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EDITORIAL COMMENTARY

Prognostic imaging of neuroblastoma

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Neuroblastoma is the most common extracranial neoplasm in children. It represents about 8 % of childhood malignancies and 90 % of those affected are under the age of 5 years. It is an embryonal tumor and develops mostly in the adrenal medulla. It is metastatic and has a high risk of relapse [1–3]. The treatment of the tumor is dependent on several factors including age, stage, location of the tumor and molecular pathology. Diagnosis is made from blood, urine and tissue samples using different biomarkers, and is completed with in vivo imaging studies. In vivo imaging studies play a central role in selection of the therapeutic approach as well as in following the therapeutic response [4]. They can also be used to obtain prognostic estimates of disease progression.

Several radiological imaging modalities are used in the diagnosis of neuroblastoma. Traditionally CT has been the first method of choice. Concerns about the radiation burden in children have resulted in the use of other imaging modalities including MRI and ultrasonography. The information obtained with all these imaging modalities consists of anatomical localization, estimation of the tumor size and detection of metastases based on the contrast in relation to the surrounding tissue. CT imaging is based on x-rays and electron density while MRI is based on proton density, and ultrasonography on the speed of sound in tissue. Although these imaging modalities are the first interventions used for diagnosis, they provide only secondary information on the stage of the malignancy based on the spread of metastases.

The INRG (International Neuroblastoma Risk Group) has published guidelines on the imaging and staging of neuroblastic tumors with the aim of optimizing imaging and uniform reporting for staging [5]. Children with an abdominal or pelvic mass should be initially investigated by ultrasonography due to its noninvasive nature and widespread availability. MRI and CT studies are recommended for further evaluation of the primary tumor. Functional imaging with nuclear medicine imaging techniques is gaining importance for staging neuroblastic tumors and for the selection of a personalized therapeutic approach, and even to obtain prognostic estimates of disease progression.

Since the presently used methods for making prognostic estimates of the disease are heavily based on semiquantitative analyses of nuclear medicine imaging enhanced with anatomical information obtained by CT or MRI, it is imperative to deeply evaluate which basic technical factors affect nuclear medicine imaging data [2, 6]. The most important factor in nuclear medicine imaging is the biological problem to be investigated (e.g. a biological dysfunction, the presence of tumor, etc.). The functional biochemistry of the problem under investigation may allow selection of a biomarker and of a possible detection ligand (drug). A method for the radiosynthesis of the drug then needs to be established and a radioisotope selected, which will indicate the most appropriate imaging modality (e.g. gamma detection, i.e. SPECT imaging, or annihilated photon detection, i.e. PET imaging). Imaging ligands have to be selective for the target cells/tissues. Presently, the biomarker/imaging ligand selected has the highest impact on diagnostic information, the design of a personalized therapeutic approach and the use of the data for prognostic purposes.

Neuroblastoma tumor cells express the norepinephrine transporter, which makes metaiodobenzylguanidine (MIBG), an analogue of norepinephrine, an ideal tumor-specific agent [6]. Once the tracer is in the cell it will accumulate in the storage granules by the action of the vesicular monoamine transporters. The presence of these transporters is necessary for functional imaging of the tracer, and their absence is the

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main cause of false-negative results. For imaging studies MIBG is labeled with either ^{131}I or ^{123}I. ^{123}I labeling is preferred because of its shorter half-life (13.2 h) compared with that of ^{131}I (8.1 days). In addition the energy of the emitted gamma rays from ^{123}I (159 keV) is preferable for SPECT imaging studies. ^{131}I has high gamma energy (364 keV) with a high radiation burden for diagnostic studies, but [^{131}I]MIBG is used for targeted therapy of neuroblastoma. Additionally there are other radiolabeled gamma-emitting markers in experimental use for detecting neuroblastoma, such as [^{111}In]octreotide for imaging somatostatin receptors which are expressed in 21 – 90 % of neuroblastoma cells. However, it should be noted that distribution of all these transmitters is not uniform in tumors, and this affects detection sensitivity.

The first positron imaging studies to detect tumors were conducted 60 years ago by Sweet and Brownell, and this approach was used intensively until CT imaging became available in the 1970s [7]. The clinical use of PET imaging has been revived over the past 10 – 15 years with the commercial availability of [^{18}F]fluorodeoxy glucose ([^{18}F]FDG). PET imaging has many advantages over SPECT imaging. Firstly, the resolution of the modern devices is of the order of 2 mm for brain systems and around 5 mm for whole-body systems. Secondly, PET radiotracers are labeled with positron emitters producing 511-keV photons with low attenuation which can be readily corrected, while in SPECT imaging attenuation has a more dominant effect and correction mechanisms are not commonly available. Also corrections for other issues related to the imaging modality, such as scatter, have been developed for PET but not for SPECT. Signal detection sensitivity is also much higher in PET imaging resulting in the need for a smaller amount of radioactivity for imaging. The clinical use of PET imaging has been limited because of the limited number of radioligands available. [^{18}F]FDG is the most widely used radioligand. This glucose analog is an outstanding ligand for the investigation of variations in metabolic function in any part of the body. It is generally used for tumor detection, grading and investigating therapeutic responses. Often PET is combined with CT allowing anatomical information to be added to the functional PET information. PET/MRI hybrid imaging systems have also been recently developed. These provide excellent anatomical soft tissue data complemented by functional PET data. Although FDG PET is a unified concept, FDG imaging is not specific to any tumor; it is a general indicator of metabolism.

Neuroblastoma cells have the ability to accumulate and decarboxylate amine precursors such as L-DOPA [8]. [^{18}F]FDOPA resembles natural L-DOPA and is actively transported into the cell by the action of various amino acid transporters, converted to [^{18}F]fluorodopamine by amino acid decarboxylase (AADC) and stored in the vesicles. Because the physical half-life of ^{18}F is 110 min, PET imaging is able to show the total radioactivity concentration in living tissue, irrespective of any biotransformation of the tracer. The increased transport and AADC activity result in intracellular retention of metabolized [^{18}F]FDOPA and increased regional accumulation seen in PET images.

There are several recently published papers compare the sensitivity and specificity of [^{123}I]MIBG, [^{18}F]FDG, [^{18}F]FDOPA and CT/MRI for the diagnosis of neuroblastoma, and the imaging data are used for modeling progression of the disease [1, 8–12]. Most of the published data are based on histological verification. The average values for sensitivity of these published data are 96 % for [^{18}F]FDOPA, 82 % for [^{18}F]FDG, and 70 % for [^{123}I]MIBG and CT/MRI. Corresponding specificity values are 90 % for [^{18}F]FDOPA, 87 % for [^{123}I]MIBG, 71 % for [^{18}F]FDG, and 45 % for CT/MRI. However, it should be noted that the studies investigating both [^{18}F]FDG and [^{18}F]FDOPA were conducted with combined PET/CT systems providing enhanced anatomical information for tumor localization as well as enhanced detection of tumor in bony tissues provided by CT. Based on the available literature, [^{18}F]FDOPA is the preferred method for diagnostic staging of neuroblastoma. Developing methods for prognostic estimates of neuroblastoma are typically based on the clinical experience including stage of malignancy, number and localization of metastases in soft and bone tissue and statistical parameters. Modeling based on these factors can be done in any phase of the disease to estimate prognosis or evaluate treatment effectiveness. However, since detection of malignances is dependent on the imaging data, high accuracy and quality of the data are required. Probably, the most informative nuclear medicine approach for diagnostic staging, therapeutic planning, and prognostic evaluation of neuroblastoma and relapse will be obtained by combining SPECT imaging using [^{123}I]MIBG and PET/CT imaging using [^{18}F]FDOPA if possible. The statistical analyses done by Piccardo et al. reported in this issue show high positive correlations between ^{18}F-DOPA PET/CT and ^{123}I-MIBG in patients with neuroblastoma relapse [13].

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