Childs Nerv Syst
DOI 10.1007/s00381-007-0307-8

INVITED PAPER

PET imaging in the surgical management of pediatric brain tumors

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Received: 20 October 2006

Abstract
Objective The present article illustrates whether positron-emission tomography (PET) imaging may improve the surgical management of pediatric brain tumors (PBT) at different steps.
Materials and methods Among 400 consecutive PBT treated between 1995 and 2005 at Erasme Hospital, Brussels, Belgium, we have studied with ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG)–PET and/or L-(methyl-^{11}C)methionine (MET)–PET and integrated PET images in the diagnostic workup of 126 selected cases. The selection criteria were mainly based on the lesion appearance on magnetic resonance (MR) sequences. Cases were selected when MR imaging showed limitations for (1) assessing the evolving nature of an incidental lesion (n=54), (2) selecting targets for contributive and accurate biopsy (n=32), and (3) delineating tumor tissue for maximal resection (n=40). Whenever needed, PET images were integrated in the planning of image-guided surgical procedures (frame-based stereotactic biopsies (SB), frameless navigation-based resections, or leksell gamma knife radiosurgery).
Results Like in adults, PET imaging really helped the surgical management of the 126 children explored, which represented about 30% of all PBT, especially when the newly diagnosed brain lesion was (1) an incidental finding so that the choice between surgery and conservative MR follow-up was debated, and (2) so infiltrative or ill-defined on MR that the choice between biopsy and resection was hardly discussed. Integrating PET into the diagnostic workup of these two selected groups helped to (1) take a more appropriate decision in incidental lesions by detecting tumor/evolving tissue; (2) better understand complex cases by differentiating indolent and active components of the lesion; (3) improve target selection and diagnostic yield of stereotactic biopsies in gliomas; (4) illustrate the intra-tumoral histological heterogeneity in gliomas; (5) provide additional prognostic information; (6) reduce the number of trajectories in biopsies performed in eloquent areas such as the brainstem or the pineal region; (7) better delineate ill-defined PBT infiltrative along functional cortex than magnetic resonance imaging (MRI); (8) increase significantly, compared to using MRI alone, the number of total tumor resection and the amount of tumor tissue removed in PBT for which a total resection is a key-factor of survival; (9) target the resection on more active areas; (10) improve detection of tumor residues in the operative cavity at the early postoperative stage; (11) facilitate the decision of early second-look surgery for optimizing the radical resection; (12) improve the accuracy of the radiosurgical dosimetry planning.
Conclusions PET imaging may improve the surgical management of PBT at the diagnostic, surgical, and post-operative steps. Integration of PET in the clinical workup of PBT inaugurates a new approach in which functional data can influence the therapeutic decision process. Although metabolic information from PET are valid and relevant for the clinical purposes, further studies are needed to assess whether PET-guidance may decrease surgical morbidity and increase children survival.

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Keywords Pediatric brain tumors · Positron-emission tomography · Stereotactic biopsy · Navigation · Infiltrative tumors · Functional imaging · Image-guidance · Tumor resection

Introduction

Rationale of the approach

In a majority of children, the accurate surgical management of a newly diagnosed brain mass on magnetic resonance (MR) imaging does not raise much discussion. However, in some cases, the choice of the accurate surgical option based on MR sequences analysis may be a real challenge [59–64] because both the sensitivity and specificity of the different MR signals and sequences to detect tumor tissue and anaplastic tissue in brain tumors are currently insufficient [55, 57].

On the other hand, positron-emission tomography (PET), a functional neuroimaging technique, provides independent and complimentary information useful in the management of adult brain tumors [1, 4, 10, 17–22, 26, 30, 37, 39–43, 48, 51, 53, 54, 58, 60, 61, 64, 75]. Although little is known about PET in pediatric brain tumors (PBT), our experience with PET in adult brain tumors allowed us to apply and evaluate PET imaging in children. Because numerous differences exist in therapeutic challenges between adult and children, PET data acquired in adult brain tumors could not be transposed to PBT without being specifically studied and validated.

Surgical challenges specific of PBTs

Specific histopathology and MR presentation

Many features differ from pediatric to adult brain tumors: (1) Some low-grade (pilocytic astrocytomas, ependymomas, teratomas) and high-grade [primitive neuroectodermal tumors (PNET), germinomas, etc.) tumors are specific to the pediatric population, and the tendency of some of them (PNET, ependymomas, pilocytic astrocytomas, germinomas) to disseminate in the cerebro-spinal fluid represents a crucial challenge in the management of PBT; (2) the intratumoral histological heterogeneity observed in adult gliomas has never been demonstrated by histological correlations in pediatric gliomas or even studied in other PBT. (3) A complete tumor removal is much more frequently feasible and crucial for the outcome in children than in adults. Indeed, PBT have a higher proportion of low-grade tumors, of tumors with mixed (glioneuronal) or atypical (xanthoastrocytoma) cell population and of lesions with very low or questionable evolving potential [hamartoma, dysplasia, dysembryoplastic neuroepithelial tumor (DNT), etc.]. Moreover, many types of supratentorial PBT (pilocytic astrocytomas, gangliogliomas, ependymomas, etc.) are rather well delineated, displace more than infiltrate the functional tissue, making them usually accessible to a total removal. Indications and place of stereotactic biopsies are subsequently less frequent than in adults, and the issue of the histological heterogeneity presents a lower priority in the surgical management of pediatric than of adult tumors.

Prognostic value of the surgical resection

Maximal surgical resection remains the main step of therapy for many tumor types, especially ependymomas, craniopharyngiomas, gliomas, and even medulloblastomas, although recent advances in therapy, especially in chemotherapeutic protocols, have improved the management of PBT [2, 3, 6, 7, 9, 15, 24, 27, 28, 32, 38, 45, 56, 63, 65, 68]. Indeed, failure to achieve complete resection often results in progression and to a need for further therapy in patients with pilocytic astrocytomas. Similarly, in most children with ependymomas, this failure is ultimately fatal.

Second-look surgery, defined as the resection of residual tumor before progression on follow-up imaging, has also been promoted with acceptable morbidity [9, 27, 38]. Early second-look surgery avoids delay in adjuvant therapy and reduces the risks related to late post-operative tissue reactions.

Limitations of preoperative MR imaging to delineate tumor tissue

Although neuronavigation might improve surgical resection, the MR guidance presents many limitations. Indeed, some PBT may be particularly infiltrative and ill defined on conventional MR imaging, especially on T1+/-Gd-DPTA [64]. Tumor enhancement may be discrete or heterogeneous and do not always allow precise delineation for complete image-guided resection. This is classically encountered in oligodendrogliomas and fibrillary astrocytomas. Moreover, the abnormal signal on T2-weighted or fluid-attenuated inversion recovery (FLAIR) MR sequences may be not sharply delineated and much more extended that the tumor itself. Magnetic resonance imaging (MRI) modalities have been shown to be inaccurate to reflect tumor boundaries in many low-grade and high-grade gliomas in adults but also in children, in which the sensitivity and specificity to detect tumor tissue are 96 and 53%, respectively, and to detect tumor grade are 72 and 65%, respectively.

Limitations of early postoperative MR imaging to detect tumor residue

As the early confirmation of the completeness of the surgical resection represents a key factor for the management of many PBT, the accuracy of the early postoperative

imaging is crucial. Unfortunately, MR imaging presents limitations in the delineation of abnormal residual signals even when performed very early within the first 3 days. MRI is also often inaccurate in the differentiation between signals related to tumor residue and inflammatory reactions even in FLAIR imaging sequences [23, 52]. Such imaging modalities cannot, therefore, be used as a sole basis of further therapy, especially for deciding a complementary surgical approach. Indeed, an early detection of a tumor residue could allow to perform an early second-look surgery offering the advantages to not postpone the adjuvant therapy and to reduce the morbidity related to the late dissection of arachnoiditis and scar tissue.

Optimization of image-guidance

Any technique that could increase the chance to achieve complete tumor removal at first attempt deserves, therefore, to be addressed. For this purpose, MR-guided neuronavigation has improved the safety and accuracy of the surgical approaches and dissections in PBT when justified by their deep location or their infiltrative aspect. However, PET might improve the image-guided resection technique by a better tumor tissue and anaplastic tissue detection. This might also be crucial for improving the patient's outcome. Thus, we evaluated PET imaging in the surgical approach of PBT according to the specific surgical challenges known in children.

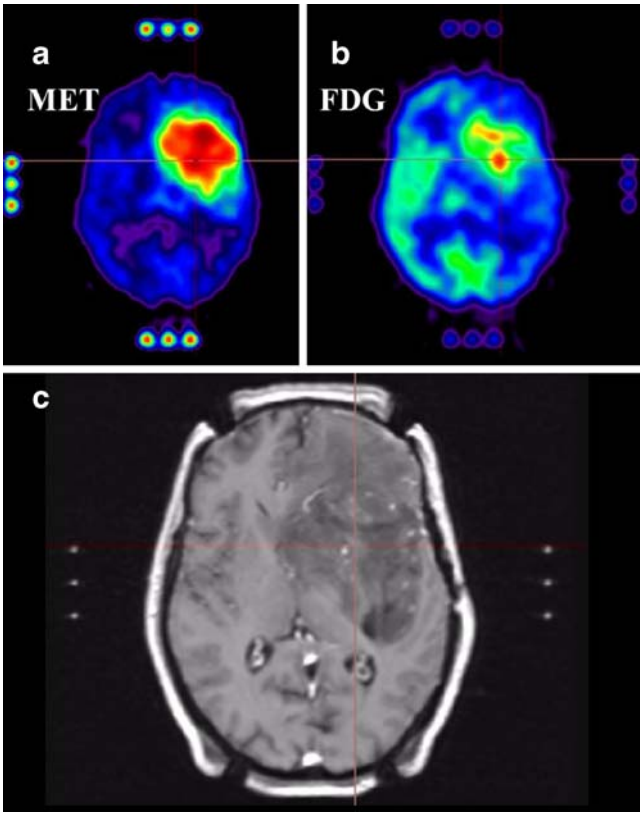

Fig. 1 Frontal fibrillar astrocytoma (WHO grade II) explored in MET–PET (**a**), FDG–PET (**b**), and MRI (**c**). MET–PET allows excellent tumor delineation while FDG–PET shows the areas of highest uptake in tumor parts that are not enhanced after MR contrast

What did we learn from PET in adult brain tumors?

Numerous studies have demonstrated the interest of integrating PET imaging in the routine clinical management of brain tumors in adults, especially with two labeled radiotracers: ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG), which assays glucose metabolism, and the L-(methyl-^{11}C) methionine (MET), which assays amino acid transport and protein metabolism [1, 4, 10, 17–22, 26, 30, 37, 39–43, 48, 51, 53, 54, 58, 60, 61, 64, 75] (Fig. 1).

Information from PET tracers in adults

The type of information obtained with PET depends mostly on the radiotracer used. The largest PET experience has been acquired with FDG in adult brain tumors. Malignant tumors are characterized by an increased FDG uptake so that FDG–PET is helpful in assessing the degree of malignancy and the prognosis of brain neoplasms, in differentiating the effects of various treatments, and in assessing tumor persistence, progression, or recurrence. When combined with anatomical imaging techniques, FDG–PET can provide information regarding tumor grading, response to chemotherapy, and survival. In particular, the FDG uptake is a more accurate reflection of tumor grade than contrast enhancement [57]. Various studies in adult gliomas have shown that FDG uptake was anatomically heterogeneous within the tumor and correlated with the degree of local histological anaplasia [30, 75]. FDG–PET has also a prognostic value independent of the histology. It was demonstrated that in low-grade gliomas in which spots of high FDG uptake are present, the risk of early malignant degeneration is significantly increased [18]. The independent prognostic factor provided by FDG–PET data has been further demonstrated in high-grade gliomas [20].

MET–PET has also been validated in neuro-oncology [17, 21, 37, 51, 61, 75]. The accumulation of MET in tissues seems to reflect the transmembrane transport that is influenced by the cellular needs in protein synthesis precursors and, therefore, correlates with tissue proliferation and malignancy [30, 37, 40, 48, 64]. The clinical interest of MET–PET is that the protein metabolism is much higher in the tumor than in the surrounding brain tissue. Therefore, MET–PET appears to be a valuable tool with high sensitivity and specificity to detect tumor tissue and to define their boundaries. Moreover, some studies have also demonstrated the prognostic value of MET uptake in gliomas.

Surgical challenges leading to develop stereotactic PET guidance in adults

Although MR imaging allows direct visualization of brain tumors, it cannot predict the histological diagnosis with absolute accuracy or differentiate between radionecrosis and tumor evolution so that MR imaging cannot be used as the sole basis for therapy. Therefore, a stereotactic biopsy (SB) is the procedure of choice for obtaining a histological diagnosis of surgically unresectable tumors. Studies correlating the diagnostic yield of stereotactic biopsies with MR imaging illustrated the limitations of MR imaging in defining tumor tissue [11, 14, 23, 29, 31, 75]. When multiple serial biopsies are performed, the success rate and the pertinence of the established diagnosis is high but failures occur due to inadequate targeting [39, 40]. A limited number of samples increase the risk of biopsy failure, while large sampling increases the risk of complication. Samples may consist, in specimens, irrelevant to the identification of brain tumors, such as non-tumoral parenchyma, gliosis, and necrosis. Moreover, adult brain tumors, especially gliomas, are characterized by geographic variations of their histological malignancy that cannot be distinguished on MR sequences even with contrast injection. Tumor histological heterogeneity may, therefore, lead to inaccurate diagnosis (necrotic tissue in tumors) or underestimated grading (low-grade tissue in high-grade tumors) from MR-guided stereotactic biopsies. Similar limitations of the MR guidance in detecting anaplastic tissue may also create inaccuracy of navigation-based volumetric resection of brain tumors [64].

Moreover, the sensitivity and specificity of MR imaging in detecting tumor tissue is not high enough to allow accurate tumor delineation. Indeed, oligodendrogliomas and fibrillar astrocytomas (more rarely, pilocytic astrocytomas and gangliogliomas) may present as particularly infiltrative and ill-defined lesions on conventional MR imaging, especially on T1+/-Gd-DPTA [6, 7, 11]. Tumor enhancement may be discrete or heterogeneous and do not always allow precise delineation for complete image-guided resection. Moreover, the abnormal signal on T2-weighted or FLAIR MR sequences may not be sharply delineated and much more extended than the tumor itself. MR modalities are inaccurate to reflect tumor boundaries in low-grade and high-grade gliomas in adults and in children (sensitivity and specificity to detect tumor tissue, 96 and 53%; and to detect tumor grade, 72% and 65%) [2, 6, 7, 11, 23, 25, 26, 29, 52, 54, 55, 57, 75].

In summary, FDG and MET are very accurate to detect anaplastic tissue; MET provides a higher sensitivity and specificity than MR imaging to detect tumor tissue and to delineate glial tumors.

PET-guided stereotactic biopsies in adults

To obtain more representative biopsy samples, we have developed a technique allowing routine integration of PET data into the planning of stereotactic biopsies [39, 40, 58]. This technique consists in the acquisition of both PET- and MR-generated images in stereotactic conditions leading to strict image correlation. A methodology of target selection on stereotactic PET-generated images allowed us to accurately direct biopsies in the abnormal metabolic foci of brain tumors. This technique improved the diagnostic yield of stereotactic biopsies. We confirmed the correlation between metabolic and histological heterogeneities in brain tumors [40]. Initial experience has been acquired with FDG, and we have secondarily considered MET as an alternative tracer for stereotactic PET guidance. We found that MET helps to better define stereotactic targets in cases with or without minor tumor FDG uptake (such as in low-grade gliomas) and in case of tumors located in close relationship with the gray matter [58, 61]. Our 15-year experience with this technique confirms that PET-guided stereotactic biopsy is a real progress in the routine management of adult brain tumors.

PET-guided navigation-based volumetric resections in adults

Because MET–PET uptake is an accurate expression of the extent of brain tumors, further integration of PET in the planning of navigation-based volumetric resection procedures may contribute in optimizing their delineation, or in defining the aggressive areas of heterogeneous tumors [64]. PET studies illustrated the large variability of metabolic contours of 80% of brain tumors when compared to those defined on MR images. Metabolic guidance, especially MET–PET-guidance, helped to increase the amount of tumor tissue removed in low-grade gliomas and to target the resection to the hypermetabolic foci representing the anaplastic foci within high-grade gliomas. Finally, our preliminary data in adults suggest that removing the entire abnormal uptake of PET tracer increases patients' survival contrary to removing the entire contrast MR enhancement.

What did we know about PET in pediatric neuro-oncology?

Very few studies were published on PET in pediatric neuro-oncology. In the 1980s, pioneer clinical studies suggested that PET was likely to aid our understanding of many neuropediatric diseases and may gain widespread application with the rapid dissemination of PET technology [10, 33, 34, 49]. The first FDG–PET studies of isolated cases showed a relationship between FDG uptake and the degree

of tumor malignancy [49], the response to chemotherapy, and highlighted the heterogeneity of FDG uptake in PBT [8, 10, 33, 34]. These authors have suggested that histological heterogeneity could exist in PBT but it has never been demonstrated.

Twenty years later, PET has not become routinely used in PBT. Literature remains relatively scarce on this matter and indications of PET are not clearly defined [46, 47, 49, 50]. Its greatest clinical utility lies in the field of intractable partial epilepsy to localize epileptogenic foci for surgical resection. The limited accessibility of PET technology is the major reason of the apparent lack of interest.

Recent works on PET have emerged in PBT. A study focused on functional brain mapping using FDG–, MET–, and [^{15}O]H_2O–PET correlated with MR images for preoperative neurosurgical planning in PBT to characterize the relationship between potentially resectable tumors and functionally eloquent brain areas [35]. Another study with FDG–PET and MET–PET in 27 untreated primary PBT found that both FDG and MET uptakes were associated with the malignancy grade and may give valuable additional information on clinical tumor aggressiveness [74]. Also, a study of FDG–PET and ^{15}O–H_2O–PET, coregistrated to MRI, has confirmed the correlation between FDG uptake and the histological grade in high-grade tumors, just as it was shown 20 years ago in adults [8].

Materials and methods: Brussels 1995–2005 experience with PET in children

Selection criteria

When we started in 1995 to evaluate prospectively the PET imaging in PBT, PET had never been integrated in the stereotactic image guidance. During the 1995–2005 period, 400 children were referred and treated for a brain mass in the Department of Neurosurgery of Erasme University Hospital at Brussels, Belgium. Newly diagnosed brain lesions were well delineated and accessible to a surgical resection in 70% of the cases. In the other 30% (n=126), the choice of the accurate surgical decision based on MR images represented a real challenge.

Practically, we observed that (1) a poor delineation of a PBT on MR imaging—especially when located near eloquent areas—may lead the neurosurgeon to perform a very limited tumor resection or even to propose a stereotactic biopsy as an unsatisfactory but safer approach; (2) when a partial removal is decided, the resection, even assisted by navigation technique, does not accurately target the most aggressive/evolving part of the tumor [64]; (3) when a biopsy is performed in infiltrative PBT, target selection may be difficult or even inaccurate, yielding to non-representative or even non-diagnostic tissue samples [11, 25, 29, 75]; (4) the low specificity of MR for detecting tumor tissue may raise, in incidental findings, the difficult choice between justifying the risk of a surgical approach and choosing a conservative follow-up with the risk of leaving the lesion in place.

Patient subgroups

We combined FDG– or MET–PET imaging to MRI in the diagnostic workup of 126 cases, selected by the analysis of the MR images as two distinct groups. The first group (n=72) included symptomatic children with ill-defined, infiltrative tumors, and the second group (n=54) included asymptomatic children with a brain lesion diagnosed incidentally. In both groups, MR signals provided insufficient sensitivity and specificity to detect tumor tissue and anaplastic tissue in brain tumors. The appearance of the lesion on MR images did not allow to (1) select targets for contributive and accurate biopsy (n=32); (2) delineate tumor for maximal resection (n=40); (3) understand or advocate the evolving nature of an incidental lesion (n=54).

In the first group (n=72), the poor tumor delineation on MR imaging may lead the surgeon—especially when the lesion is located close to eloquent areas—to perform an open surgical approach with very limited resection or even to propose a stereotactic biopsy as an unsatisfactory but safer option approach. One step further, when a partial removal is decided, the neurosurgeon cannot be sure even with navigation-based assistance that his resection accurately targets the most aggressive/evolving part of the lesion. Similarly, when a biopsy is chosen for a diagnostic and prognostic assessment, the target selection in infiltrative lesions may be difficult or even inaccurate, yielding to non-representative or even non-diagnostic tissue samples.

In the second group (n=54), the incidental diagnosis of brain lesions in asymptomatic children may show MR appearance or signals (no edema, no enhancement, etc.) advocating an indolent tumor or even a non-tumor lesion. This group also included cases with stabilized long-term epilepsy in which a similar lesion has been identified. Such a situation may lead the attending team to the difficult choice between justifying to the parents the risk of a surgical approach and choosing a conservative follow-up with the risk of leaving the lesion in place.

PET images were integrated into the planning of image-guided surgical procedures in 62 children (frame-based stereotactic biopsies in 25 or frameless navigation-based resections in 37) according to a methodology widely described elsewhere [59, 63].

Results

PET improves the detection of tumor tissue at the diagnostic stage

PET was very helpful at the diagnostic step when a brain lesion is an incidental finding in asymptomatic children or in those with controlled chronic epilepsy.

Lesions presented rather as well delineated and accessible to resection, but showed neither enhancement nor edema. These features suggested a non-evolving/indolent tumor, such as a dysembryoplastic neuroepithelial tumor (DNT) or even a non-tumor lesion such as a dysplasia. The indication of the surgical approach seemed, therefore, questionable, and the conservative option limited to a comparative MR follow-up could be considered. In such situations, the clinicians needed to gather arguments suggesting the tumor or the evolving potential of the lesion to sustain and justify the surgical option to the parents waiting for the most appropriate decision.

In 54 children, FDG–PET was performed in 13 and MET–PET in 41. In all 16 cases in which PET showed a significantly increased tracer (FDG or MET) uptake, the surgical option was decided, considering these features were highly suggestive of a tumor tissue, potentially anaplastic in cases with high FDG uptake. A tumor diagnosis was confirmed in all cases presenting with an increased PET tracer uptake. In the other 38 cases, a low or absent PET tracer uptake was considered to correspond to indolent low-grade tumor or to non-tumor tissue and sustained a conservative option. Nevertheless, 16 of these 38 patients were finally operated because the lesion seemed accessible to surgery and because we needed histological diagnosis. In these 16 cases, a low-grade tumor tissue (two fibrillar astrocytomas, five DNT, one giant-cell astrocytoma associated with cortical dysplasia) or a non-tumor disease (three vasculites, one sarcoidosis, three glioses) was diagnosed [36, 44, 66]. Our short experience with MET–PET in DNTs showed us that a high MET uptake makes that diagnosis unlikely. In summary, PET imaging helped to orientate the therapeutic management in 38:54 children (70%).

Stereotactic PET guidance for stereotactic biopsies in children

PET guidance to improve target definition in selected cases

We integrated PET imaging into the MR-guided stereotactic planning of stereotactic biopsies in 32 selected children with non-resectable brain lesions in which biopsy trajectories could not be easily defined in areas of contrast enhancement or in areas of highest signal on FLAIR or T2-weighted MR sequences because the lesion was infiltrative or very heterogeneous. Indeed, target selection in such lesions may be either impossible or even inaccurate, leading to non-diagnostic sampling or to underestimated grading. Although intratumoral histological heterogeneity has never been demonstrated in PBT, we postulated that it might limit the diagnostic yield of stereotactic biopsies in children as in adults. We used PET guidance according to the technique described in adults, allowing to direct biopsies in the abnormal metabolic foci of brain tumors [39, 40, 58, 59]. We hypothesized that metabolic information would help to better define targets for biopsy, improve the diagnosis accuracy, and reduce the sampling.

PET guidance is technically feasable in children

Our experience showed that the technique was applicable to children. Adaptations to pediatric population were limited. Under 5 years of age, a general anesthesia was used systematically before frame fixation and data acquisition to reduce discomfort and movements [59]. This required the long-lasting presence of a senior anesthesiologist and specific equipment in the PET and MR units adapted to pediatric narcosis. The procedure was, therefore, demanding in terms of anesthesia. We did not encounter frame instability in young children. Technical considerations on PET tracer dosimetry and image magnification in children have been discussed [67, 69, 70, 72]. The choice of radiotracer for PET guidance depends on the type of information expected. Using multiple tracers to broaden the metabolic information in PET-guided stereotactic biopsy is time-consuming and costly; it should certainly not be performed on a routine basis. The choice of the radiotracer was based on the pre-operative imaging information, as in adults.

PET guidance improves detection of anaplastic tissue and target selection

PET-guidance significantly reduced the number of non-contributive trajectories (PET-defined targets never yielded a non-diagnostic sample) and improved the diagnostic yield of the biopsy without increasing the sampling [59] (Figs. 2 and 3). Secondarily, PET guidance allowed reduction in the number of biopsy targets. Indeed, in all the lesions located in functional areas in which multiple sampling should be avoided, we only used one biopsy trajectory guided by PET. This technique also illustrated the histological heterogeneity in pediatric gliomas and showed that it could impede the diagnostic accuracy of stereotactic biopsies in PBT.

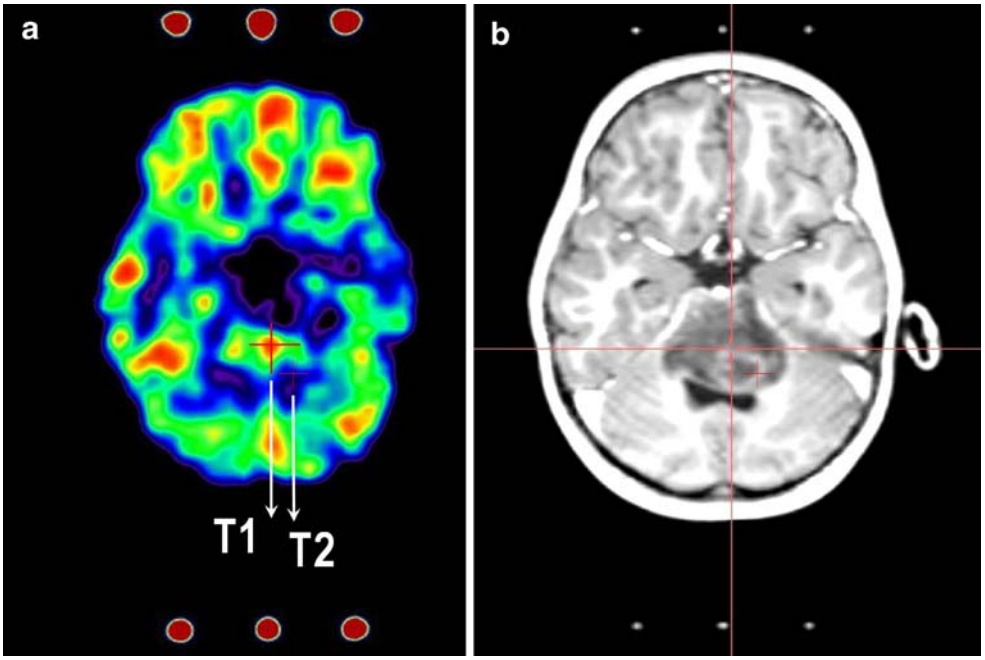

Fig. 2 Pontine intrinsic anaplastic astrocytoma (WHO grade III) in an 8-year-old girl. Two biopsy targets were selected based on MR contrast enhancement (*red crosses* in **b**). Only the target corresponding to the increased FDG uptake (*T1* in **a**) provided the diagnosis, while the other (*T2* in **a**) was non-diagnostic

PET provides additionnal prognostic information

In addition to what was expected, PET guidance also improved the understanding and the quality of management of some children. Indeed, the technique offered additional prognostic information that provided a stronger prognostic value than histology itself, leading to predict worse evolution. This prompted us to resect secondarily some tumors in an attempt to improve the outcome.

Stereotactic PET guidance for volumetric tumor resections in children

MET–PET guidance to improve tumor delineation in selected cases

Experience showed that the stereotactic PET guidance was also applicable to the surgical resection of brain tumors [63]. This strategy included the integration of PET information in the neurosurgical planning of neuronavigation. Indeed, when the lesion is ill defined on MRI and when a partial resection is performed, the neurosurgeon cannot be really sure that the surgery targets the most representative or evolving part of the lesion. Integration of PET in neurosurgical procedures may contribute to a better management of PBT, either in optimizing the delineation of their extension, or in defining the aggressive areas within heterogeneous tumors.

We have used PET images and information in the image-guided volumetric resection of PBT in 40 selected children with ill-defined low-grade brain tumors in which a complete resection was considered a key factor of survival. Both PET and MR data were always acquired in the same brain coverage conditions. The methodology was described in details elsewhere [63, 64].

PET guidance for improving tumor delineation

MET–PET provided better tumor delineation than MRI (Figs. 4 and 5). In the first 22 children operated [63], the technique improved tumor resection in 20 by providing a resection contour that was different and better defined than with MR alone (Figs. 6 and 7). The validity of MET–PET and MR imaging in delineating tumor tissue was studied by comparing tissue samples taken on operative margins at the

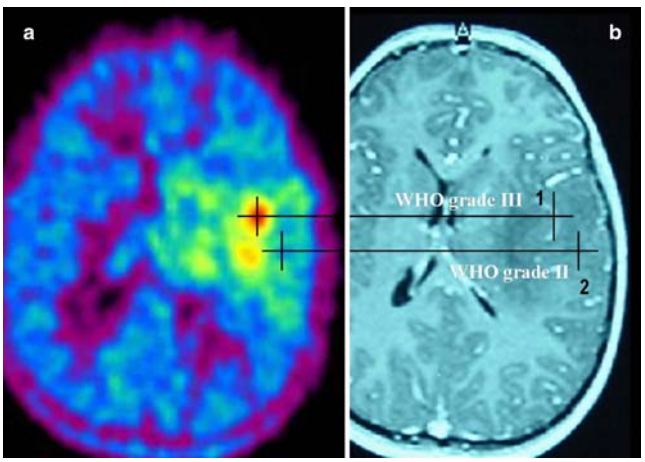

Fig. 3 Infiltrative anaplastic astrocytoma (WHO grade III) in a 9-year-old boy. The biopsy sampling of the trajectory guided by the increased MET uptake (**a**) yielded the anaplastic diagnosis, while the second trajectory guided outside the area of increased MET uptake yielded a low-grade diagnosis

end of surgery and local MR signals/MET–PET uptake levels, as assessed by immediately post-operative MR and MET–PET imaging in all cases (Fig. 8).

The total resection of the PET uptake, considered as total tumor resection, was achieved in 15:20 cases. Subtotal resection of the PET uptake was achieved in five others. A second surgery led to total resection in two children, and therapy escalation was performed in three. In the remaining two children, PET guidance was not contributive to the final target contour definition because there was no MET uptake in one, and PET and MR contours were similar in another.

PET guidance for increasing the amount of tumor removed in low-grade tumors

MET–PET helped to improve the surgical management of ill-defined low-grade tumors by increasing the number of total resections and the amount of tumor removed. This statement was sustained by the observation that whatever the residual post-operative MR signals on the margins of the operative cavity, the presence of residual tumor tissue on resection margins was always (n=14) correlated with the presence of a residual local MET uptake.

These data illustrated the high specificity and sensitivity of MET–PET to detect tumor tissue, as confirmed by the presence of tumor tissue in two children re-operated (neither false negative nor false positive of MET in the detection of tumor tissue) [62, 63]. The present data confirm that MET–PET is a better tool for tumor delineation than MR, with T1+/-Gd-DTPA but also with other imaging modalities.

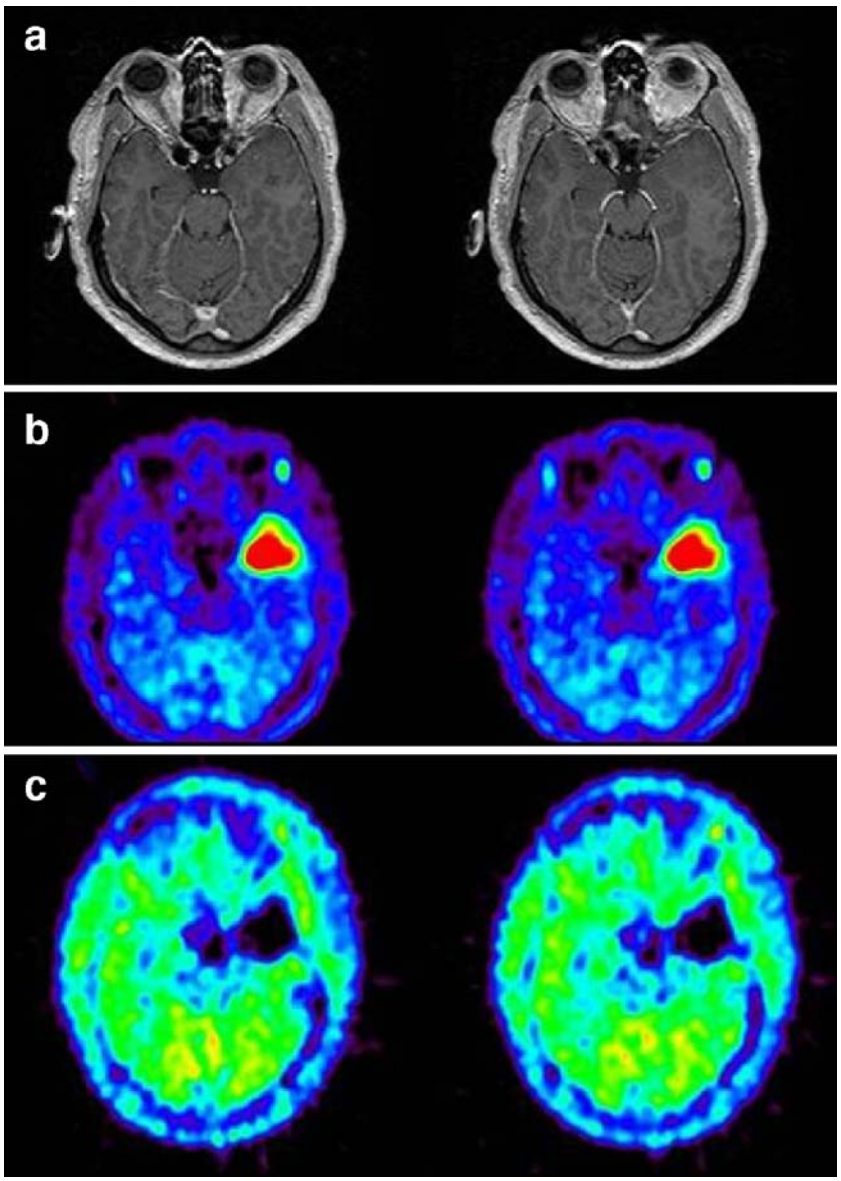

Fig. 4 Integration of PET images in the MR-guided navigation for volumetric resection of pediatric brain tumors: preoperative MR imaging (**a**), preoperative MET–PET imaging (**b**), and postoperative MET–PET imaging (**c**)

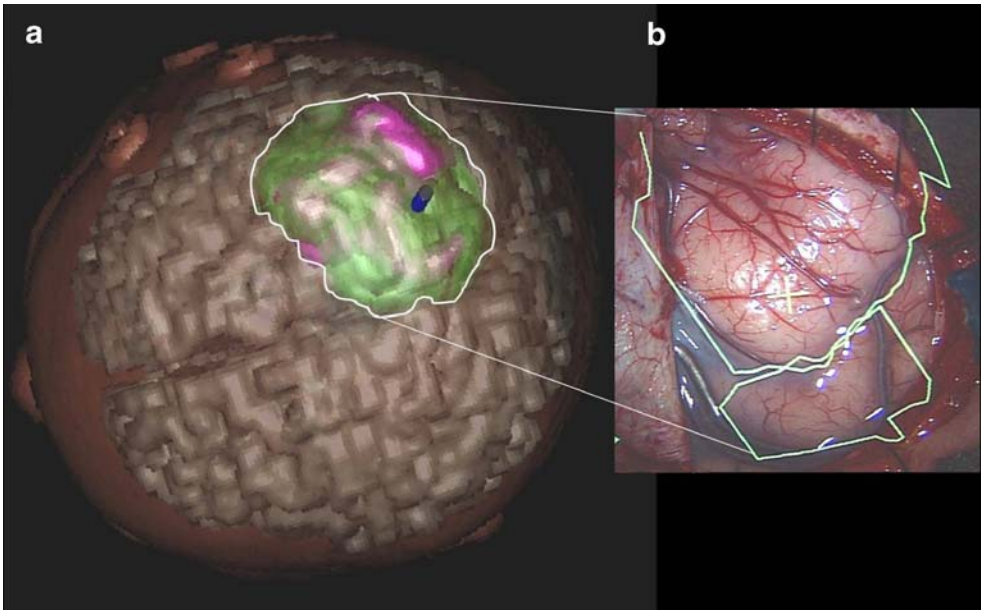

Fig. 5 Parietal ganglioglioma (WHO grade I) in a 10-month-old boy. Combined MET–PET and MR tumor contours displayed on the preoperative 3D planning (**a**) and subsequently projected in the eyepiece of the navigation microscope (**b**)

PET could improve the child's prognosis

Although some studies have demonstrated that the level of MET uptake had a prognostic factor in gliomas [18, 19], nobody knows whether a partial surgical resection focused on the area of highest MET uptake could provide a benefit to the child's outcome. However, because the quality of resection represents a key factor for increasing the child's survival in ependymomas, pilocytic astrocytomas, oligodendrogliomas, and gangliogliomas, the technique could improve the prognosis of children harboring ill-defined brain masses. Further experience will help to better define the clinical benefit of this approach and to distinguish the type of contribution PET may have in relation with the different PBT types.

PET also improved the understanding and the quality of management of some children. PET imaging allowed to differentiate cortical abnormalities from tumor infiltration and to better understand and manage epilepsy in some cases. In a few patients, MET uptake, as found on the initial preoperative PET, was already scaled at the upper limit of the normal range for low-grade glial tumors. These metabolic information provided a prognostic value leading to predict worse evolution [59, 62].

PET helps the decision process of second-look surgery

Early postoperative PET improves detection of tumor residue

Early postoperative MET–PET (within 7 days) were performed in 20 children, in which the surgical team was convinced to have achieved a total tumor resection while the immediate postoperative MR showed linear or bulky signals/enhancement suggesting a tumor residue [62]. We studied the interest of PET in the postoperative stage and showed that MET–PET is highly accurate to detect tumor tissue compared to MR images including FLAIR imaging sequences. A tumor residue was found at reoperation in all

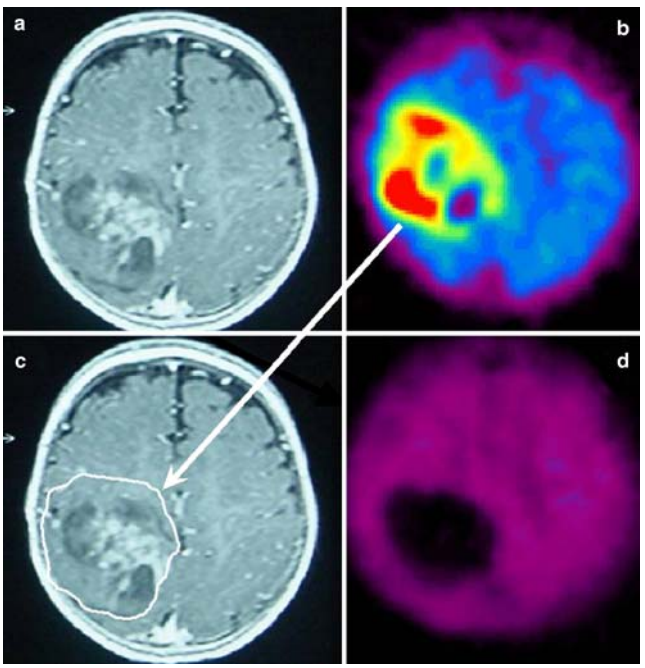

Fig. 6 Parietal ganglioglioma (WHO grade I) in a 10-month-old boy. Tumor boundaries were ill defined on MR images (**a**). MET–PET showed a sharply delineation (**b**) that was subsequently projected on stereotactic MR images (**c**). Combination of MET–PET and MR tumor contours showed in this case that PET-defined contour was more extended than the contour on MR, allowing a complete tumor resection, as confirmed by post-operative MET–PET (**d**)

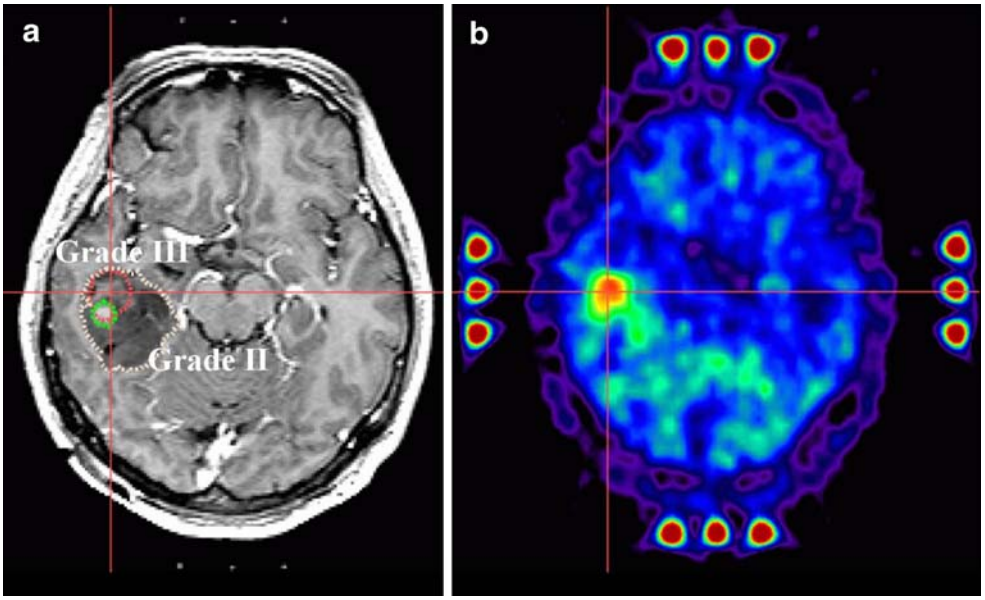

Fig. 7 Left temporal lobe astrocytoma in which there was no concordance between the area of MR contrast enhancement (**a**) and the area of increased FDG uptake (**b**). Only the area of increased FDG uptake corresponded to a zone of anaplastic tissue

cases presenting a residual MET uptake on PET, while such correlation was not constant with the MR signals (false positive results). Also, PET data did not present false negative results because long-term MR and PET follow-up showed no tumor progression in children with no postoperative PET tracer uptake, whatever the MR signals were.

Postoperative PET improved, therefore, the diagnostic accuracy of conventional imaging to detect tumor residue and allowed to consider the absence of MET uptake as complete tumor resection.

Postoperative PET is a valid basis for deciding early complementary surgery

Early postoperative MET–PET helped the therapeutic decision process regarding the opportunity of a reoperation, especially in cases where postoperative MR imaging suggest subtotal removal. This was particularly crucial for nonmalignant glial tumors (ependymomas, low-grade astrocytomas, hemangiopericytomas) in which radical surgery is a key factor of prognosis [2, 9, 15, 24, 32]. Indeed, PET allowed to take an appropriate therapeutic decision, avoided unnecessary surgery in five children, or led to consider reoperation in 11 children of which 8 could be favorably reoperated. The decision of second-look surgery also considered the risk of surgery-related morbidity. In four cases, reoperation was assisted by image-guided navigation in which PET images had been integrated [59]. It allowed to partially resect the lesion left in place, focusing the resection on the area of highest tracer uptake. Therefore, postoperative MET–PET can be considered as a valid basis for decision of complementary surgery.

PET optimizes the dosimetry planning in radiosurgical treatment

The present experience also indicates that alternative complementary therapies may also benefit from PET

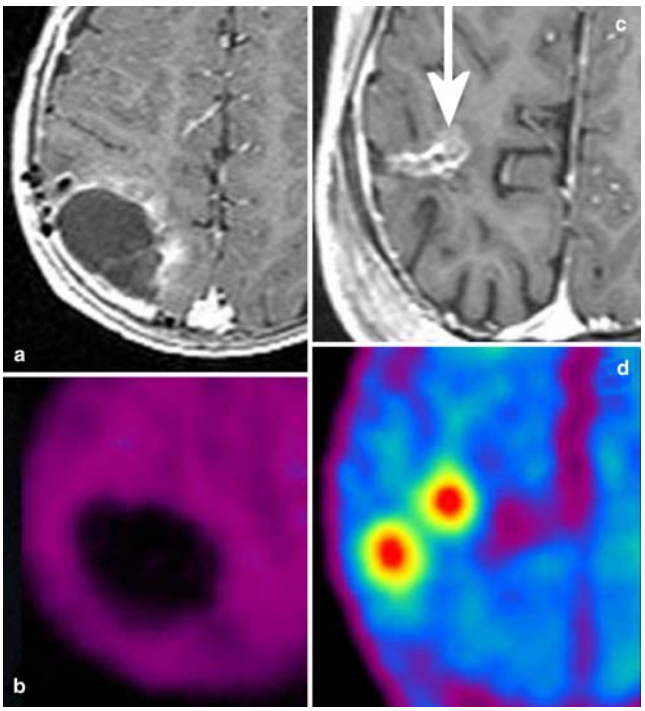

Fig. 8 Early postoperative study with MR and MET–PET showing the different signals observed on operative margins. The comparison between these signals and the histology of tissue samples taken on the operative margins at the end of surgery showed no residual tumor tissue in cases with no residual MET uptake (**b**), whatever the MR signals were (**a** and **c**). In cases with residual MET uptake (**d**), reoperation always found residual tumor tissue at the same place

information. PET guidance has actually found application in Leksell Gamma Knife® (LGK) radiosurgery, which we have started to use in PBT. The integration of stereotactic PET in LGK allowed us to treat 130 patients (including 10 children) with the combination of MR/CT and PET guidance. Abnormal PET uptake was found in 88% of the lesions; information provided by PET altered significantly the MR-based definition of the tumor in 73%. Our experience suggests that the integration of PET in radiosurgery provides additional functional information, opening new perspectives for the treatment of PBT [42, 43].

Discussion

Limitations of PET guidance and alternatives

PET imaging and PET guidance for surgical procedures may present some limitations: (1) The sensitivity and specificity of MET–PET to detect tumor tissue remain about 90% (10% of false negative and false positive results). (2) The level of MET uptake may show variability among different low-grade tumor types (pilocytic astrocytomas or oligodendrogliomas usually express a higher MET uptake than low-grade astrocytomas). (3) PET is a costly technology with limited accessibility in many countries or centers (no cyclotron/PET facility available).

More specific PET tracers are on study. Indeed, ^{18}fluoro-ethyl-tyrosine has recently been tested in the routine PET studies of brain tumors [12, 13]. This tracer offers equivalent sensitivity and specificity to detect tumor tissue as MET but has a much higher availability related to a longer half-life of the labeled ^{18}fluoride. New tracers linked to antibodies, neurotransmitters, or nanoparticles are under study, offering tremendous developments of molecular imaging in neuro-oncology.

Cheaper single-photon emission computed tomography (SPECT) technology might represent a more accessible alternative to PET, although sensitivity and specificity of SPECT tracers are not high. MR spectroscopy will soon represent a valid tool for high-resolution tumor delineation. In our center, we have started to evaluate and compare data from PET and MR spectroscopy for the purpose of tumor delineation in image-guided navigation. Diffusion/perfusion MR imaging or magnetoencephalography are other functional neuroimaging modalities that might be integrated in surgical image guidance [5, 16, 36, 44, 66, 71, 73]. Other techniques offering high sensitivity and specificity in tumor delineation have emerged. Fluorescence-guided tumor resection is a very promising tool that has not been explored in PBT yet [71, 73]. Further studies are required, however, to demonstrate whether these imaging improves the prognosis of children with brain tumors.

Developments and perspectives

The integration of PET in the clinical management of PBT inaugurates a new approach in neuro-oncology in which functional data take a part in the therapeutic decision process. As PET represents a functional neuroimaging, our experience suggests that other functional neuroimaging techniques might be integrated in the diagnostic workup and in frame-based or frameless image guidance. Investments in functional equipment will become a major financial challenge for neurosurgical centers in the following decades.

Conclusions

Our preliminary experience integrating PET imaging in the diagnostic workup of PBT showed that metabolic data influenced the surgical management at different steps in selected situations accounting for about 30% of all PBT admitted. The use of PET guidance in children also represents an opportunity for the evaluation of the role of functional neuroimaging in pediatric neuro-oncology and inaugurates a new approach in the management of PBT, in which functional data may influence the therapeutic decision process.

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