Clinical Experience in Surgical Treatment of Gastrointestinal Neuroendocrine Tumors

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Gastroenteropancreatic neuroendocrine tumors (GEP NET) represent heterogenous group of very rare neoplasms. Nevertheless, these tumors have been increasingly diagnosed recently. Authors present own experience with surgical treatment of gastrointestinal neuroendocrine tumors.

The aim of the study was to analyse retrospectively own material of patients with gastrointestinal neuroendocrine tumors treated surgically in the Department of General and Transplant Surgery of Medical University in Łódź.

Material and methods. The analysis included all patients with neuroendocrine tumors surgically treated from January 2007 to June 2009 in the Department of General and Transplant Surgery of Medical University in Łódź. The clinical patients data were obtained from medical histories, operative protocols and outcomes of final histopathological examinations. Analyzed data were as follows: age, gender, type and localization of tumor, clinical signs, results of preoperative tests and type of surgical procedure.

Results. Analysis revealed that 17 patients were operated on for gastrointestinal neuroendocrine tumors between years 2007-2009 in the Department of General and Transplant Surgery. Foregut tumors (5 gastric neuroendocrine tumors and 4 pancreatic insulinomas), midgut tumors (1 neuroendocrine cancer of ascending colon, 3 hepatic neuroendocrine cancers metastases, 2 primary hepatic neuroendocrine cancers, 1 gall bladder neuroendocrine cancer) and hindgut tumors (neuroendocrine cancer of rectum) were diagnosed in nine cases (53%), in seven cases (41%) and in one case (5%), respectively. Wide range of surgeries were performed in the Department, as follows: in 2 cases right hemihepatectomy, in 3 cases extended right hemihepatectomy, in 1 case left hemihepatectomy, in 4 cases pancreatic tumor enucleation, in 2 cases gastric resection, in 3 cases gastrectomy, in 1 case right hemicolectomy and in 1 case anterior resection of the rectum. The vast majority (11/17 patients; 64%) of tumors were poorly-differentiated neuroendocrine carcinomas with high grade of histological malignancy. In one case coincidence of insulinoma and nesidioblastosis was confirmed. One patient suffered from signs of neuroglycopenia with loss of consciousness and convulsion preoperatively, incorrectly diagnosed as epilepsy.

Conclusions. Treatment of patients with gastrointestinal tumors is complex process and most commonly require close cooperation of various professional clinicians. Since asymptomatic course of disease and late stage of tumor advancement at diagnosis, technically difficult operations are often essential. Thus, surgeon who perform operations of patients with neuroendocrine tumors should be well experienced in carrying out extensive surgical procedures.

Key words: neuroendocrine tumors, diagnosis, surgical treatment
enteropancreatic neuroendocrine tumors have been increasingly diagnosed recently, with incidence of 3 new cases/100000 population/year. According to WHO guidelines classification (2000 year) three different types of neuroendocrine tumors have been distinguished: well-differentiated neuroendocrine benign tumor, well-differentiated neuroendocrine carcinoma and poorly-differentiated neuroendocrine carcinoma. Contemporaneously, neuroendocrine neoplasms are divided into hormone producing and non-producing tumors (1, 2).

Gold standard for treatment of GEP NET tumors is complete resection of neoplasm with margin of healthy tissues. In cases of non-radical operations, pharmacological adjuvant treatment with somatostatin analogues, interferon 1, chemotherapy or radiotherapy can be applied. Since rarity and asymptomatic natural history, GEP NET tumors are diagnosed with late stage, what may considerably interfere therapeutic process (1-7).

The aim of the present study was assessment of patients with GEP NET tumors treated from January 2007 to June 2009 in the Department of General and Transplant Surgery (Medical University of Łódź).

MATERIAL AND METHODS

The analysis included all patients with neuroendocrine tumors surgically treated from January 2007 to June 2009 in the Department of General and Transplant Surgery of Medical University in Łódź. Clinical patients data were obtained from medical histories, operative protocols and outcomes of final histopathological examinations. Analyzed data were as follows: age, gender, type and localization of tumor, clinical signs, results of preoperative tests and type of surgical procedure (tab. 1).

RESULTS

During 2007-2009 period of time, 4 patients with insulin secreting tumors were operated on in our Department. In all patients, tumors were localized in pancreas corpus, with diameter below 2 cm. Results of preoperative imaging studies (USG, CT scans of abdominal cavity) were verified by high-resolution intraoperative ultrasonography, with confirmation of tumor localization. In all cases of insulinoma, enucleation procedure was performed. All insulin producing tumors were proved to be benign. During preoperative time, all patients were suffering from hypoglycaemia. Furthermore, one patient suffered from signs of neuroglycopenia with loss of consciousness and convulsion preoperatively, incorrectly diagnosed as epilepsy. In one case, symptoms of intermittent hypoglycaemia were not resolved postoperatively. Final histopathological examination revealed insulinoma accompanied by hyperplasia of pancreatic β – cells (nesidioblastosis) (tab. 2).

Material analysis revealed 5 cases of gastric neuroendocrine tumors; 2 gastric tumors belong to group IA (Ki – 67 <2%) according to gastric NET classification in ENETS modification, in three cases poorly-differentiated carcinoma with perigastric lymph nodes metastases were confirmed (Ki-67 >20%). In none of theese cases of gastric neuroendocrine carcinoma, distant liver metastases were diagnosed. Moreover, preoperative clinical signs of gastric NETs were non-specific. All tumors were incidentally diagnosed during gastroscopy examinations performed for presence of dyspeptic signs. In patients with carcinoid tumors, typical signs of carcinoid syndrome including cardiac disturbances, flushing of facial skin and diarrhoea were not observed.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No of patients</th>
<th>Gender</th>
<th>Median age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulinoma</strong></td>
<td>4</td>
<td>M – 1</td>
<td>49,75</td>
<td>35-60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>K – 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Carcinoid</strong></td>
<td>2</td>
<td>K – 2</td>
<td>57,5</td>
<td>52-63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M – 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neuroendocrine cancer</strong></td>
<td>11</td>
<td>K – 6</td>
<td>60,66</td>
<td>45-72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M – 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>17</td>
<td>K – 9</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M – 8</td>
<td></td>
<td>–</td>
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</tbody>
</table>
In all, five patients were operated on for hepatic neuroendocrine carcinoma and liver resections were performed. In three cases metastatic tumors of neuroendocrine carcinoma of small and large intestitne were presented. Two of all patients mentioned above, were operated on for tumors of primary origin in other center. In one case simultaneous liver and small intestine resection were performed. In two cases primary neuroendocrine carcinoma of the liver were confirmed. Extended right hemihepatectomy for gall bladder neuroendocrine carcinoma was performed in one patient (tab. 3).

The presence of neuroendocrine carcinoma in two postoperative specimens after low anterior resection and right hemicolecotomy was found. In all cases, poor tumor differentiation (group 3 according to GEP NET classification) and high histopathological grading (mitotic activity >20; proliferative activity >20) were confirmed. R0 resections were achieved in all cases.

### DISCUSSION

Neuroendocrine tumors of gastrointestinal tract are very rare neoplasms. Analysis revealed that 17 patients were operated on for gastrointestinal neuroendocrine tumors between years 2007-2009 in the Department of General and Transplant Surgery. Foregut tumors (stomach and pancreas), midgut tumors (small intestine, ascending colon, gall-bladder, liver) and hindgut tumors (rectum) were diagnosed in nine cases (53%), in seven cases (41%) and in one case (5%), respectively. The vast majority (11/17 patients; 64%) of tumors were poorly-differentiated neuroendocrine carcinomas with high grade of histological malignancy. According to the National Neuroendocrine Tumors Registry, the most commonly diagnosed neuroendocrine tumors in Poland are well-differentiated neoplasms which belong to group 1A of WHO classification (2). The difference mentioned above is the result of profile of surgical procedures which are performed in the Department; vast majority of patients were operated on for hepatic neuroendocrine tumors, which most commonly represent distant metastases of malignant neuroendocrine neoplasms.

Solely four persons (23%) from all patients operated in the Department demonstrated preoperatively symptoms related with tumor hormone production activity; other tumors were hormonally non-active. All insulinomas showed hormonal activity. Insulin producing tumors remain major condition responsible for development of hypoglycaemia accompanied with hyprinsulinemia among adults. Furthermore, insulinoma is the most common neuroendo-

### Table 2. Types of neoplasms and localization

<table>
<thead>
<tr>
<th>Type of Neoplasm</th>
<th>Pancreas</th>
<th>Liver</th>
<th>Gall-bladder</th>
<th>Stomach</th>
<th>Colon</th>
<th>Rectum</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulinoma</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Neuroendocrine cancer</td>
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<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>11</td>
</tr>
</tbody>
</table>

### Table 3. Types of neoplasms and surgical treatment

<table>
<thead>
<tr>
<th>Type of Neoplasm</th>
<th>Right hemihepatectomy</th>
<th>Extended right hemihepatectomy</th>
<th>Left hemihepatectomy</th>
<th>Pancreatic resection</th>
<th>Anterior resection of rectum</th>
<th>Gastric resection</th>
<th>Gastrectomy</th>
<th>Right hemicolectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulinoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neuroendocrine cancer</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Total</td>
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<td>4</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>
crine tumor of pancreas, which mainly affects women, with highest incidence in fifth decade of life. In superior portion, insulin producing tumors are benign, with positive Whipple’s triad. In benign cases, patients can be cured by surgical resection of tumor (3, 5).

Data analysis proved, that in the one case, insulin producing tumor was accompanied by nesidioblastosis, which is well-known condition of permanent hiperinsulinemia associated with hypoglycaemia occurring among infants; nevertheless, this disease is diagnosed in adults very rarely. So far, there are only 71 case reports of nesidioblastosis in adults in the literature (8). Low morbidity and uniqueness of this condition disenable potential creation of clear and final diagnostics standards which may allow to give precise preoperative diagnosis.

Still, in majority of cases of endogenic hipcrine insulinomas associated with hypoglycaemia, diagnostics and therapeutic strategies is resultant of clinical tests, imaging studies, intraoperative investigation and final histopathological examination. Exploarative laparotomy with pancreas palpation, intraoperative ultrasonography and eventually, portal blood insulin level test are the most common last point of this strategy. Although, identification and enucleation of insulinoma is not sufficient to exclude simultaneous co-ocurrence of nesidioblastosis. In this controversial cases, postenacluation portal blood insulin level test may be indicated. If high blood concentration of this hormon is preserved, extension of pancreas resection should be considered.

In the one case of female patient with insulinoma, symptoms of neuroglikopenia including loss of conciousness and convulsion were observed. Convulsion seizures related with prior obscured metabolic disturbances were misdiagnosed as epilepsy. Relief from all symptoms and discontinuation of anti-epileptic treatment were obtained postoperatively. Supposedly, key diagnostic step in evaluation of transient loss of consciousness and occurence of convulsion seizure, is precisely obtained medical history concerning peri-seizure symptoms. However, misdetection of causes of temporary loss of consciousness may result in serious complications including patient’s decease (9, 10).

From 2007 to 2009 in Department of General and Transplant Surgery none of patients were operated on for other than insulinoma pancreatic neuroendocrine tumors. Second, most commonly diagnosed pancreatic neuroendocrine tumor is gastrinoma, which according to various statistical data may affect even 30% of patients with NET. Majority of these tumors are characterized by agressive natural history. Other hormon producing pancreatic tumors including glucagonoma, carcinoid, somatostatinoma or vipoma are extremely rare (5).

Case of mixed, poorly-differentiated neuroendocrine and glandular carcinoma of gallbladder needs to be discussed separately. Gall-bladder malignant tumors occur very rarely and represent less than 0.5% of all gastrointestinal cancers diagnosed worldwide. Most of these tumors are adenocarcinomas, incidentally found during elective cholecystectomy, performed for cholecystolithiasis. Gall-bladder neuroendocrine tumors are very uncommon and represent less than 0.5% of all its neoplasms. So far, only 14 cases of gall-bladder mixed tumors have been described worldwide. Since, uniqueness of composite gastrointestinal tumours their histogenesis remain enigmatic. Two hypothesis explaining coincidence of neuroendocrine and glandular cancer have been proposed: coincidental neoplastic change in two different cell types and neoplastic change of a single common precursor cell line. In our case both components of composite tumor were separated, thus potential independent synchronic or metachronic development of both types of neoplasms cannot be excluded. However, taking into consideration histological definiton of cancer which postulate monoclonal proliferation of singel cell, occurence of tumor deriving from two mutated precursor lines of the same localization seems very unlikely (11).

Gastric neuroendocrine tumors represent approximately 10% of all GEP NET tumors and marked incrase in incidence has been observed recently. Due to the etiology, histopathological image and natural history of the disease, three distinct types of neuroendocrine tumors have been distinguished; type I developing on the basis of atrophic gastritis, type II related with Zollinger-Ellison syndrome and type III developing on the basis of normal gastric mucous membrane. In all patients operated on for gastric neuroendocrine tumors in our Department, coincidence of gastritis was confirmed in preoperative endoscopy, including
tumors classified in group IA. All patients with gastric neuroendocrine cancer underwent total gastrectomy with perigastric and celiac trunk lymphadenectomy (lymphadenectomy D2), irrespective of tumor location. All neuroendocrine cancers proved to infiltrate gastric serosal membrane and were characterized by high mitotic index, aggressive course and presence of regional lymph nodes metastases. The size of benign gastric neuroendocrine tumors exceeded 1cm in diameter, thus in every case partial resection of stomach was performed. In cases of smaller benign neoplasms endoscopic tumor resection is feasible, on the condition, that final histopathological examination reveals no features of deeper gastric wall layers infiltration (4, 12).

Neuroendocrine cancers are the most common neoplasms of low malignant potential, nevertheless, since asymptomatic course they are diagnosed with late-stage of advancement; up to 75% of these patients demonstrate liver metastases at diagnosis. Simultaneously, it is estimated that above 70% of patients with confined disease who are radically treated, would develop distant liver metastases during postoperative follow-up (13, 14, 15). Hepatic metastatic tumors occur the most commonly among patients with gastrinoma and intestine neuroendocrine cancer (15). In all cases treated in our Department primary origin of hepatic metastases was localized in small and large intestine. During evaluation of resectability of hepatic tumors, not only their size but also localization is valid. If unradicality of surgical procedure is presumed, major liver resection should be discontinued. Presence of liver metastases decreases overall 5-year survival of patients with neuroendocrine cancer from 75% to 30%, although it is still superior than among patients with metastatic glandular cancer. The only effective treatment of patients with liver metastases is surgical procedure with resection of the tumor and margin of normal hepatic parenchyma. Since late stage of advancement of neoplasms at diagnosis, most commonly large tumors are observed which require wide surgical procedures including hemihepatectomy and extended hemihepatectomy. Unfortunately, wide and radical operations are feasible only in less than 10% of all cases of metastatic to the liver, neuroendocrine cancers (2, 15). Analysis revealed that all cases of neuroendocrine liver metastases appeared to be resectable. In remaining group of patients, it is recommended to perform palliative resections, if 90% of metastases are able to be excised. Unfortunately, these operations are feasible among solely 10-15% of patients (16, 17). In cases of hormon producing tumors, not responded well to conservative treatment with somatostatine analogues, operations of 60-70% tumor mass reduction are recommended. Choice of method of surgical treatment is not dependent on the origin of neuroendocrine cancer metastases (16, 17). In cases of synchronous hepatic metastases, simultaneous primary tumor and liver metastases resections are feasible. Liver resections are also allowed in cases with metastases in both hepatic lobes, on condition that amount of normal liver parenchyma postoperatively (Child Pugh type A) is noninferior than 25% of primary volume. Contraindications for wide hepatic resections are infiltration by the neoplasm above 75% of liver parenchyma and other distant metastases. According to recent studies, 5- and 10-year patient survival after radical hepatic metastases resection may reach even 84 and 94% respectively with median survival of 21-50 months, irrespective of tumor localization (15). The patients operated on for metastases of neuroendocrine cancers in our Department between January of 2007 and June of 2009 have been followed-up; so far, no local recurrence and other distant metastases have been observed.

The major side effect accompanying liver resection is blood loss. Although, the volume of blood loss fluctuated. Further well known complications of massive blood volume transfusion consist of thrombocytopenia, coagulation factor depletion, oxygen affinity changes, hypocalcemia, hyperkalemia, acid–base disturbance, hypothermia and acute respiratory distress syndrome. The considerable knowledge of anatomy of liver segments, intraoperative ultrasonography and Pringle manoeuvre usage allow to significantly decrease amount of blood loss, what enable to extend liver resection. None of these complications occurred in the present study. The mean blood loss in cases did not exceed 1000 ml.

Still, orthotopic liver transplantation remains controversial type of treatment of patients with neuroendocrine cancer hepatic metastases. It has been estimated, that just 0.1% of patients with neuroendocrine cancers
may be candidates for liver transplantation. Up till the present, liver transplanatation procedures have been performed solely among patients with hepatic metastases from primary small intestine and pancreatic tumors (18).

In palliative treatment of patients with hepatic neuroendocrine cancer metastases in specified group of patients, tumor alcoholization, kryotherapy, radiofrequency ablation, hepatic artery embolization and chemoembolization may be applied (15). Indications for these procedures are either liver tumors not suited for surgery or local recurrence after prior liver resection. Undoubtedly advantageous of these procedures is their repeatability in consecutive tumor recurrence. Various analyses resulted in contralateral outcomes concerning 5-year survival of patients after these procedures (ranged from 0 to 71%, with a median survival of 20 to 80 months). Evaluation of these procedures' position in the treatment algorithms of patients with hepatic neuroendocrine cancer metastases may be feasible on the basis of outcomes of multicentre randomized studies (15).

Majority of liver neuroendocrine tumors are metastases. Primary hepatic neuroendocrine tumors occur very rarely. Analysis revealed two cases of primary hepatic neuroendocrine cancers. In every case of suspicion of primary liver neuroendocrine tumor presence of extrahepatic neoplasms should be excluded. Most of the hepatic neuroendocrine cancers are misdiagnosed as metastatic tumors of unknown origin (FPI – focus primarius ignotus), thus their incidence seems to be underestimated. So far, only a few cases of primary hepatic tumors have been reported worldwide. According to published reports, most of these tumors occur among middle-aged women. Signs and symptoms are nonspecific, thus they are diagnosed with late stage of advancement. Primary hepatic neuroendocrine cancers may imitate hepatocellular cancer and cholangiogenic tumors in preoperative imaging studies. Final diagnosis of primary hepatic neuroendocrine cancer may be established on the basis of precise histopathological examination and chromogranin and synaptophysin positive immunostainings. The mainstay of curative treatment of primary hepatic neuroendocrine tumors is liver resection. Data regarding palliative chemotherapy in patients with unresectable tumors is insufficient. An enhanced awareness about the rare, untypical sites of neuroendocrine tumours (such as liver) will result in an optimal management of these patients (19, 20, 21).

Large bowel neuroendocrine tumors represent approximately 20% of all GEP NET tumors and most commonly are localized in rectum. Large bowel neuroendocrine tumors demonstrate poorest prognosis of all GEP NETs. The principles of surgical treatments are identical with standards generally accepted in other malignancies. In cases of tumor size below 2 cm, local tumor resection is allowed (3, 7). All cases of large bowel neuroendocrine cancers treated in our Department were diagnosed with the late stage of local advancement, thus aggressive surgical treatment was applied.

SUMMARY

Gastrointestinal neuroendocrine tumors are very rare; this heterogenous group of neoplasms with various natural history, prognosis, and treatment modality, which may be frequently complex and may require close cooperation of various professional clinicians such as surgeons, pathologists, endocrinologists, oncologists of invasive radiologists. Thus, these patients should be treated in centers experienced in neuroendocrine neoplasms therapy. Since asymptomatic course of the disease and late stage of tumor advancement at diagnosis, technically difficult operations are often necessary. Thus, surgeon who perform operations of patients with neuroendocrine tumors should be well experienced in carrying out extensive surgical procedures concerning stomach, intestine, liver and pancreas.

REFERENCES
