Original

Can treatment using radiolabelled somatostatin analogue increase the survival rate in patients with non–functioning neuroendocrine pancreatic tumours?

Anna Sowa-Staszczak[1], Dorota Pach[1], Agnieszka Stefańska[1],
Monika Tomaszuk[1], Wioletta Lenda-Tracz[1],
Renata Mikołajczak[2], Dariusz Pawlak[2], Robert Chrzan[3],
Aleksandra Gilis-Januszewska[1], Elwira Przybylik-Mazurek[1],
Alicja Hubalewska-Dydejczyk[1]

[1]Department of Endocrinology, Jagiellonian University, Medical College, Krakow, Poland
[2]Research and Development, IAE Radioisotope Centre POLATOM, Otwock-Swierk, Poland
[3]Department of Radiology, Jagiellonian University, Medical College, Krakow, Poland

Abstract

BACKGROUND: The aim of the study was to assess the effectiveness of peptide receptor radionuclide therapy (PRRT) in patients with non-functioning neuroendocrine pancreatic tumours (NFPNTs) and to compare survival rates in patients with NFPNTs and in patients with other neuroendocrine tumours (NETs) treated using radiolabelled somatostatin analogue in our Department. We would like to analyze factors potentially determining the effectiveness of the therapy and also to assess the myelo- and nephrotoxicity.
MATERIAL AND METHODS: Fourteen patients with disseminated disease and/or inoperable NFPNT were qualified to PRRT based on positive SRS (somatostatin receptor scintigraphy). There were 5 men and 9 women, with Karnofsky's index > 70%.
RESULTS: In the whole group of patients, partial response was observed in 21.4%, stabilization of the disease in 42.9%, and progression of the disease in 35.7% of patients. Mean observation time was 19 ± 13 months, mean time to progression was 12 ± 9 months, and mean time to death was 16 ± 9 months. Six patients died — four of them due to progression of the disease, two due to myocardial infarction. After PRRT we did not observe clinically significant haemotoxicity and/or nephrotoxicity.
CONCLUSIONS: 1. Peptide receptor radionuclide therapy may be a safe and effective treatment option in patients with NFPNTs, leading to stabilization or regression of the disease in the majority of patients. 2. There is no statistically significant difference in survival rate between patients with NFPNTs and NETs of other localization treated with PRRT.
Key words: non-functioning neuroendocrine pancreatic tumours, peptide receptor radionuclide therapy, radiolabelled somatostatin analogues

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Correspondence to: Alicja Hubalewska-Dydejczyk
Department of Endocrinology
ul. Kopernika 17, 31–501 Krakow
Tel: + 48 12 424 75 20, fax: +48 12 424 73 99
e-mail: alahub@cm-uj.krakow.pl

Introduction

Non-functioning neuroendocrine pancreatic tumours (NFPNTs) are clinically silent; however, the presence of various hormones such as insulin, glucagon, pancreatic polypeptide, so-

matostatin, neurotensin, or calcitonin may be demonstrated by immunohistochemistry [1]. The incidence of NFPNTs has been reported to be 15–53% in a clinical series of pancreatic endocrine tumours. More than 50% of NFPNTs are malignant — this is connected with their local invasion, regional lymph node metastases, and distant metastases especially to the liver [2]. Predominant symptoms are abdominal pain, weight loss, jaundice, and pancreatitis [3]. NFPNTs are usually localized in the posterior part of the pancreatic head [1, 4]. A tumour size of about 20 to 40 mm in diameter is a preoperative clinical risk factor for an increasing rate of metastases [1]. Somatostatin receptor scintigraphy (SRS) enables localization of pancreatic NET (neuroendocrine tumours) and its small, distant metastases. In some cases SRS may differentiate between exocrine and endocrine pancreatic tumours [1]. Pancreatic adenocarcinomas are rarely diagnosed with the use of SRS, whereas about 65% of PNT (pancreatic neuroendocrine tumours) can be localized with SRS [5].

The first line treatment is surgery. Candidates for surgery are patients with incidental NFPNTs that are symptomatic and asymptomatic patients with presumably benign tumours > 10 mm in diameter [1]. Whether a pancreatoduodenectomy, central pancreatectomy, or distal pancreatectomy is required depends on the site of the tumour [3]. For asymptomatic patients with well-differentiated metastatic disease and therefore better prognosis, a conservative approach might be suggested — waiting for the progression of the disease or occurrence of the symptoms before initiating therapy such as systemic chemotherapy, hormonal therapy, radiofrequency ablation, selective transcutaneous arterial chemoembolization (TACE), or transplantation [3]. Resection of the liver metastases and primary tumour from patients with liver metastases seems rational only if complete tumour removal is possible [1]. Chemotherapy using a combination of streptozotocin plus 5-fluorouracil (5-FU) or doxorubicin has been the gold standard for treatment of different types of endocrine pancreatic tumours. The objective responses so far were assessed for 60% among treated patients, but recent studies using MRI/CT evaluation have reduced the objective responses to 16–30% [6]. Therefore, the therapeutic option for this group of patients has still not been found. New strategies with tyrosine kinase inhibitors and anti-angiogenic treatment have been tested [7, 8]. Peptide receptor radionuclide therapy provides the option to treat patients with inoperable non-functioning pancreatic endocrine tumours with sufficient uptake in SRS [9]. The side effects of this therapy are absolutely lower than chemotherapy and the median time to progression can be similar [7].

The aim of the study was to assess the effectiveness of PRRT (peptide receptor radionuclide therapy) in patients with non-functioning neuroendocrine pancreatic tumours and to compare survival rates in patients with NFPNT and in patients with other NETs treated using radiolabelled somatostatin analogue (^{90}Y-DOTA-TATE and ^{90}Y/^{177}Lu-DOTA-TATE) in our Department. Moreover, we would like to analyze factors potentially determining the effectiveness of the therapy and also to assess the myelo- and nephrotoxicity.

Material and methods

Nineteen patients with metastatic non-functioning pancreatic tumours were diagnosed in the Department of Endocrinology UJCM or referred to our Department from other centres.

Fourteen patients with disseminated disease and/or inoperable [9] NFPNT were qualified to PRRT with ^{90}Y-DOTA-TATE and ^{90}Y/^{177}Lu-DOTA-TATE based on positive SRS. There were 5 men and 9 women, with mean age 56.1 ± 12.8 years and Karnofsky's index > 70%. In one patient with an inoperable pancreatic tumour, no distal metastases were found despite a high Ki index (Ki = 20%).

The median size of the primary tumour was 57 mm, SD 57 mm, min 21 mm, and max 230 mm. Thirteen patients (93%) had Ki-67 less than 15% (WHO type 2). Each patient received 7.4 GBq/m^2 of PRRT divided into 4–5 infusions (most often 3.7 GBq per cycle), every 6 to 9 weeks. For nephroprotection amino acids formula Vamin 18, before and after each infusion of PRRT, was administered. In 5 patients chemotherapy (Zanosar and 5-FU) was used before the PRRT cycle; the mean time to start the PRRT after chemotherapy was 6 months. After PRRT, long-term acting somatostatin analogues were used in five cases. The patients' data are presented in Table 1.

Among the five patients with a high proliferation index (Ki ≥ 20%, WHO type 3) four had a negative SRS result. The size of the tumours was 30 to 70 mm in diameter. One of those patients with a positive SRS result received one infusion of PRRT but was then qualified to chemotherapy. The four others received chemotherapy as the first line treatment.

Twenty-eight patients with disseminated NETs assessed as NET G2 according to WHO criteria (18 females, 10 males, aged 31–78, mean: 59.7 ± 11.9 years) with histopathologically confirmed NET and positive ^{99m}Tc-[EDDA/HYNIC]-TOC SRS were treated with PRRT due to progression of the disease and compared to a group of patients with NFPNT. There were fourteen patients with foregut tumours (six with functioning pancreatic tumours), eleven with midgut tumours, two with hindgut tumours, and three with unknown primary focus (PFU). In all of the patients a similar protocol of treatment was used. The patients received 7.4 GBq/m2 of PRRT divided into 4–5 infusions (most often 3.7 GBq per cycle), every 6 to 9 weeks.

SRS with the use of ^{99m}Tc-[EDDA/HYNIC]-TOC was performed in order to assess somatostatin receptor expression at the Nuclear Medicine Unit of Endocrinology Department in the University Hospital in Cracow. CT examinations were performed in the 1st CT Unit of Radiology Department using a spiral multirow CT scanner — Siemens Somatom Sensation 16. The protocols of SRS and CT examinations have been presented earlier in detail [10]. After injection of the tracer (740 MBq), all patients underwent whole-body scans after 1, 4, and 24 hours and SPECT of the abdomen and/or thorax with use of a dual-head, large-field-of-view gamma camera (Siemens) with parallel, low-energy, high-resolution (LEHR) collimators. Standard protocol of CT for the abdomen and pelvis and/or chest was performed (detector configuration 16 × 0.75 mm, slice thickness and reconstruction increment 2 mm, reconstruction kernel B31f or B41f, before and multiphase after IV non-ionic contrast media administration in dose 1 ml/kg, flow 2.5 ml/s, delay of arterial phase 30 seconds and venous phase 60 seconds after the start of contrast administration). The semiquantitative analysis showed the uptake in the tumour type 2, 3, and 4 according to a four-point scale, where 1 is uptake smaller than in the liver, 2 is uptake the same as in the liver, 3 is uptake bigger than in the liver, and 4 is uptake bigger than in the kidney and spleen. For assessment of the effectiveness of PRRT leading to disease regression, the SRS scans were qualitatively analyzed before and after therapy. For quantitative analysis, the 1–3

Table 1. Patients with non-functioning neuroendocrine pancreatic tumours

Initials	Age	Sex	Size of tumor [mm]	Localization	Meta	Surgery	Y-90 DOTA-TATE therapy	PRRT Y-90 [GBq]	Chemotherapy	Response to the PRRT
MK	33	F	58	Tail	Lymph nodes, cns	Explorative laparotomy	Y90/Lu177 — 11.2008– 09.2009	10.36	Y	PD
TO	73	F	21	Head	Liver	N	08.2006–11.2006	11.10	N	PR
WK	54	F	49	Tail	Liver	Explorative laparotomy	06.2008–01.2009	12.58	N	SD
DM	71	F	26	Tail	Liver	Explorative laparotomy	07.2007–12.2007; and 06.2009	11.84 + 3.70	Y	PD
RN	34	F	230	Tail	Liver	N	09.2009–03.2010	13.32	Y	PD
JO	77	F	150	Tail	Liver	N	11.2005–03.2006	13.32	N	PR
AP	56	M	88	Head and stem	Liver	Explorative laparotomy	09.2009–02.2010	13.32	N	SD
JP	52	F	57	Stem and tail	Liver	Y	2006	14.80	Y	SD
TR	61	M	122	Stem	Liver	N	05.2009–09.2009	14.80	N	PD
HT	60	F	105	Head and stem	No	N	02.2007–09.2007	12.58	N	SD
ZW	60	M	57	Tail and stem	Liver	Y	07.2007–12.2007	11.84	N	PD
AŻ	54	F	56	Tail and stem	Liver	Y	08.2007–01.2008	13.32	Y	PR

SD — stable disease; PD — progressive disease; PR — partial response; CNS — central nervous system; N — no; Y — yes

biggest changes were chosen. In CT scans measurable lesions were analyzed according to RECIST criteria before and after the treatment. Based on SRS and CT scan fusion, the target to non-target ratios before and after therapy for the same lesions were assessed using volumetric analysis with isoconture 20%.

To assess nephro- and myelotoxicity each patient had parameters assayed such as creatinine, platelets, leukocytes, and haemoglobin before and every month after treatment. Myelotoxicity was assessed according to WHO classification. The level of chromogranin A (CgA) was measured prior to and after PRRT.

Statistical methods

The correlation between T/nT ratio difference in SRS before and after treatment and lesion cross-section difference in CT before and after treatment was assessed using Pearson's correlation coefficient. The statistical connection between the size of the primary tumour and response to PRRT, and also between the amount of therapeutic activity and response to PRRT, were assessed using Kruskal-Wallis test. The connection between surgical intervention prior to PRRT and response to the therapy was assessed (using U Mann-Whitney test). Kaplan-Meier curves and Cox F test were used for the comparison of the two groups' survivals: the first group — patients treated with non-functioning pancreatic tumours (6 complete observations, 8 censored observations, mean time of observation 21.2 months ± 14.9 months, max 52.5 months, min 5.9 months), the second group — patients treated with the PRRT because of diseases other than non-functioning pancreatic tumours (8 complete observations, 20 censored observations, mean time of observation 26.6 months ± 15.3 months, max 77.3 months, min 6.1 months). The second group consisted of 28 patients.

A 95% confidence level was assumed in all statistical analysis.

Results

Thirteen out of fourteen patients received ^{90}Y-DOTA-TATE in 4–5 infusions; the minimum activity was 11.1 GBq, maximum 15.54 GBq (median activity 13.32 GBq). One patient received a mix of ^{90}Y/^{177}Lu-DOTA-TATE (total activity 10.36 GBq).

In the whole group of patients, partial response was observed in 21.4%, stabilization of the disease in 42.9%, and progression of the disease in 35.7%. Mean observation time was 19 ± 13 months, mean time to progression was 12 ± 9 months, and mean time to death was 16 ± 9 months. Six patients died – four of them due to progression of the disease and two due to myocardial infarction. Two patients received a repeated cycle of PRRT, the first — one application of 3.7 GBq 18 months after the end of the first PRRT cycle, and the second — one application of 2.96 GBq 8 months after the end of the first PRRT cycle. One of them died one month after the second PRRT cycle.

Semiquantitative analysis of the tracer uptake in SRS showed uptake types 3 and 4 in metastases of the tumours in 6 and 7 of the cases, respectively, and 3 and 4 in primary tumours in 3 and 5 of the cases, respectively. Two patients with metastases of PNT had somatostatin receptor expression in metastases only (not in primary tumour). In the group with uptake 4 in liver metastases after the treatment, five patients had uptake type 3 and two uptake type 2. In the whole group of patients with uptake 4 in the metastases, stabilization of the disease was observed in three cases, regression in two, and progression in two patients after the PRRT. In the whole group with uptake type 3 after the PRRT, stabilization of the disease was observed in two cases, regression in one, and progression in three patients.

In the group of nine patients with inoperable PNT, regression of the primary tumour after PRRT was observed in one of them.

Additionally, in three patients regression of the liver lesions was observed. But in one of them, 18 months later, progression of the disease was observed. We observed stabilization of the disease in three of the patients.

There was no correlation between the grade of the uptake in SRS and response to the therapy. The patients with uptake types 3 and 4 in SRS had either regression or progression of the disease. In the case of disease regression, we observed a decline in the target/non-target ratio and a decline in the dimensions of the tumour in a CT scan. There was, however, no statistically significant correlation between T/nT ratio difference in SRS before and after treatment and lesions cross-section difference in CT before and after treatment (Figure 1 and Figure 2).

There was no statistically significant relationship between the amount of therapeutic activity and response to the therapy ($p = 0.60$). There was also no statistically significant relationship between surgical intervention prior to PRRT and response to the therapy. The same result was observed for the size of the primary tumour and response to PRRT ($p = 0.95$ and $p = 0.45$, respectively).
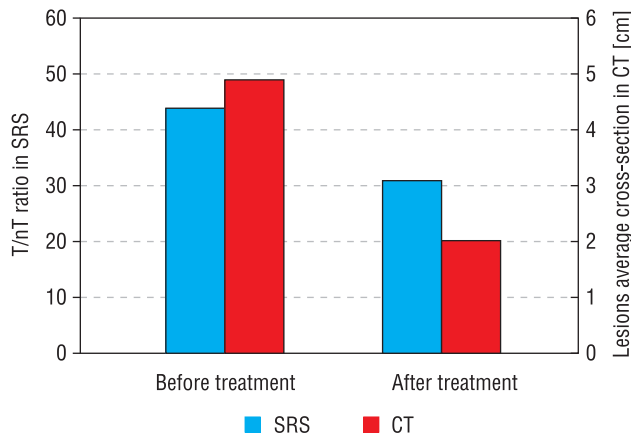

Figure 1. Lesions in the liver prior to and after peptide receptor radionuclide therapy (PRRT) — uptake in somatostatin receptor scintigraphy (SRS) and size in computed tomography (CT) studies.
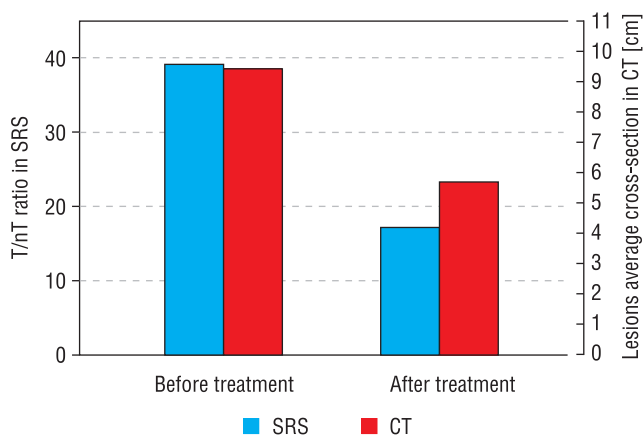

Figure 2. Primary pancreatic tumours prior to and after peptide receptor radionuclide therapy (PRRT) — uptake in somatostatin receptor scintigraphy (SRS) and size in computed tomography (CT) studies.

The comparison of the survival rates between the group of patients with NFPNT and patients with neuroendocrine tumours at other localizations treated in our Department with PRRT, particularly midgut tumours, did not show any statistically significant difference (Figure 3). Median survival time (the survival time at which the cumulative survival function is equal to 0.5) for the first group was 25.7 months and for the second group was 46.7 months.

After PRRT we did not observe clinically significant haemotoxicity and/or nephrotoxicity. According to WHO classification, transient myelotoxicity grade 2 in leucocyte level was observed in three patients. In eight cases, transient toxicity grade 2, and in one patient grade 3 in haemoglobin level was observed. That patient required a blood transfusion. We have not observed toxicity types 2, 3, or 4 in platelet levels so far.

In three patients, the creatinine level was higher than normal 20 months after commencing therapy, but without clinical symptoms of renal insufficiency (Figure 4).

We observed a decrease in the values of the morphological parameters compared to initial values in consecutive months after commencing therapy in the whole group of patients, but the median values for each parameter were within normal ranges (Figure 5).

The levels of liver parameters did not change after therapy.

There was no statistically significant correlation between the chromogranin A level and the response to the therapy.

Discussion

Patients with non-functioning pancreatic tumours (NFPNTs) do not usually present any specific symptoms, and therefore they are usually discovered in the advanced stage with distant, usually liver, metastases, which are often the first symptom of the disease. The best treatment option in patients with pancreatic neuroendocrine tumours is surgery [1, 3, 9–11]. Surgical resection is also beneficial for patients with advanced, disseminated malignant pancreatic
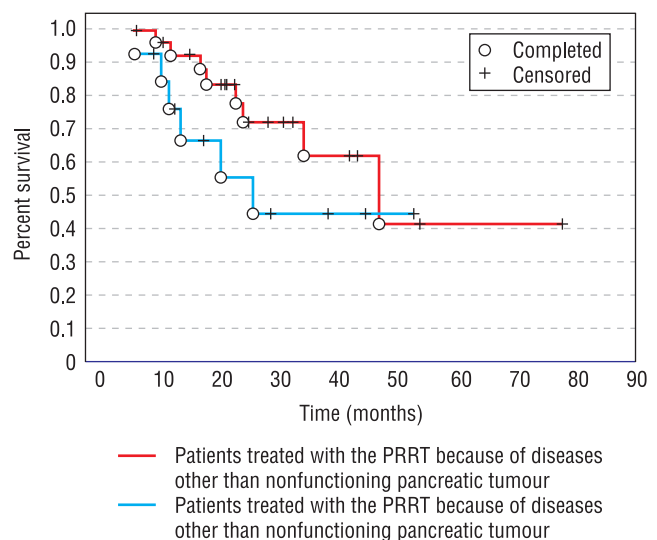

Figure 3. Comparison of survival of patients with non-functioning neuroendocrine pancreatic tumours (NFPNTs) and patients with neuroendocrine tumours (NETs) of different localization.
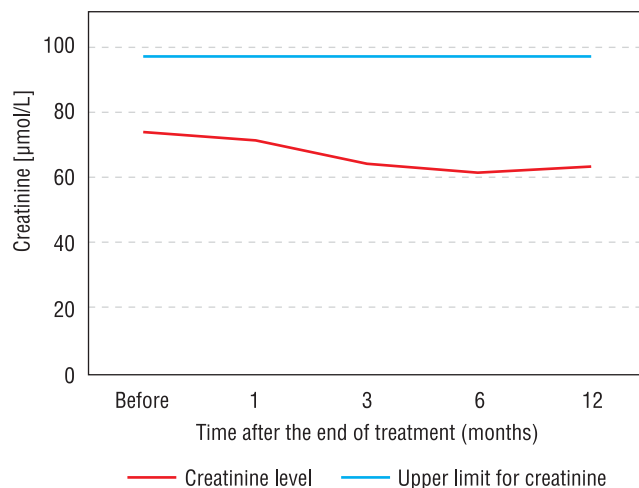
Figure 4. Creatinine levels after peptide receptor radionuclide therapy (PRRT).

Figure 5. Morphological parameter levels after peptide receptor radionuclide therapy (PRRT). HgB — hemoglobin; WBC — white blood cells; PLT — platelets.

tumours [11, 13]. However, surgery is not possible in all patients [1, 3]. The effectiveness of chemotherapy appears to be lower than previously estimated [6]. Treatment with radiolabelled somatostatin analogues might be another therapeutic approach in the case of patients with NFPNTs with sufficient uptake in SRS.

In our group of 14 patients, in five cases surgery was not performed and in four cases an explorative laparotomy revealed inoperable pancreatic tumours. Only one patient did not have distant metastases at the time of diagnosis. With the exception of one case — a patient with inoperable primary tumour without distant metastases and Ki-67 20%, almost all our patients had Ki-67 less than 15%. All patients had positive results of SRS studies, and were therefore qualified to peptide receptor radionuclide therapy. Five of them underwent previous chemotherapy. The response to the therapy was assessed with standard criteria for solid tumour, which took into consideration only the tumour size. We were trying to find out whether the changes in SRS after PRRT might be useful in assessment of the response to the therapy. There was no correlation between the grade of the uptake in SRS and response to the therapy. Therefore, the uptake ratio could not be considered as a prognostic factor for the therapy response. In the case of disease regression a decline in the target/non-target ratio corresponded with the decline in the dimensions of the tumour in a CT scan. According to RECIST criteria, we observed disease stabilization in nearly 50% of patients and partial response to the therapy was seen in 21.4% of cases. But we did not find any predictors of the effectiveness of the PRRT because there was no correlation between the uptake grade in SRS and response to therapy as mentioned above, and also between target non-target ratio difference in SRS before and after treatment and lesion cross-section difference in CT before and after treatment. There was also no correlation between tumour size and response to the PRRT. Surgical intervention prior to radioisotope therapy also did not correlate with the results of the previous one. But a very important factor in the safety of the therapy is that there was no clinically significant myelotoxicity and/or nephrotoxicity observed after PRRT in our group of patients.

In one of our patients we observed regression in the primary inoperable pancreatic tumour size after PRRT [10]. The patient
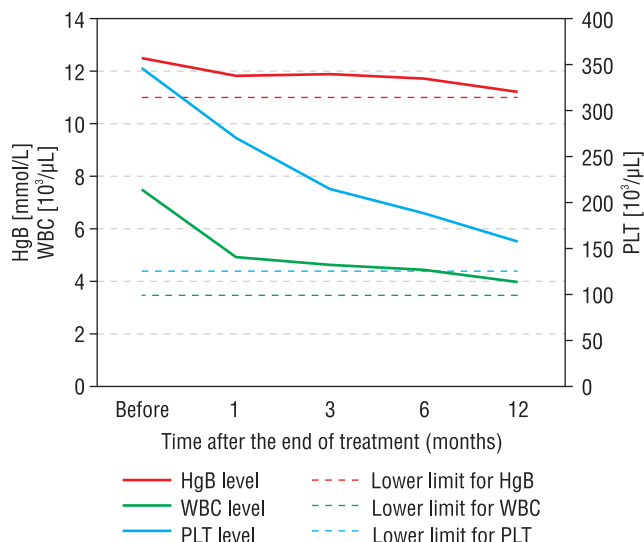
was referred to the Department of Surgery, but the surgical resection of the tumour was still not possible due to infiltration of the large vessels. The regression of the tumour size, as also suggested by other authors, is an indication that PRRT might also be considered as neoadjuvant therapy in the case of patients with pancreatic tumours [9, 10, 12]. Moreover, Stoeltzing et al. presented a case showing that PRRT might be used also to decrease the size of liver metastases of pancreatic neuroendocrine tumours and therefore further improve surgical therapy of hepatic lesions [13].

We also compared the survival rate in the group of patients with pancreatic neuroendocrine tumours and patients with NETs of other localization treated in our Department with radiolabelled somatostatin analogues. We did not find any statistically significant difference in survival rates between these two groups of patients. We believe this is an important finding because, as presented by Panzuto et al., a pancreatic site of the primary tumour represented as an independent variable predictive of an unfavourable outcome [14]. Despite the nonsignificant difference between survival curves in these two groups, a difference between median survival times could be observed. The explanation of this fact may be the generally known worse response of NFPNTs to the PRRT. However, we assess responses to PRRT in our group of patients with NFPNTs as very good.

The observation that the survival rate for patients with pancreatic NETs treated with PRRT was similar to that of patients with other NET localizations, along with the effects presented above and the safety of the therapy with radiolabelled somatostatin analogues, confirms the usefulness and effectiveness of PRRT as a therapeutic option in patients with inoperable and/or disseminated non-functioning pancreatic tumours.

Conclusions

1. Peptide receptor radionuclide therapy may be a safe and effective treatment option in patients with non-functioning

pancreatic neuroendocrine tumours leading to stabilization or regression of the disease in the majority of patients.

2. There is no statistically significant difference in survival rates between patients with pancreatic neuroendocrine tumours and NETs of other localizations treated with PRRT.

Dates of any congresses at which the paper has already been presented: XII Congress of the Polish Association of Nuclear Medicine, Wroclaw 2010; 10th Annual Congress of the European Association of Nuclear Medicine, Vien 2010 (mentioned during the highlight lecture); 14th International Congress of Endocrinology, Kyoto 2010.

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