

SURGICAL TREATMENT OF PANCREATIC NEUROENDOCRINE TUMOURS – CLINICAL EXPERIENCE

*BEATA JABŁOŃSKA, DARIA DRANKA-BOJAROWSKA, HANNA PALACZ,
ADAM LEWIŃSKI, PAWEŁ LAMPE*

Department of Gastrointestinal Surgery, Silesian Medical University in Katowice
Kierownik: prof. dr hab. *P. Lampe*

The aim of the work was the clinical characteristics and analysis of preliminary results for surgical treatment of pancreatic neuroendocrine tumors (PNETs), based on own material.

Material and methods. In the period from 2005 to 2009, in the Department of Gastrointestinal Surgery, Silesian Medical University in Katowice, there were 27 patients (15 males and 12 females) treated surgically for pancreatic neuroendocrine tumours, constituting 65.86% (27/41) of all gastroenteropancreatic neuroendocrine tumours. Prior to the surgery, the following diagnostic examinations were performed: laboratory tests and imaging examinations (abdominal ultrasound and CT scan). The following tumour localisation was established: head of the pancreas – 14, body of the pancreas – 4, tail of the pancreas – 5, body and tail of the pancreas – 1, retroperitoneal space – 4. There were found 24 (88.89%) primary tumours and 3 (11.11%) recurrences. The following methods of surgical treatment were applied: pancreatoduodenectomy – 11, distal pancreatic resection with splenectomy – 6, middle segment resection with anastomosis between the pancreatic tail and jejunal loop: Roux-Y procedure – 1, pancreatic resection by Beger procedure – 1, pancreatic head and body resection with splenectomy – 1, tumour enucleation or local excision – 4, exploratory laparotomy with specimen collection – 3.

Results. The mean hospitalisation period was 25 days (4–78 days). The mean procedure duration was 4.2 hours (1.15–9.15 hours). Early post-operative complications were observed in 10 patients (37.04%). The following early complications were observed: intra-abdominal abscess – 2, wound suppuration – 2, pancreatic fistula – 1, acute pancreatitis – 1, pancreaticojejunal anastomosis leak – 1, peritoneal cavity haemorrhage – 1, acute cholangitis – 1, adhesion obstruction – 1, subobstruction – 1, portal vein thrombosis – 1, sepsis – 1, fluid in pleural cavity – 1, acute heart failure – 1. There were performed 2 (7.41%) repeat surgeries: one due to adhesion obstruction and one due to peritoneal cavity haemorrhage. Death of 1 patient (3.71%) was recorded in the post-operative period due to acute heart failure.

Conclusions. Pancreatic neuroendocrine tumours constituted the majority of gastroenteropancreatic neuroendocrine tumours in the analysed patient group. Most commonly, PNETs were localised in the head of the pancreas. In the presented material, the mortality rate does not exceed 4%, similarly as in other renowned centres.

Key words: neuroendocrine tumours, pancreas

Pancreatic neuroendocrine tumors (PNETs) are classified in the group of gastroenteropancreatic neuroendocrine tumours. According to the WHO classification of 2000, neuroendocrine tumours cover four categories, depending on the differentiation level and the histopathological malignancy potential – the proliferative index (PI): (1) well-differentiated neuroendocrine tumour (PI < 2%), (2) well-differentiated neuroendocrine carcinoma (PI 2–15%), (3) poorly-differen-

tiated neuroendocrine carcinoma (PI > 15%), (4) mixed endocrine/exocrine tumour (1–5).

PNETs originate from the endocrine part of this organ, formed by the Langerhans islet cells dispersed in the exocrine part. The islet of Langerhans cells produce and secrete to the bloodstream the hormones that regulate the level of glycaemia and are responsible for the control of the gastrointestinal tract function (1–5). The first case of a tumour originat-

ing from the pancreatic endocrine cells was described by Nicholls in 1902 (6). Neuroendocrine tumours constitute approx. 1-2% (according to some sources 5%) of all pancreatic tumours. Their estimated incidence stands at approx. 4 cases per 1,000,000 persons (1-5).

The aim of the study was the clinical characteristics and analysis of preliminary results for surgical treatment of pancreatic neuroendocrine tumors (PNETs) based on the material and practical experience of the Department of Gastrointestinal Surgery, Silesian Medical University in Katowice.

MATERIAL AND METHODS

In the period from 2005 to 2009, in the Department of Gastrointestinal Surgery, Silesian Medical University in Katowice, there were surgically treated 41 patients with gastroenteropancreatic neuroendocrine tumours: 21 (51.22%) males and 20 (48.78%) females. The mean patient age was 55.42 ± 13.13 (23-76). PNETs were diagnosed in 27 patients (65.86%), including 15 males (55.55%) and 12 females (44.45%) aged 55.85 ± 11.74 (34-76). The patients were qualified for the surgical procedure based on laboratory blood tests and imaging

examinations (abdominal ultrasound and computed tomography scan), in most cases at grade 2 of general anaesthesia risk according to the ASA (American Society of Anesthesiologists) classification – 14 (48.15%). Depending on the localisation, size and advancement of the neoplasm, the following surgical approaches were employed: pancreatoduodenectomy – in 11 patients (40.74%), distal pancreatic resection with splenectomy – 6 patients (22.22%), middle segment resection with anastomosis between the pancreatic tail and jejunal loop: Roux-Y procedure – 1 patient (3.71%), pancreatic resection by Beger procedure – 1 patient (3.71%), pancreatic head and body resection with splenectomy – 1 patient (3.71%), tumour enucleation or local excision – 4 patients (14.81%), exploratory laparotomy with specimen collection – 3 patients (11.11%). The surgically excised specimen was subject to histopathological examination at the Department of Pathomorphology, Silesian Medical University in Katowice.

The analysis covered tumour localisation, dimensions, histopathological type and clinical advancement stage, as per the guidelines of the Polish Network for Neuroendocrine Tumors (2008) (tab. 1), hospitalization period

Table 1. Stages of clinical and pathological advancement of pancreatic neuroendocrine tumours (7)

Klasyfikacja TNM / TNM classification
T – primary tumour
TX – primary tumour cannot be assessed
T0 – no evidence of primary tumour
T1 – tumour limited to pancreas, of <2 cm in diameter
T2 – tumour limited to pancreas, of 2-4 cm in diameter
T3 – tumour limited to pancreas, of >4 cm in diameter, or infiltrating duodenum or common bile duct
T4 – tumour infiltrating near organs (gut, spleen, colon, adrenal glands) or walls of large vessels (celiac artery or superior mesenteric artery)
N – regional lymph nodes
NX – regional lymph nodes cannot be assessed
N0 – no regional lymph node metastasis
N1 – regional lymph node metastasis
M – distant metastasis
MX – distant metastasis cannot be assessed
M0 – no distant metastasis
M1 – distant metastasis
Advancement Staging Parameter T Parameter N Parameter M
Stage I T1 N0 M0
Stage IIa T2 N0 M0
Stage IIb T3 N0 M0
Stage IIIa T4 N0 M0
Stage IIIb any parameter T N1 M0
Stage IV any parameter T any parameter N M1

T, tumour; N, lymph node metastasis; M, distant metastasis

(total and post-operative), type and period of clinical symptoms, duration of the procedure, volume of perioperative blood loss, as well as early complications, repeat procedures and post-operative mortality.

The most common PNET localisation in the studied patient group was the head of the pancrea – 14 cases (34.15%). The detailed distribution of PNETs is presented in tab. 2. There were diagnosed 24 primary tumours (88.89%) and 3 disease recurrences (11.11%). The clinical symptoms reported by patients included: abdominal pain – 13 (48.15%), body weight loss – 9 (33.3%), nausea and vomiting – 6 (22.22%), jaundice – 2 (7.41%), heartburn and epigastric burning – 1 (3.71%), hypoglycaemia symptoms – 4 (14.81%), and diarrhoea – 2 (7.41%). The mean time of clinical symptoms persistence was 6.84 ± 9.86 months (0.75-36 months).

RESULTS

The mean hospitalization period was 25 ± 20.36 days (4-78 days). The mean post-operative hospitalization time was 18 ± 17.9 days (1-64 days). The mean procedure duration was 4.2 ± 1.93 hours (1.15-9.15 hours). The mean volume of perioperative blood loss was 727.5 ± 391.85 ml (100-1500 ml).

Early post-operative complications were observed in 10 patients (37.04%). The following early complications were seen: intra-abdominal abscess – 2 (7.41%) post pancreatoduodenectomy and pancreatic resection by Beger procedure, wound suppuration – 2 (7.41%) post pancreatoduodenectomy, pancreatic fistula – 1 (3.71%) post pancreatic body tumour enucleation, acute pancreatitis – 1 (3.71%) post pancreatoduodenectomy, pancreaticojejunal anastomosis leak – 1 (3.71%) post pancreatoduodenectomy, peritoneal cavity haemorrhage – 1 (3.71%) post pancreatic resection by Beger procedure, acute cholangitis – 1 (3.71%) post pancreatoduodenectomy, adhesion obstruction – 1 (3.71%) post pancreatoduodenectomy, subobstruction – 1 (3.71%) post local tumour excision, portal vein thrombosis – 1 (3.71%), sepsis – 1 (3.71%), fluid in pleural cavity – 1 (3.71%) post pancreatic head and body resection with splenectomy, acute heart failure – 1 (3.71%) post pancreatic tail resection with splenectomy.

There were performed 2 repeat surgeries (7.41%): 1 due to adhesion obstruction and

1 due to peritoneal cavity haemorrhage. There was one patient death (3.71%) recorded in the post-operative period due to acute heart failure post pancreatoduodenectomy (tab. 2).

The mean PNET dimension were 5.92 ± 6.06 cm (0.4-25 cm). By histopathology, the most common PNET type was well-differentiated neuroendocrine tumour (class 1 as per the 2000 WHO classification) – 13 (48.15%). The most rare was mixed endocrine/exocrine tumour (class 4) – 1 (3.71%). Metastases to lymph nodes were found in 9 patients (33.33%). Metastases to the liver were seen in 7 patients (25.92%), all synchronous. According to the TNM classification, the most common tumour type was T2 – 12 (44.45%), while the most rare was T4 – 3 (11.11%). The most commonly tumours operated on were at stage IIa and IVa of clinical advancement – 7 patients (25.92%), while most rarely – stage IIb: 3 (11.11%). None of the analysed tumours was at stage IIIa (tab. 3).

DISCUSSION

Depending on the hormonal production and secretion, pancreatic neuroendocrine tumours are divided into hormonally active (producing and secreting a given hormone) manifesting clinically by hormone hypersecretion, and hormonally inactive ones. The majority of pancreatic endocrine tumours (70-85%) are hormonally active tumours, while those inactive are reported for 15-30% of cases (1, 8).

PNETs may develop at any age, yet most commonly at 30-60. In the analysed group, the mean patient age was 55.85 ± 11.74 (34-76), which is in agreement with published epidemiological data. The reported PNETs incidence was comparable in both genders, with slight predominance in males (55.55%). Pancreatic neuroendocrine tumours are seen in isolated cases or constitute a part of multiple endocrine neoplasia type I (MEN I), Von Hippel-Lindau disease, neurofibromatosis type I or tuberous sclerosis. The available publications indicate that the most common form of pancreatic neuroendocrine tumour (15-20%) is insulin-releasing insulinoma (of which < 10% are malignant). Other, less common PNETs include: gastrin-producing gastrinoma (15%), pancreatic polypeptide-releas-

Table 2. Clinical characteristics of patients

Demographical characteristics of patients	
Age (years)	55,85±11,74 (34-76)
Female/Male	12 (44,45%) / 15 (55,55%)
Surgical procedure	
Pancreatoduodenectomy	11 (40,74%)
Traverso procedure	7 (25,92%)
Whipple procedure	2 (7,41%)
Flautner procedure	2 (7,41%)
Distal pancreatic resection with splenectomy	6 (22,22%)
Middle segment resection	1 (3,71%)
Pancreatic resection – Beger procedure	1 (3,71%)
Pancreatic head and body resection with splenectomy	1 (3,71%)
Tumour enucleation or local excision	4 (14,81%)
Exploratory laparotomy with specimen collection	3 (11,11%)
ASA classification	
I	1 (3,71%)
II	14 (48,15%)
III	6 (22,22%)
IV	1 (3,71%)
I/II	1 (3,71%)
II/III	3 (11,11%)
III/IV	1 (3,71%)
Clinical symptoms	
BAbdominal pain	13 (48,15%)
Body weight loss	9 (33,3%)
Nausea and vomiting	6 (22,22%)
Jaundice	2 (7,41%)
Heartburn and epigastric burning	1 (3,71%)
Hypoglycaemia signs	4 (14,81%)
Diarrhoea	2 (7,41%)
Symptom duration (months)	22,94±51,36 (0,1-332)
Total hospitalization period (days)	25±20,36 (4-78)
Post-operative hospitalization (days)	18±17,9 (1-64)
Surgical procedure duration (hours)	4,2±1,93 (1,15-9,15)
Volume of perioperative blood loss (ml)	727,5±391,85 (100-1500)

ASA – American Society of Anesthesiologists

ing PPoma (8-10%), vasoactive intestinal polypeptide-secreting VIPoma (2-5%), and glukagon-producing glucagonoma (1-2%). Very rare pancreatic neuroendocrine tumours (approx. 1%) include somatostatinoma (producing somatostatin), bombesinoma (producing bombesin), ACTHoma (producing adrenocorticotrophic hormone – ACTH) and others. In our material, we observed 3 cases of glucagonoma (including 1 metastatic tumour) and 2 cases of insulinoma. Neuroendocrine tumours have better prognosis than neoplasms of pancreatic exocrine origin (1, 8). The prognosis is affected by the histopathological structure of the tumour and its differentiation. Well-differentiated tumours (class 1)

have better prognosis and are associated with higher survival as compared with other PNET histopathological types. In the analysed patient population, the most common histopathological PNET type (48.15%) was well-differentiated neuroendocrine tumour (class 1 as per 2000 WHO classification), which is in agreement with previously published data (9, 10).

Surgical treatment remains the primary approach in primary gastroenteropancreatic neuroendocrine tumours, including pancreatic tumours. Surgery is the golden standard in the treatment of pancreatic neuroendocrine tumours, both as radical tumour excision and as palliative treatment aimed at alleviating

Table 3. Clinical characteristics of PNETs

Tumour location	
Head	14 (34,15%)
Body	4 (14,81%)
Tail	5 (18,52%)
Body and tail	1 (3,71%)
Retroperitoneal space	4 (14,81%)
Tumour dimensions (cm)	5,92±6,06 (0,4-25)
Histopathological type as per WHO	
I	13 (48,15%)
II	3 (11,11%)
III	10 (37,04%)
IV	1 (3,71%)
TNM classification	
T1	3 (11,11%)
T2	12 (44,45%)
T3	9 (33,33%)
T4	3 (11,11%)
N0	9 (33,33%)
N1	9 (33,33%)
NX	9 (33,33%)
M0	20 (74,08%)
M1	7 (25,92%)
Clinical advancement stage	
I	4 (14,81%)
IIa	7 (25,92%)
IIb	3 (11,11%)
IIIa	0 (0%)
IIIb	6 (22,22%)
IV	7 (25,92%)

PNETs, pancreatic neuroendocrine tumours
ASA – American Society of Anesthesiologists

the clinical complaints and improving the quality of life (1, 5, 8-16).

The indications for surgical treatment of gastroenteropancreatic neuroendocrine tumours may be divided into three categories: radical or palliative tumour excision, regional or distant metastasis resection for cytoreduction (reduction of the tumour mass by over 90%) and tumour resection as palliative treatment aimed at complaints alleviation – e.g. in cases of obstruction, jaundice, gastrointestinal bleeding, pain (1, 5).

The type and scope of surgical tumour resection is dependent on its localisation and the tumour advancement stage. Radical resection of the primary tumour is the treatment of choice in cases of local neoplastic advancement (R0 resection with tumour-free margins in microscopy). For mild pancreatic neoplasms, enucleation (for tumours located 5 mm from the major pancreatic duct) or resec-

tion are sufficient forms of treatment. In the case of certain mild pancreatic neuroendocrine tumours, laparoscopic enucleation is possible. Laparoscopic access is contraindicated for tumours exceeding 10 cm in diameter, with metastases and infiltration of major blood vessels. For malignant tumours and in cases of their more pronounced clinical advancement, the scope of the procedure should be adequately larger (1, 5, 7, 8, 11, 13-18).

Casadei and colleagues (2010), in their study on 82 patients, have compared the results of surgical treatment of PNETs with the use of 2 methods: tumours enucleation and pancreatic resection. Tumours qualifying for enucleation were of < 4 cm in diameter and those localised further from the duct of Wirsung, with no pathology in lymph nodes. In the remaining patients, pancreatic resection was performed. Comparative analysis revealed

similar long-term results in both patient groups, while a significant difference was observed in the histopathology of excised tumours (more enucleation procedures than resections for mild tumours). Applying the above-cited qualification criteria for enucleation, satisfactory long-term results may be achieved. In our material, enucleation of local resection was used in 14.81% of patients. The small percentage of enucleation procedures was caused by a marked advancement of the majority of tumours (mean tumour diameter: 5.92 ± 6.06 cm). Also for this reason, the patients operated on in our Department were most often qualified for pancreatic resection (74%).

Depending on the tumour localisation, different types of resection are possible: pancreatoduodenectomy – for tumours located in the head of the pancreas; middle segment resection (body of the pancreas resection) – for tumours localised in the pancreatic head; and distal pancreatic resection (resection of the pancreatic body and/or tail) – for tumours localised in the body and/or tail of the pancreas (1, 7). Due to the tumour localisation within the pancreatic head in the majority of patients (34.15%), the most common type of procedure was pancreatoduodenectomy (40.74%). Of note is the middle segment resection, recommended in available literature for the treatment of mild tumours (including neuroendocrine) localised in the middle pancreatic segment. The advantages of this surgical procedure are its efficacy and safety with low risk of post-operative endocrine or exocrine pancreatic failure resulting from saving of the major portion of the pancreatic parenchyma (21-25).

Early post-operative complications were observed in 37.04% of patients. The most com-

mon ones were: intra-abdominal abscess – 2 (7.41%) and wound suppuration – 2 (7.41%). Repeat surgeries were performed in 7.41% of patients. The recorded post-operative mortality rate was 3.71%. The obtained results are in agreement with the published data concerning pancreatic resection. In the international centres with vastest experience in pancreatic surgery, the percentage of complications stands at 30-50%, with 1-5% post-pancreatoduodenectomy mortality rate (in some centres the percentage of complications exceeds 50%) and 12% post distal pancreatic resection. Recently, the post-pancreatoduodenectomy mortality rate has dropped (initially it stood at 20%), while the incidence of complications post pancreatic resection remains at a level comparable with previous years. The lowest risk of complications (approaching 0%) is associated with local tumour enucleation (the least invasive surgical procedure). One of the most common complications in pancreatic surgery is pancreatic fistula, with the reported incidence of 2-20%. It should be emphasised that this complication was found in the population described in this paper in 3.71% of patients (25-30).

CONCLUSIONS

1. Pancreatic neuroendocrine tumours constituted the majority of gastroenteropancreatic neuroendocrine tumours in the analysed patient group.
2. Most commonly, PNETs were localised in the head of the pancreas.
3. In the presented material, the mortality rate did not exceed 4%, similarly as in other, renowned, centres.

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Adress correspondence: 40-752 Katowice, ul. Medyków 14