tumours in MEN1 is discussed controversially. Aggressive surgical treatment may prevent metastatic disease and can be performed by preserving apparently healthy parts of the pancreas (Thompson 1998, Bartsch et al. 2000, Azimuddin & Chamberlain 2001). On the other hand, sequelae of pancreatic surgery have to be considered. Besides complications closely related to the surgical procedure, increased
morbidity and mortality due to possibly occurring diabetes mellitus have to be taken into account.

In the future, surgical strategy may be adapted to certain mutations in the \textit{MEN1}-gene which seem to determine benign or malignant courses (Bartsch \textit{et al.} 2000).


Management of asymptomatic pancreatic tumours is being discussed. Very aggressive surgical strategies, i.e. removing everything that has been detected, have been suggested (Akerstrom \textit{et al.} 2002). A possible malignant course which seems to be correlated to tumour size is the most relevant problem (Sato \textit{et al.} 2000). Early detection of small hormone inactive tumours in MEN1 is not yet very frequent (Plöckinger \& Wiedenmann 2002).

$\text{Ct}$, $\text{srs}$, percutaneous sonography and angiography are established imaging procedures (Meko \& Norton 1994). However, tumours $<1\text{ cm}$ are rarely detected (Weinel \textit{et al.} 1994, Skogseid \& Öberg 1995). Intraoperative sonography and palpation have a better sensitivity, lesions $<0.3\text{ mm}$ may even be missed (Skogseid \& Öberg 1995).


\textbf{Figure 1} Follow-up of the largest diameter of 61 small asymptomatic neuroendocrine pancreatic tumours in MEN1 obtained by EUS imaging (data of one patient with rapid progressive disease and where due to a relevant increase in the number of pancreatic tumours reidentification of each particular tumour was not possible during follow-up are not displayed in this figure).
We are now able to find more and smaller tumours in MEN1-patients that formerly were undetectable *in vivo*. Since knowledge about natural course of growth, proliferation and metastatic distribution of small neuroendocrine pancreatic tumours in MEN1-disease is fragmentary, change in largest tumour diameter and metastatic behaviour of such lesions was assessed in this study. Furthermore, annual tumour incidence rate was assessed in affected patients.

Our results indicate that small asymptomatic neuroendocrine pancreatic tumours in MEN1 usually seem to grow slowly. In average, doubling of tumour diameter can be expected after 5–10 years. However, patients with rapidly progressive disease, i.e. with faster growing tumours and high annual tumour incidence rate can be observed. Spontaneous decrease of tumour size may occur by nature, however can also be a result of variation of repeated measuring, which is of course higher in small than in large tumours.

No metastatic disease was found in our cohort during the study period. Thus, risk for metastatic disease from slowly growing, asymptomatic, endocrine inactive pancreatic tumours <15 mm may be considered low. However, it has to be taken into account that criteria for metastatic disease were suspicious lesions in ct and/or srs and/or mri. These methods were unable to detect the primary pancreatic lesions in our cohort in almost all cases. Systematic hepatic imaging by EUS has not been established yet. It needs to be stated in this context that the imaging techniques used in this study are unable to detect or exclude micrometastases.

In conclusion, the data obtained from this study referring to 33.8 patient years and 106.7 tumour years can be taken as an information on the natural course of small, asymptomatic, neuroendocrine pancreatic tumours in MEN1-disease. Usually they grow slowly and there is no obvious evidence for a high tendency to be metastatic. However, exceptions showing different biological behaviour (in this study patient no. 18) can be observed and need to be considered.

These data may justify a conservative approach in the typical situation: no symptoms, tumour(s) <15 mm, missing or slow growth velocity as assessed by repeated competent EUS imaging. Based on our data, ‘usual or slow progression’ may be defined as mean increase of largest tumour diameter(s) of about 15% per year and detection of maximally one new neuroendocrine pancreatic tumour every 2 years by EUS. In such patients with ‘usually’ or ‘slowly’ progressing asymptomatic small neuroendocrine pancreatic tumours associated to MEN1-disease, besides aggressive surgical treatment, also an assessment of follow-up and a later decision about surgical seem to be possible. However, this has to be discussed extensively with the patient.

**Acknowledgements**

This study was supported by the Foundation for Innovation of Rhineland-Palatinate, Mainz/Germany and Novartis Pharma GmbH, Nuremberg/Germany. The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

**References**


