Adding variables to complexity. Molecular imaging and molecular biology: a no-longer-secret liaison in NETs

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Neuroendocrine tumours (NETs) are a challenging model for both researchers and clinicians. NETs comprise a very heterogeneous family of tumours: they are rare but with an increasing incidence, indolent lesions but often metastatic at the time of diagnosis, secreting or not, and sometimes very small and sometimes very large. Their high clinical complexity and wide biological diversity, and the restricted diagnostic armamentarium (including limited imaging resolution and lack of reliable biomarkers), make diagnostic flow charts and treatments uncertain in NET patients. A multidisciplinary and integrated approach is the only way to improve the management of these patients. The tumour grading according to histopathology (e.g. Ki67) is widely accepted as a prognostic factor. However, correlation with *in vivo* functional imaging by PET (metabolism, proliferation, receptors) is not always found, and findings are discordant. Researchers and clinicians are working together to develop more reproducible prognostic factors and markers of response to therapy and recurrence. Within this context, the work by Bodei et al. develops new and interesting perspectives [1].

Cancer is a multifactorial disease whose development and progression are affected by intrinsic genetic and molecular features, by the host environment and by their reciprocal interplay. In this regard, cancer may be considered as a nonlinear, open, and intrinsically dynamic system of interconnected

and mutually dependent components. Every element participates in the construction of the system and is tightly interconnected with the others. It is now becoming evident that a reductionist approach, in which one or few selected variables are analysed to explain or predict disease status, is largely insufficient to address the complexity of the “cancer system”. A strong rationale exists to believe that there is a direct link between molecular imaging and molecular biology of tumours. The degree of uptake of a radioactive tracer as measured in PET is a reflection of tumour metabolism and is a direct consequence of the molecular properties of the tumour. As the use of PET in the clinical management of cancer patients is becoming a standard widely available technique, some investigators have explored the correlation between SUV and gene expression.

Osborne et al. investigated the possible correlation between ¹⁸F-FDG uptake and estrogen receptor (ER) status and gene expression profile of locally invasive breast cancer. They found that high SUV correlates with ER-negative status and with the expression of genes associated with increased glucose metabolism [2]. In liver cancer, high ¹⁸F-FDG uptake has been shown to correlate with increased expression of genes involved in cell adhesion, motility and metastasis [3], while in giant cell tumours, high ¹⁸F-FDG accumulation correlates with the expression of genes involved in angiogenesis and cell proliferation [4]. The evidence from these studies provides a partial explanation for the prognostic value of ¹⁸F-FDG SUV and emphasizes that radioactive tracer accumulation and the expression of pro-oncogenic genes are generally interconnected. By contrast, still very limited information is available on the possible correlation between ⁶⁸Ga-DOTA peptide uptake and the specific gene expression profile of tumours. In their work, Bodei and colleagues evaluated the concordance between the ⁶⁸Ga-SSA-PET and the expression of a panel of 51 blood circulating RNA transcripts (NETest) previously

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established as having high sensitivity and specificity in identifying NETs. They found that imaging parameters (including SUVmax) correlate well with the levels in the blood of some of the NET fingerprint genes and that the combination of imaging with the measurement of some of these blood biomarkers may help to better differentiate progressive from stable diseases [1].

The rationale for combining imaging data with data on molecular features is to develop better tools to stratify patients and to predict disease progression. However, a possible limitation of these studies is that the data on molecular features used for the correlation refer to the tumour tissue, which represents a static picture of the disease at the time of surgery and may be insufficient to predict disease evolution. In this regard the work by Bodei and colleagues is novel because the NET fingerprint analysed and correlated with the imaging parameters is a panel of blood circulating transcripts [1]. The monitoring of tumour-specific markers in the blood holds promise for a more dynamic and reliable approach to following disease progression, and increases the possibility of adding prognostic value to the molecular imaging analysis. On the other hand, the low stability of molecules such as mRNA, the paucity of tumour specific molecules in circulation and the fact that blood circulating components may vary very rapidly depending on the context and on the stimuli, are important issues that may limit the feasibility of this approach, and should be carefully evaluated in this type of analysis. Thus, even if still preliminary, the evidence described by Bodei and colleagues lays the basis for the development of new

noninvasive tools to help predict NET progression and treatment failure. This new diagnostic strategy needs to be confirmed and implemented in larger and prospective studies.

The amazing technological progress of the past years has provided high-throughput platforms that have dramatically improved our ability to capture and quantify the complexity of organisms and diseases. The construction of new strategies for a more precise and personalized risk assessment in NETs as in other malignancies will require increasing integration of different datasets from various levels of organization including deep biological investigations, detailed imaging profiles and clinical phenotypes.

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