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PICTORIAL ESSAY

Hypoxia ^{18}F-FAZA PET/CT imaging in lung cancer and high-grade glioma: open issues in clinical application

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Abstract
Purpose Hypoxia can influence response to chemo and radiotherapy in different tumours, including non-small cell lung cancer (NSCLC) and high-grade gliomas (HGG). PET/CT can non-invasively investigate hypoxia and ^{18}F-FAZA seems to be the most promising radiotracer. However, there are still controversial issues related to image analysis and data interpretation hampering the effective possibility to translate the use of this imaging modality in clinical applications. The aim of the present pictorial review is to provide insights and answers on the open issues related to the potential clinical applicability of ^{18}F-FAZA PET/CT for hypoxia delineation.
Methods From Pubmed and Scopus databases, a literature research has been performed with the following research filters for both NSCLC and HGG: (1) time frame: last 10 years; (2) language: English; (3) species: human. Applied searching keywords were "hypoxia" or "hypoxic" and "PET" and "lung cancer" for NSCLS and "hypoxia", "PET" and "glioma" for HGG. Papers not strictly matching the imposed search filters have not been considered.
Results The literature search led to 76 papers for NSCLC, but for the purpose of the review only 10 have been considered, after double-checking and exclusion if not matching the imposed search filters. For HGG, the selected filters lead to 19 papers but only 8 have been considered for data analysis. Results on the use of ^{18}F-FAZA PET/CT in two different settings are reported in the present pictorial essay and methodological suggestions for clinical practice are presented through the description of addressed representative case reports.
Conclusions Based on literature evidence and presentation of relevant clinical case reports, issues related to ^{18}F-FAZA PET/CT in clinical settings have been addressed, providing possible solutions that may help the reliable use of this imaging method in clinical practice.

Keywords Tumour hypoxia · FAZA · FDG · PET · NSCLC · Glioma · Immunohistochemistry

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Introduction

Tumour hypoxia has been identified as a major independent prognostic factor influencing response to therapy and overall survival in many malignancies and contributing to reduced tumour response to both chemotherapy and radiotherapy [1–3]. Although the gold standard to measure tumour hypoxia is represented by direct oxygen measurement by means of Eppendorf electrodes, this method is invasive and technically demanding, thus it has only been applied in research settings, not being attractive in the clinical scenario [4].

Positron emission tomography/computed tomography (PET/CT) using several hypoxia-specific tracers have been proposed for tumour hypoxia imaging in vivo.

One of the most investigated radiotracer for hypoxia imaging is fluorine-18-labeled fluoromisonidazole (^{18}F-FMISO), although the clinical applications of this tracer are limited because of its unfavorable biokinetics [5].

The copper complex of diacetyl-bis(N4-methylthiosemicarbazone) (Cu-ATSM) labeled by positron emitting copper has also been proposed and it has been used for imaging tumour hypoxia, with better performance compared to ^{18}F-FMISO, including faster clearance from normoxic tissues (allowing a short time between injection and imaging), a simple method for quantification, and very good image quality [6].

Fluorine-18 labelled fluoroazomycin-arabinoside (^{18}F-FAZA) has been shown to be particularly promising for clinical purpose. The safety and feasibility of ^{18}F-FAZA PET/CT imaging has been already investigated in head and neck cancer patients showing that this modality is adequate for clinical detection of hypoxia both in primary tumour and in lymph node metastasis [7–9]. Further sporadic additional results on lung cancer and glioma have been also reported [3, 4, 10–13].

Although imaging hypoxia seems very promising using specific radiotracers, available published data are very heterogeneous in terms of methodology regarding image interpretation and data validation with histological analysis. For these reasons, nuclear medicine physicians, oncologists, radiotherapists and clinicians in general currently lack of practical methodology that could be applied for an efficient translation of hypoxia imaging in clinical practice. In fact, the possibility to accurately use a non-invasive method able to assess hypoxia in vivo, might certainly improve patients' management in terms of diagnosis, tailored treatment planning and evaluation of therapy response.

In the present pictorial review, we sought to address the main unsolved issues regarding the use of ^{18}F-FAZA PET/CT such as optimal scan acquisition time, methods for image quantification of hypoxic fraction and correlation with immunohistochemistry in the oncology field, focusing on NSCLC and HGG. The illustration of specific case reports will be used aiming to provide a practical interpretation of the main controversial issues regarding hypoxia imaging in clinical setting.

Materials and methods

A literature search from PubMed and Scopus databases have been performed with the purpose of identifying previous reports on the overall issues of hypoxia in NSCLC and high-grade glioma. Specifically, the reason for the literature search relies on the need to provide a literature background, briefly introducing the currently available studies on the presented topics and addressing the critical issues regarding the possible use of hypoxia imaging in the clinical settings of NSCLC and HGG, thus supporting the illustrated results.

The following research filters have been applied for both NSCLC and HGG: (1) time frame: last 10 years; (2) language: English; (3) species: human.

For NSCLC, searching keywords "hypoxia" or "hypoxic" and "PET" and "lung cancer" have been used. The literature lead to 76 manuscripts, which have been all double-checked and excluded if not matching the imposed search filters, thus coming to a selection of 37 original articles. Among these 37 papers on NSCLC, only 10 original articles have been considered for the purpose of this pictorial review.

For HGG, "hypoxia", "PET" and "glioma" for HGG have been used as searching keywords; among the 19 papers that came up, 8 original articles have been considered for the analysis.

Case histories on hypoxia and non-small cell lung cancer

The clinical use of PET/CT with ^{18}F-FAZA in lung cancer, by assessing hypoxia distribution within the tumour in a non-invasive way, might have an high impact on patients therapeutic workflow and prognosis. In fact, hypoxia detection with PET/CT might be considered as an important tool to select patients for hypoxia-directed therapies, to direct concomitant boost radiotherapy treatment and to monitor the changes in tumour hypoxia after therapy itself [14–16].

Currently, there in still no consensus regarding optimal scan acquisition time, image quantification of hypoxic fraction in terms of methodology to be applied and correlation with immunohistochemistry on ^{18}F-FAZA PET/CT in NSCLC.

Case 1: optimal scan acquisition time

A 65-year-old ex-smoker patient underwent a chest CT scan for recurrent fever during the last year. The CT scan showed an opacity in the right inferior–posterior lung and a nodule in the left upper lobe. The patient underwent to ^{18}F-FDG PET/CT to characterize the lung findings, showing radiotracer uptake in both right and left lung. Being the CT and ^{18}F-FDG PET/CT findings highly suspected for a malignant nodule in the left lung, a CT guided biopsy was then performed in correspondence of this finding confirming the presence of malignant tumoural cells. A ^{18}F-FAZA PET/CT scan was then performed as part of a clinical research protocol to investigate the hypoxic areas within the lung cancer.

In panels A, B and C the coronal PET images of FAZA scan at 60, 120 and 240 min, respectively, are reported, showing radiotracer uptake in correspondence of the pathological finding in the upper lobe of the left lung. Although at 60 min is possible to identify a faint uptake in correspondence of the pathological finding (blue arrow), image resolution and quality are clearly better at 120 and 240 min (red arrows). The acquisition at 120 and 240 min did not significantly differ in terms of image quality or presence of additional findings. The patient underwent both right inferior lobectomy and left upper lobectomy. Histological analysis showed the presence of inflammation in the right specimen, confirming a poorly differentiated adenocarcinoma in the left lung (G3; pT1 pN0; stage IA).

Regarding scan acquisition time, our results are in agreement with previous published data in which a single acquisition at 2-h have been usually performed [8, 17]; in fact, this timing of acquisition holds an image quality as good as the 4-h acquisition, with also a higher possibility of patients compliance who is not required to be scanned in the longer period (Fig. 1).

Case 2: image interpretation of ^{18}F-FAZA PET/CT images: methodology

A 76-year-old patient underwent X-ray for chest pain, showing an opacity in the right lung. A CT scan confirmed a right lung mass (9 cm) with concomitant ipsilateral hilar lymphadenopathy. A ^{18}F-FDG PET/CT was subsequently performed to characterize the lung finding; the lung mass visible on CT scan (A) showed intense ^{18}F-FDG uptake on PET/CT images (B) with high uptake in correspondence of the carinal, subcarinal and hilar ipsilateral lymph nodes as well.

A ^{18}F-FAZA PET/CT was performed as part of the procedure listed in the clinical study in which the patient had been enrolled, showing moderate radiotracer uptake at the level of the right pulmonary lesion (C).

Right pneumonectomy and hilo-mediastinal lymphadenectomy have been performed and histological examination confirmed the presence of a poorly differentiated adenocarcinoma (G3; pT3, pN1; stage IIIA).

Immunohistochemistry analysis was in agreement with imaging, showing moderate-high staining for hypoxia inducible factor 1 (HIF-1; 20%), carbonic anhydrase IX (CA-IX; 70%) and glucose transporter 1 (GLUT-1; 30%) as reported in panel D, E and F, respectively.

A tumour-to-blood ratio (T/B) greater than or equal to 1.2 was used as a criteria to define the presence of tumour hypoxia and the lung mass seen on PET images presented a T/B $>$ 1.2 (G), thus being defined as hypoxic.

The presence of hypoxia on ^{18}F-FAZA PET/CT images was calculated using both 1.2 and 1.4 as threshold to depicted possible significant differences.

In panel G, the lung tumour seen on ^{18}F-FAZA PET/CT image shows an hypoxic subvolume of 100.54 cc at 2-h using a T/B threshold $>$1.2; using a threshold $>$1.4, the hypoxic volume was 87.2. In this case, the hypoxic volumes assessed using T/M ratio with threshold $>$1.2 and $>$1.4 were 99.9 and 84.1, respectively, thus resulting comparable to the ones estimated using T/M ratio. Since the images related to the estimation of hypoxic fraction using T/M ratio would have been identical to the ones of T/B ratio, we decided not to show them to avoid repetitions.

T/M and T/B ratio resulted comparable and thus being mutually assessed and used to evaluate hypoxia in NSLCC patients undergoing ^{18}F-FAZA PET/CT.

The majority of published literature use either T/B or tumour to muscle (T/M) ratio with thresholds varying between 1.2 and 1.4 to define hypoxic fraction, regardless the adopted radiotracer or the types of tumour investigated [8, 17–20].

However, few available data and different heterogeneous approaches to evaluate hypoxic fraction have been performed. For instance, as alternative to blood, the T/M uptake ratio to be use in all those situations where no great vessels (e.g. aorta) or the heart itself are included in the field of view, to compare the hypoxic fraction estimated by T/B and T/M ratios.

According to the presented case report, on a practical point of view T/M uptake ratio can be used in all those scenarios where blood pool cannot be estimated because not included in the same field of view of the tumour (Fig. 2).

Case 3: hypoxia, glucose metabolism and immunohistochemistry

A 62-year-old patient underwent ^{18}F-FDG PET/CT as part of the routine follow-up for a previous breast cancer. The scan showed the growth of a left lung nodule with the concomitant appearance of radiotracer uptake, thus being suspicious for a malignant finding. A CT-guided biopsy was then performed confirming the presence of an adenocarcinoma compatible with lung origin. A ^{18}F-FAZA PET/CT was then performed. Panels A, B and C show the transaxial CT, ^{18}F-FDG and ^{18}F-FAZA scans, respectively, with high tumour uptake on ^{18}F-FDG PET/CT images and faint uptake on ^{18}F-FAZA PET/CT in correspondence of the left lung nodule. The low uptake of hypoxia radiotracer is likely due to the small diameter of the lesion. Moreover, lesions with 1.5–2 cm, which otherwise would have been inoperable, may not have all those mechanism such as leaking vasculature characterizing neo-angiogenetic process which may increase hypoxia. An upper lobectomy and

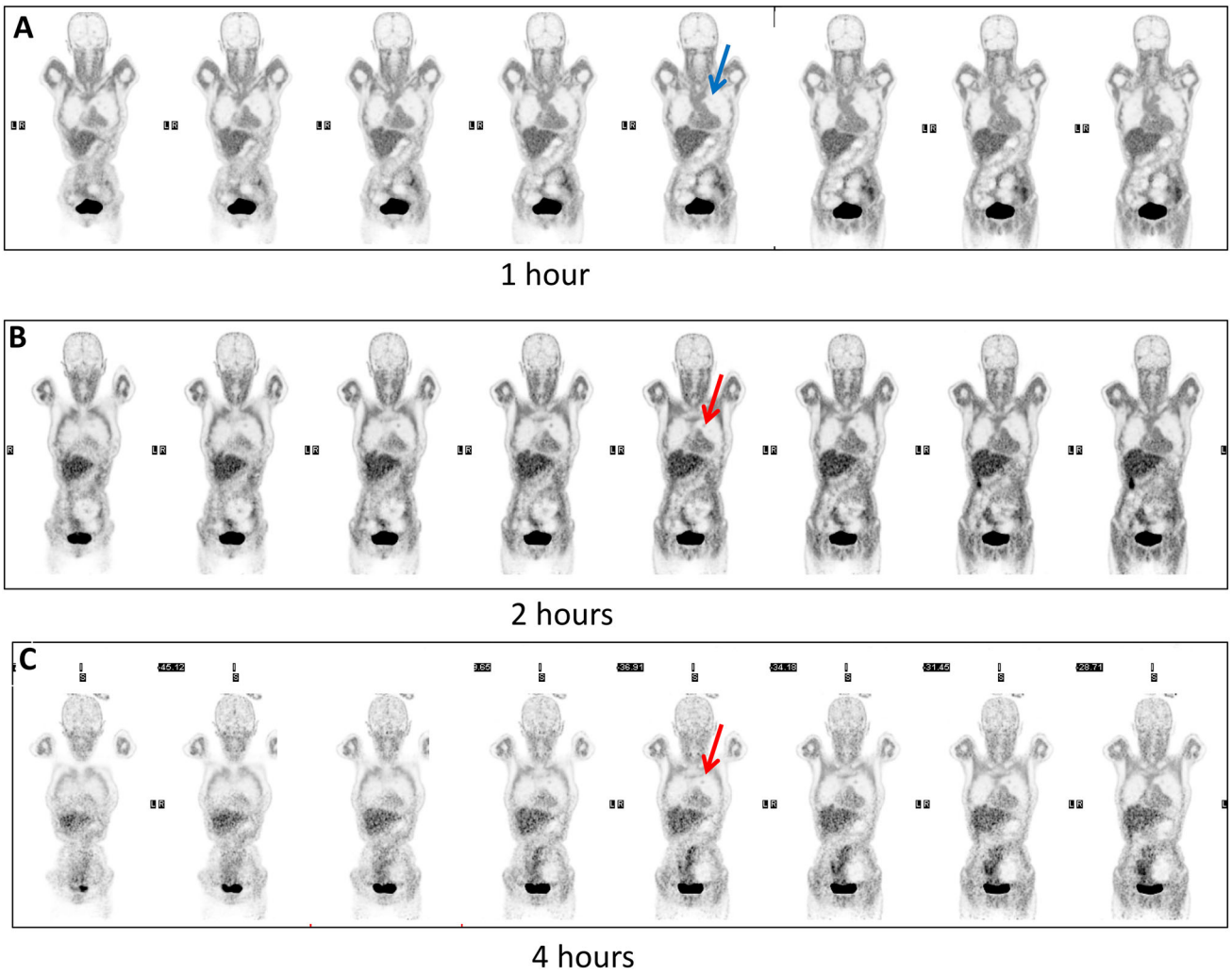

Fig. 1 Optimal scan acquisition time for ^{18}F-FAZA PET/CT in NSCLC

a hilo-mediastinal lymphadenectomy were then performed; the histological analysis confirmed the presence of adenocarcinoma (G2; pT1a, pN0; stage IA). Immunohistochemical analysis supported imaging results as represented in panels D, E, and F where staining for hypoxia biomarkers HIF-1, CA-IX and GLUT-1 is represented, respectively, showing absence of staining.

Hypoxia and glucose metabolism are distinct metabolic processes, although they seems to be tightly interlinked as suggested by the Warburg effect according to which cancer cells use anaerobic glycolysis to produce energy, instead of oxidative phosphorylation, with an increasing of glucose uptake [21]. HIF-1 represents one of the link between hypoxia and glucose metabolism. In fact, GLUT1 gene expression and glucose transport can be stimulated in a variety of cells under hypoxic conditions, a response that is mediated by the transcription factor HIF-1 itself [22].

A relationship between ^{18}F-FDG uptake and GLUT-1 expression has been demonstrated, suggesting that ^{18}F-FDG uptake could represent a biomarker of hypoxia, although other publications failed to show a clear relation between the two tracers [1, 23–25].

However, only sporadic data regarding correlation between hypoxia imaging and immunohistochemistry has been reported.

The reported case is representative for a clear correlation between ^{18}F-FDG, ^{18}F-FAZA PET/CT and immunohistochemistry (Fig. 3).

Case 4: ^{18}F-FAZA PET/CT in cerebral metastases of lung cancer

A 72-year-old patient underwent brain MRI for severe neurological symptoms, showing a brain mass in the right parietal lobe. Being the MRI findings suspicious for high-grade glioma, the patient underwent ^{18}F-FAZA PET/CT as part of a clinical protocol. The scan showed inhomogeneous uptake of the radiotracer with photopenic areas of

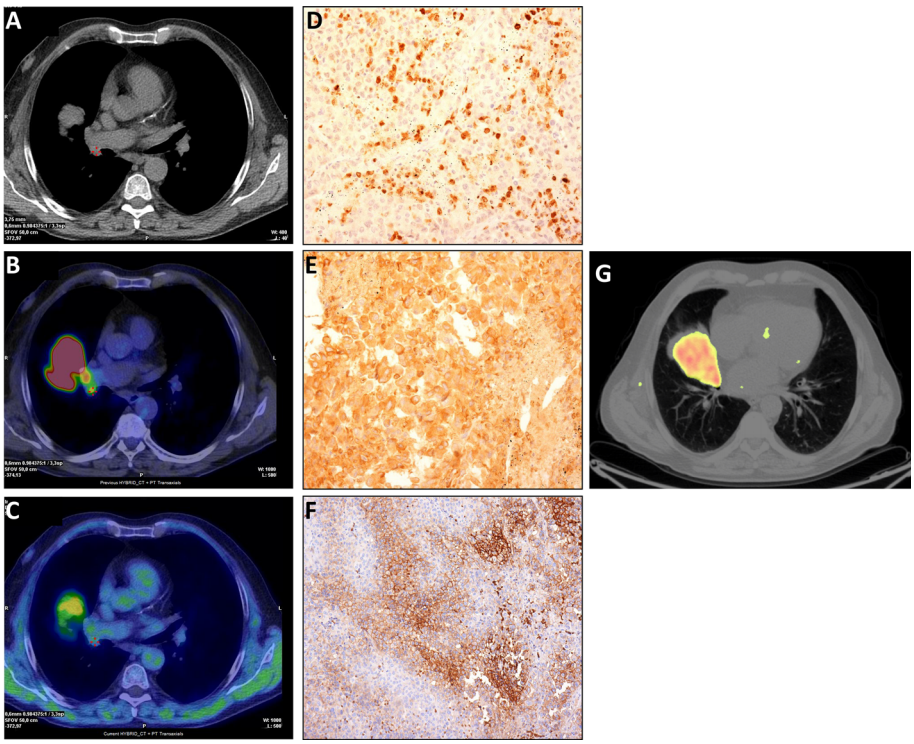

Fig. 2 Image analysis of hypoxic fraction on ^{18}F-FAZA PET/CT images

necrosis on ^{18}F-FAZA PET (A) and PET/CT (B) transaxial images, respectively.

The patient underwent surgical intervention and the histological examination revealed a metastatic lesion from a poorly differentiated carcinoma compatible with lung origin. After surgical removal of the lesion, the histological examination showed the presence of a metastatic lesion from a poorly differentiated carcinoma compatible with lung origin. A representative image of formalin-fixed paraffin-embedded tumour specimen haematoxylin and eosin stained (20×) is represented in panel C, with red arrow indicating a mitotic figure. Neoplastic cells were immunoreactive for anti-CK antibody (20×) as represented in panel D. The analysis of hypoxia biomarkers showed a positivity for GLUT-1 staining (30%; E) with no immunoreactivity for CA-IX (F) and HIF-1 (G).

To identify the primary tumour, a CT scan was performed showing a lung nodule in the superior lobe of the left lung, along with hilar ipsilateral adenopathy. To complete the staging, a ^{18}F-FDG PET/CT scan was performed. The maximum intensity projection of ^{18}F-FDG PET/CT scan (H) showed tracer uptake in correspondence of the left lung nodule (I), hilar ipsilateral and subcarinal adenopathy was also present (L).

There are few available data published on ^{18}F-FAZA and lung cancer and they are all mainly focused on the evaluation of primary tumour.

To the best of our knowledge, this is the first report visualizing the hypoxic status of cerebral metastases from lung cancer, previously identified by other imaging modalities, using ^{18}F-FAZA PET/CT (Fig. 4).

Case history on hypoxia and high-grade glioma

Intratumoural necrosis and vascular endothelial proliferation are histological features of high-grade gliomas (III–IV) that are known to distinguish low-grade from high-grade gliomas and it has been demonstrated that the extent of necrosis correlates inversely with patient outcome and survival [26, 27]. High-grade gliomas are highly vascularized human tumours, but their microcirculation is functionally very inefficient compared with that of normal brain [28, 29]. Hypoxia imaging-guided biopsy could properly represent the vascular heterogeneity within the tumour, disclosing areas with highest grade within the tumour heterogeneity. Furthermore, it could be of great value for treatment planning and predicting patient outcome.

Case 5: ^{18}F-FAZAPET/CT in guiding tumour biopsy in high-grade glioma

A 77-year-old patient was admitted for progressive left leg hypertonia together with difficulty to walk and move the left hand. Brain MRI was then performed showing an enhancing, edematous lesion in the right basal ganglia and corona radiata with mass effect on the right ventricle on T1-weighted images, suggestive for high-grade glioma. In

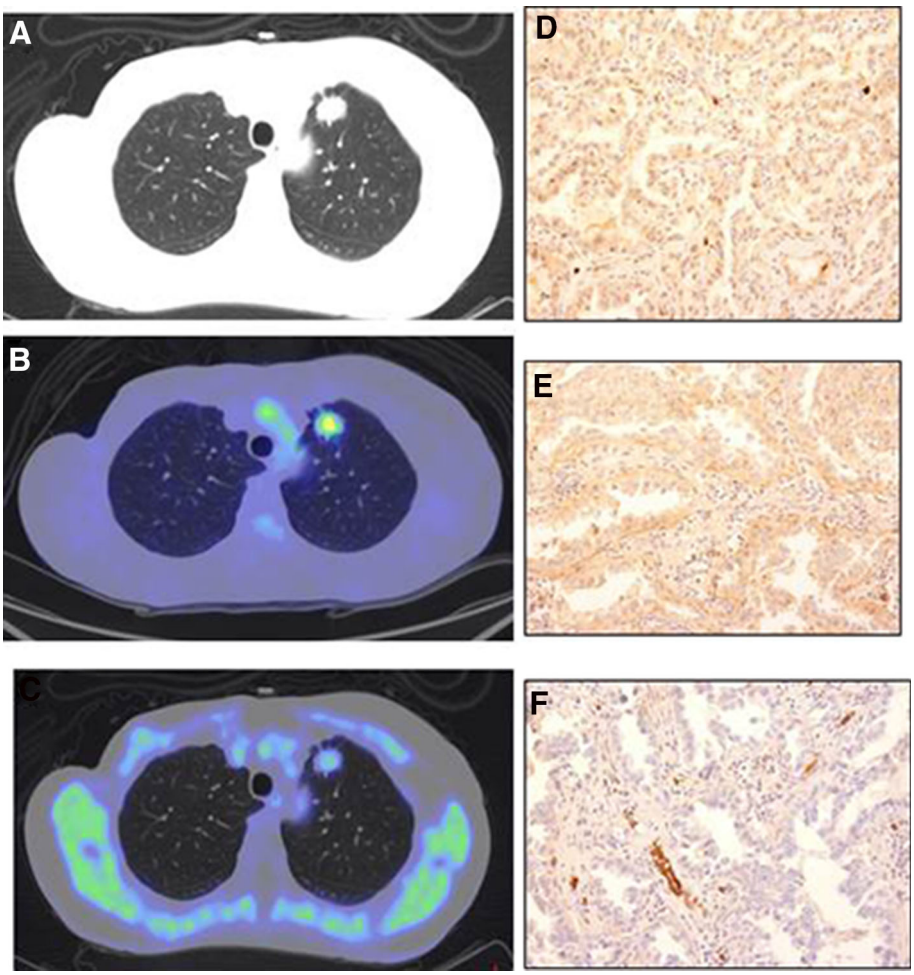

Fig. 3 Comparison between hypoxia, glucose metabolism and immunohistochemistry

particular, dynamic susceptibility contrast (DSC) and dynamic contrast enhanced (DCE) perfusion were acquired. In panel A, the gadolinium-enhanced T1 images shows an enhancing, edematous lesion in the right basal ganglia and corona radiata with mass effect on the right ventricle. The lesion also showed high values of relative Cerebral Blood Volume (rCBV; yellow arrow), transfer constant (Ktrans; C: red arrow) and fractional plasma volume (*Vp*; D: white arrow), suggesting the diagnosis of high-grade glioma.

^{18}F-FAZA PET/CT was performed to assess tumour hypoxia, thus identifying those regions more likely to be resistant to chemo and/or radiotherapy. ^{18}F-FAZA PET images showed uptake in correspondence of the brain lesion with a central photopenic area possibly due to necrotic tissue (E). MRI and ^{18}F-FAZA PET/TC images were then co-registered and an area of both high perfusion MRI markers and high ^{18}F-FAZA uptake was selected for biopsy after appropriate image fusion (F) to select the most representative tumour region to be sampled. The histological analysis confirmed the presence of a grade IV glioblastoma.

Although several studies on ^{18}F-FAZA PET/CT and glioma have been reported, to the best of our knowledge, no clinical cases have been previously reported regarding the role of ^{18}F-FAZA PET/CT in guiding stereotactic biopsy in high-grade glioma patients (Fig. 5).

Discussion

Hypoxia imaging in lung cancer and high-grade glioma with ^{18}F-FAZA PET/CT, supported by histological confirmation, might have strong impact on patients' therapeutic workflow in terms of diagnostic and prognostic purpose and for response assessment. Although this is particularly relevant for cancer imaging, it has to be noted that hypoxia is a biological phenomenon that could be present in several clinical conditions beyond oncology, underlying even more the need for practical suggestions on image interpretation and data analysis that could be used by clinicians in different fields [30].

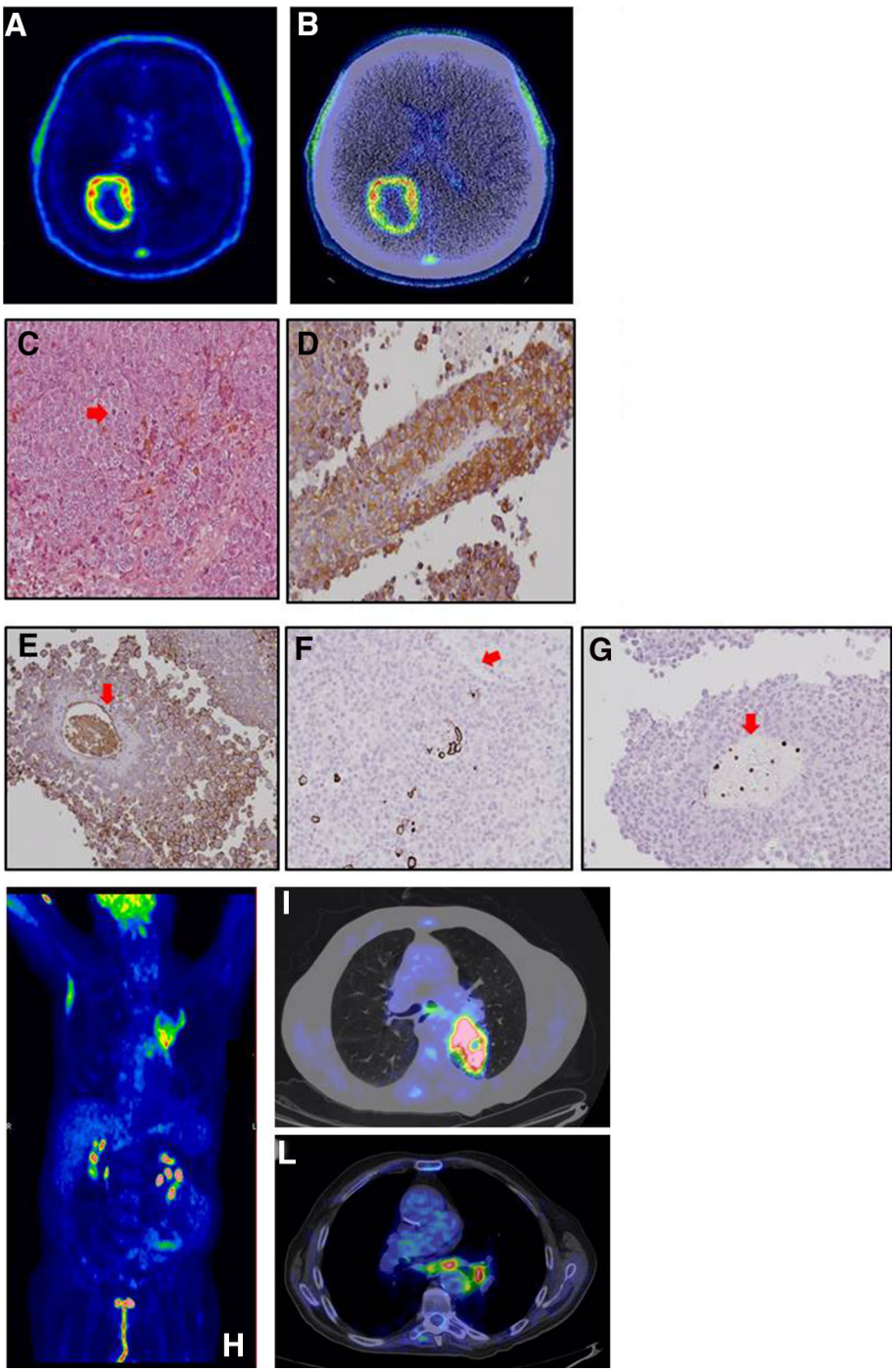

Fig. 4 Cerebral metastases of NSCLC identified on ^{18}F-FAZA PET/CT

The heterogeneous information regarding hypoxia imaging in terms of image interpretation, that are currently available, hamper the effective possibility to translate the use of this imaging modality in clinical use.

The present pictorial essay addressed the main issue related to ^{18}F-FAZA in the settings of NSCLC and high-grade glioma, providing possible solutions that might help the reliable use of this method in clinical practice.

Conclusion

Summing up the above reported clinical cases, and considering the available published data we can suggest that:

1. A scan acquisition time 2-h post injection of ^{18}F-FAZA represents a good compromise in terms of image quality and information provided.

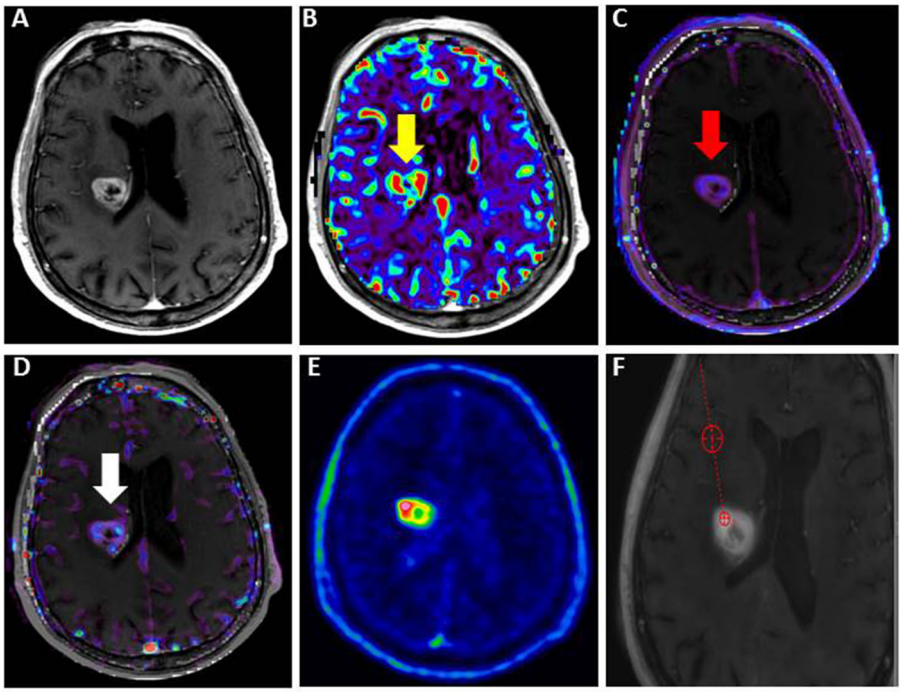

Fig. 5 Tumour biopsy in high-grade glioma guided by ^{18}F-FAZA PET/CT

2. The quantification of hypoxic fraction within the tumour can be assessed both with T/B or T/M with the same accuracy.
3. Immunohistochemistry analysis supports and confirm the image findings obtained with ^{18}F-FAZA PET/CT.
4. ^{18}F-FAZA PET/CT can reliably guide sophisticated procedures such as stereotactic biopsy providing specific information on the most representative tumour areas to be sampled.

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Author contribution PM: project development, data collection and management, data analysis, writing, editing, content planning. EI: data collection and management, editing. VB: data collection and management, data analysis, editing. GMC: neuroradiology-data collection and management, data analysis. FF: data collection and management, data analysis. MB: neurosurgery, data collection. MV: data management, editing. MC: pathologist, data analysis. LG: data management, editing. MP: project development, data collection and management, data analysis, writing, editing, content planning.

Compliance with ethical standards

Conflict of interest Mapelli P, Incerti E,Bettinardi V, Conte GM, Fallanca F, Bailo M, Vuozzo M, Callea M, Gianolli L, Picchio M declare that they have no conflict of interest.

Ethical approval The studies described in the present paper (EudraCT:2011-002647-98 and EudraCT:2015-000679-28) have been approved by the appropriate institutional and national research ethics committee. All performed procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Protocol related informed consent was obtained from all individual participants included in the reported cases.

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