PNETs

Subjects: Others
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The incidence of pancreatic neuroendocrine tumors (pNETs) is less or equal to one case per one hundred thousand people per-year, and they account for roughly 5% of all pancreatic cancers. However, in the last few decades, their incidence has risen.

Keywords: pancreas ; neuroendocrine tumors

1. Introduction

Many biological features make these tumors clinically heterogeneous, including mutational status [1], hormone production, and histopathological grade. Among them, NETs grading, which is mainly related to Ki-67 expression and mitotic index, has several diagnostic, therapeutic, and prognostic implications. In well-differentiated pNETs (G1, G2, and well-differentiated G3) the slow cancer growth is related to good long-term survival even in the presence of liver metastases [2], while poorly differentiated G3 neuroendocrine carcinomas (NECs) show higher proliferation rates and lower overall survival [3]. Moreover, tumor grade is strictly related to the expression of somatostatin receptors (SSR1-5) on the neoplastic cellular surface [3][4]. In low-grade pNETs, the high SSR expression allows the therapeutic use of somatostatin analogs and makes these neoplasms ideal for targeted radionuclide imaging [5]. In contrast, the down-regulation of SSR makes high-grade NEC less suitable for these approaches.

Currently, three radio-labelled somatostatin analogs are used in the clinical practice for targeted SSR radionuclide imaging of pNETs: 68Ga-DOTATATE (DOTA, Tyr(3)-octreotate), 68Ga-DOTANOC (DOTA,1-Nal(3)-octreotide), and 68Ga-DOTATOC (DOTA, D-Phe1, Tyr (3)-octreotide). Although these positron-emitting radiotracers have a different affinity to the various types of SSR [6], they showed a similar diagnostic accuracy [7][8].

Targeted SSR molecular imaging with positron emission tomography and computed tomography (PET/CT) plays a significant role in pNETs clinical management, particularly in the staging phase. Indeed, surgery is the only curative treatment approach, and an accurate assessment of both tumor detection and disease widespread is of utmost importance to avoid unsuccessful procedures. In the present systematic review and meta-analysis, we investigate the diagnostic performance of SSR-PET/CT for the detection of the primary lesion and initial staging of pNETs.

2. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis specifically addressing the identification of the primary lesion and initial staging by using SSR-PET/CT in patients with pNETs. Several studies have used SSR-PET/CT imaging to achieve this aim, reporting variable results. However, most of these studies have limited power due to the relatively small number of enrolled patients, and the lack of specific studies precisely focused on pNETs. To derive more robust estimates on the SSR-PET/CT diagnostic accuracy in this clinical setting, we have pooled the published studies.

Heterogeneity of selected studies may represent a limitation in a meta-analysis. Differences among patients' selection criteria, diversity in methodological aspects, and variable study quality are the most common potential sources of bias. We detected only a moderate heterogeneity among the studies included in the pooled analysis. However, due to the relatively low number of selected studies for the quantitative analysis, subgroup analyses aiming to explain this heterogeneity was not performed. For the same reasons, subgroup analyses, including functioning or non-functioning pNETs as well as hereditary or sporadic pNETs, were not performed.

Obtained data confirm that SSR-PET/CT represents a robust diagnostic tool in pNETs showing a high pooled true positive rate both at patient-based and lesion-based analysis, due to the low number of the observed false-negative findings.

We observed high accuracy in the diagnosis of the primary lesion. However, when compared with similar meta-analyses conducted on mixed gastroenteropancreatic (GEP)-NET populations, a reduction in sensitivity was observed. Indeed, in the meta-analysis by Geijer and Breimer [9], which included 2105 GEP-NET patients, a pooled sensitivity of 93% (95%CI: 91–94%) was reported. Obviously, this difference may be related to the spatial resolution of PET/CT hampering the detection of smaller pancreatic lesions and the inclusion of higher histopathological grades pNETs, which might have increased the occurrence of some false-negative findings due to the lower SSR expression [6]. However, the inclusion of patients affected by insulinoma in many of analyzed studies might have also contributed. Indeed, compared to carcinoids (the commonest GEP-NET histopathological subtype), insulinomas have limited SSR expression, thus potentially reducing SSR-PET sensitivity [10]. On the other hand, pancreatic SSR expression might represent a potential source of false-positive results in the primary lesion detection by SSR-targeted molecular imaging (thus reducing specificity). Indeed, particularly the head and uncinate process, represent a site of physiological SSR overexpression [11][12][13]. Previous studies proposed a cutoff value of SUVmax for differentiating between physiologic and neoplastic pancreatic uptake [13], but there is some overlap of SUV reported in the literature for these two different conditions. This topic was assessed by three of the selected studies [14][15][16]. Overall, they showed that caution is suggested when dismissing foci of enhanced uptake seen on functional but not on anatomic imaging as false positive, especially in patients with repeat PET findings on follow-up period.

Of note, a wide heterogeneity in SUVmax values was observed between primary pancreatic lesions and distant metastases. This is coherent with the heterogeneity in SSR-2A expression between the primary site and distant metastases, since metastatic lesions, being comparatively new as compared to the primary, may be subject to less intense down-regulation of SSR [17]. This difference may theoretically impact the SSR-PET/CT diagnostic accuracy, introducing in a site-specific detection rate heterogeneity. However, contradictory findings were reported in the analyzed studies. The use of different SSR tracers, the variable sample size, the inclusion of a mixed patient population of pNET and GEP-NET, and the variability of histopathological tumor subtypes are possible reasons behind this contradictory finding. The combined use of FDG and SSR-PET/CT imaging may at least partially solve this clinical issue [18].

When compared with conventional imaging, SSR-PET/CT offered a relevant advantage in the detection rate of most metastatic sites. These additional findings have prompted therapeutic interventions in some patients, as shown by Ilhan et al. [19]. They also have a prognostic implication because unknown distant bone metastases are considered as a negative prognostic factor, possibly requiring a more aggressive treatment regime [20]. Therefore, this method is now the choice to fully stage and localize the extent of disease in patients with non-insulinoma pNETs in the preoperative setting by the current guidelines of the European Neuroendocrine Tumor Society (ENETS) [21].

Only in a few cases, the SSR-PET/CT approach was integrated with contrast-enhanced (ce) CT [22][23]. In the study by Kazmierczak et al. [23], this combination resulted in an improvement in sensitivity of 50% and an improvement in accuracy of 30% in primary tumor detection. However, Mayerhoefer et al. [22] showed that sensitivity improvement is only moderate while hardly affecting specificity, concluding that unenhanced images may be enough for routine PET/CT in NET patients. Moreover, none of these studies was conducted exclusively in pNET patients. Similarly, combining PET with MRI may take the theoretical advantage of the combination of high soft-tissue contrast for MRI with metabolic data from PET, helping to recognize small lesions. Moreover, MRI is a tool-free of ionizing radiation. However, only a few studies demonstrated a positive impact of PET/MRI in studying NETs [24][25][26][27], and evidence specifically addressing pNETs is still anecdotal [28][29]. Further studies are needed to understand better the potential role of this tool in this field.

3. Conclusions

SSR-PET/CT has a high detection rate and diagnostic performances for primary lesion and initial staging of pNETs. Further studies are needed to validate the integration of SSR-PET with contrast-enhanced CT or MRI in this clinical setting.

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