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Well-differentiated neuroendocrine neoplasms (NENs) of the digestive system – a diagnostic and therapeutic problem

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The WHO classification system has emerged to distinguish between well-differentiated and poorly differentiated neuroendocrine neoplasms (NENs) in order to prognostically stratify the neuroendocrine tumors (NETs) that are further classified according to the TNM classification [1].

Typically, well-differentiated NETs are slow growing malignancies, of which about 30–60% are metastatic at diagnosis and even approximately 30% of patients with completely resected localized disease develop metastases during follow-up [2]. Except for rare cases of radically resected liver metastases, distant dissemination of NENs inevitably results in patient death. However, in some patients, death is related to heart failure in the course of carcinoid heart disease or a massive unresectable retroperitoneal desmoplastic reaction.

Surgery is the only curable treatment for NENs. However, the expression of somatostatin receptors on the tumor cell surface makes NENs accessible for diagnostic and therapeutic approaches (theranostics) using radiolabeled peptides. The first somatostatin receptor imaging (SRI) was performed in 1989 with a gamma camera using somatostatin analogs radiolabeled with iodine 123 in a patient with a pancreatic neuroendocrine tumor. Since that time, SRI has developed and numerous studies have demonstrated the superior sensitivity of Ga-68-based PET/CT (around 90–100% in most NEN localizations except for insulinoma). As a result, the current 2017 ENETS guidelines for radiological, nuclear medicine, and hybrid imaging [3] and follow-up of NET [4] guidelines consider SSA-PET/CT, if available, as the first-line diagnostic procedure for staging and NEN follow-up. A positive SRI scan means lesion uptake that is equal to or greater than the liver uptake and is a good predictor factor for effective biotherapy and radiolabeled therapy with somatostatin analogs [5,6].

In the present issue of *Nowotwory. Journal of Oncology* Tyrybon et al. presented a case of a patient with low-grade NEN of the small intestine who underwent surgery due to subileus. Although emergency surgery could suggest an aggressive disease, a retrospective study did not show that the signs of bowel obstruction before surgery were a prognostic factor of death in small-intestine NET (SI-NET) patients [1, 7]. However, emergency surgery is related to a lower number of resected lymph nodes and the risk of inappropriate staging [1]. This underlines the need for adequate postoperative staging using CT and SRI, which is in line with our opinion. Leaving the metastatic lymph node and a severe desmoplastic reaction may have resulted in relapse in this patient.

When well-differentiated NETs recur with distant metastases, somatostatin analogs (SAs) are the first-line options in most patients except for fast growing tumors or with the risk of visceral crisis. For patients with oligometastatic disease, SA is the most reasonable treatment option, which results in disease stabilization of 12 months. Since SI-NETs have a poor response to chemotherapy, TOR inhibitors [8, 9] or radiolabeled somatostatin analogs are the second line of therapy [10]. mTOR inhibitors are not reimbursed in Poland. Therefore, radiolabeled somatostatin analogs (PRRT) are the only available option with an estimated median time of disease stabilization of about

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3 years. High radiopeptide uptake in metastatic disease is the predictive factor for long-term response [6].

Of note, during treatment, progression occurs in some lesions despite isotope accumulation. If it occurs in a vital organ, a patient must be carefully monitored and consulted in terms of the possibility of using other cytoreductive therapies. In the presented case, progression of recurrence in the heart may have resulted in the patient's death. In oligometastatic disease without the symptoms of the carcinoid syndrome other causes are unlikely.

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