Comparisons of $^{18}$F-FDG PET/CT with $^{123}$I-MIBG imaging in patients with neuroblastoma

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Dr Nikolaos Papanastasiou
Institute of Nuclear Medicine
University College Hospital, London
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by Nikolaos D Papathanasiou
Institute of Nuclear Medicine
University College Hospital, London

Neuroblastoma arises from the sympathetic nervous system and is the most common extra-cranial solid tumour of childhood, accounting for 8-10% of paediatric malignancy. The most common primary site is the retroperitoneum (65% of cases), with adrenal glands more often involved than prevertebral, presympathetic ganglia. Less often, it arises from the posterior mediastinum (20%), pelvis or neck, while in some cases no primary site is identified.

The most important prognostic features for neuroblastoma are age and stage. “Low-risk” patients (younger than 18 months at presentation with low-stage, localised tumours) have an excellent prognosis. They are treated with surgery alone, which achieves long-term survival rates of >90-95%. More invasive locoregional tumours (infiltrating across the midline or with contralateral nodal involvement) are treated successfully with a combination of induction chemotherapy, surgery and radiotherapy.

Unfortunately, more than half of neuroblastoma patients are characterised as “high-risk” based on unfavourable prognostic features such as age ≥18 months at presentation, presence of distant metastases (in lymph nodes, cortical bone, bone marrow and liver), tumour histology and MYCN oncogene amplification. Until the early 80s very few children with metastatic disease were alive at five years from diagnosis. During the last two decades there has been a substantial progress with the advent of multimodality aggressive treatment. This initiates with intensified induction chemotherapy; during this phase, stem cells are harvested for the next phase of treatment. High-dose consolidation follows, to eliminate any remaining tumour, with cytotoxic agents and autologous haemopoietic stem cell support, then tumour resection if possible and eradication of minimal residual disease with retinoids. Such aggressive treatment has increased response rates; nevertheless a significant proportion of patients (15%) are resistant to induction chemotherapy, while 50% will relapse after consolidation. Overall, long-term cure rate is poor, less than 25-30%.

Several diagnostic modalities are applied to define disease status in patients with neuroblastoma. Computed tomography (CT) is useful for the extent of primary tumour, to define vascular or other vital organ encasement and to detect contiguous or distant nodal metastases. Magnetic Resonance Imaging (MRI) is the preferred modality for the assessment of any tumoral extension in the spinal cord. Both these modalities are particularly useful for planning surgery in patients with localised tumours.

$^{123}$I-metaiodobenzylguanidine ($^{123}$I-MIBG) imaging and $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) PETCT

$^{123}$I-MIBG (metaiodobenzylguanidine) scintigraphy is the functional method of choice in neuroblastoma. MIBG is a noradrenaline analogue selectively concentrated in nerve terminals and has high specificity at initial staging, identifying the primary tumour and metastases in lymph nodes, bone and bone marrow. $^{123}$I-MIBG should be performed in newly-diagnosed patients as it may upstage them by detecting distant metastases, particularly in bone/bone marrow, not evident by other imaging modalities. In the setting of intensifed therapy protocols, $^{123}$I-MIBG is used effectively in patient’s management to detect residual, recurrent or occult disease.

$^{123}$I-MIBG has also been used as a prognostic indicator; the extent of MIBG-positive disease before, during and after treatment has been shown to correlate with a poor outcome and decreased survival.

$^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) PETCT is an established imaging standard for many adult cancer types; however, its clinical role in paediatric malignancy is less well addressed.

$^{18}$F-FDG is a non-specific tracer, a glucose analogue concentrated in malignant cells. It is more avid compared with normal cells. Lymphomas, primary brain neoplasms and sarcomas have been most frequently studied in children. Very few studies have investigated the use of $^{18}$F-FDG in neuroblastoma. Initial small studies (<20 patients) have shown tumoural avidity for $^{18}$F-FDG and later a single study proposed $^{18}$F-FDG PET as a sole imaging modality, to assess neuroblastoma progression. However, the diagnostic accuracy and role of $^{18}$F-FDG PETCT have not been defined, especially for “high-risk” neuroblastoma, in which determination of disease status is critical to guide therapeutic management. Beyond disease detection, it is not known whether $^{18}$F-FDG PETCT may provide prognostic information and identify patients who are likely to fail multimodality treatment, within this cohort of high-risk aggressive tumours.

In our department we performed a prospective study to compare the diagnostic performance of $^{18}$F-FDG PETCT with $^{123}$I-MIBG (combined planar and SPECT/CT) imaging in “high-risk” neuroblastoma. We evaluated 28 refractory-relapsed, Stage IV (with distant metastases; 25/28 with osteoscleroderllas lesions) patients with a pair of $^{18}$F-FDG – $^{123}$I-MIBG scans. We compared these methods according to the extent of disease and the intensity of positive lesions, identified on each patient. Separate comparisons for a) the soft tissue and b) the bone/bone marrow compartments of tumour burden were performed. We also carried out a survival analysis to investigate for the prognostic significance of $^{18}$F-FDG and $^{123}$I-MIBG imaging parameters.

$^{123}$I-MIBG imaging was positive in all (28/28) patients, while $^{18}$F-FDG PETCT in 25/28 patients. $^{18}$F-FDG missed four cases of disease in the soft tissue, five cases in the bone/bone marrow compartments and six cases of skull lesions, all positive on $^{123}$I-MIBG. Statistical comparisons showed superiority of $^{123}$I-MIBG for disease detection in both soft tissue and bone/bone marrow compartments. In the majority of cases, $^{123}$I-MIBG was superior to $^{18}$F-FDG (12/28 cases) in mapping tumour load, or at least equivalent with $^{18}$F-FDG (12/28 cases) (Figure 1). In only, 4/28 (14%) patients $^{18}$F-FDG was better. Interestingly, this group of patients (4/28) with $^{18}$F-FDG being superior to $^{123}$I-MIBG had significantly lower survival rates than the others. Tumoural avidity for $^{18}$FDG (as measured by SUV*) was associated with decreased survival.

Our experience showed that most neuroblastomas are myocardium, salivary glands, bowel, urinary tract and thyroid; mild uptake is sometimes noted in normal adrenals. $^{18}$F-MIBG has shown high diagnostic sensitivity (>85%) and even higher specificity at initial staging, identifying the primary tumour and metastases in lymph nodes, bone and bone marrow. $^{123}$I-MIBG should be performed in newly-diagnosed patients as it may upstage them by detecting distant metastases, particularly in bone/bone marrow, not evident by other imaging modalities. In the setting of intensified therapy protocols, $^{123}$I-MIBG is used effectively in patient’s management to detect residual, recurrent or occult disease. $^{123}$I-MIBG has also been used as a prognostic indicator; the extent of MIBG-positive disease before, during and after treatment has been shown to correlate with a poor outcome and decreased survival.

$^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) PETCT and $^{123}$I-metaiodobenzylguanidine ($^{123}$I-MIBG) imaging in "high-risk" neuroblastoma – our experience
18F-FDG avid; however, 123I-MIBG imaging was overall superior in mapping the extent of disease. The main advantage of 123I-MIBG over 18F-FDG was its superiority in identifying accurately bone/bone marrow lesions without being confounded by bone marrow activation due to prior therapies. 123I-MIBG does not show physiological distribution in the skin, so any bone 123I-MIBG uptake should be considered abnormal/disease (figure 2). On the contrary, 18F-FDG may exhibit physiological accumulation in the bone marrow due to activation after chemotherapy, resulting in lower accuracy for bone/bone marrow disease detection. 18F-FDG was inferior in detection of skull lesions, unless these demonstrated a considerable soft-tissue component (figure 1), due to high 18F-FDG activity in the adjacent cortical brain. SPECT/CT added to planar 123I-MIBG imaging has been particularly useful to clarify equivocal findings and to provide better anatomical definitions for MIBG-avid lesions. It was very helpful in the detection of liver lesions, which can be masked due to physiological tracer distribution in the liver.

Beyond disease detection, our results showed significant prognostic implications of 18F-FDG PETCT in “high-risk” neuroblastoma. 18F-FDG tumoural uptake, as measured by the semi-quantitative index SUV, was associated with decreased survival. A pattern of increased 18F-FDG activity, surpassing tumoural avidity for MIBG, corresponded to more aggressive disease and worse outcome. Whether this pattern mirrors neuroblastoma de-differentiation is unknown.

Conclusions
According to our experience, 18F-FDG PETCT cannot replace 123I-MIBG in the assessment of “high-risk” neuroblastoma, mainly due to its limitation in identifying bone/bone marrow infiltration. 18F-FDG PETCT can be valuable in the evaluation of a minority of neuroblastomas which do not accumulate 123I-MIBG, or in cases where greater than depicted with 123I-MIBG extent of disease is suspected. Neuroblastoma avidity for 18F-FDG was associated with decreased survival, within this cohort of already poor prognosis. The practical incorporation of 18F-FDG PETCT in treatment decision-making would, however, require the development of novel more effective treatments, which would increase cure rates. In such a setting, 18F-FDG PETCT could identify patients for whom a more aggressive treatment strategy would be required.

*SUV (Standardised Uptake Value) is a semi-quantitative measure of the 18F-FDG activity within a lesion, calculated by the formula: 

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SUV = \frac{Q_l}{Q_{inj}} \frac{Q_{inj}}{BW}
\]

where \(Q_l\): the activity in the lesion in mCi/ml, \(Q_{inj}\): activity injected in mCi and \(BW\): patient’s weight in grams.

Suggested reading

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