^{18}F-FAZA PET/CT Hypoxia Imaging of High-Grade Glioma Before and After Radiotherapy

Paola Mapelli, MD, Flavia Zerbetto, MD,† Elena Incerti, MSc,* Gian Marco Conte, MD,‡ Valentino Bettinardi, MSc,* Federico Fallanca, MD,* Nicoletta Anzalone, MD,‡ Nadia Di Muzio, MD,† Luigi Gianolli, MD,* and Maria Picchio, MD**

Abstract: A 57 year-old man underwent MRI with dynamic susceptibility contrast and dynamic contrast-enhanced perfusion for neurological symptoms suggesting the diagnosis of high-grade glioma. A ^{18}F-FAZA PET/CT was performed because of the enrollment in a prospective clinical trial. Subsequent radiotherapy treatment has been planned based on conventional imaging; moreover, a ^{18}F-FAZA PET/CT–guided treatment planning highlighting hypoxic regions has been simulated. After radiotherapy treatment, the man underwent MRI and ^{18}F-FAZA PET/CT, showing partial response.

Key Words: ^{18}F-FAZA, dynamic contrast-enhanced, dynamic susceptibility contrast, glioma, hypoxia, PET/CT, MRI, radiotherapy, stereotactic biopsy

(*Clin Nucl Med* 2017;00: 00–00)

Received for publication July 3, 2017; revision accepted August 21, 2017.

From the *Nuclear Medicine Department, IRCCS San Raffaele Scientific Institute; †Radiotherapy Department, San Raffaele Scientific Institute; and ‡Neuroradiology Unit and CERMAC, San Raffaele Scientific Institute and Vita-Salute San Raffaele, Milan, Italy.

Conflicts of interest and sources of funding: The present work was supported by the Italian Association for Cancer Research (grant IG 2014 Id.1524; EudraCT:2015-000679-28). None declared to all authors.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from the participant included in the study.

Correspondence to: Maria Picchio, MD Nuclear Medicine Department, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy. E-mail: picchio.maria@hsr.it.

ISSN: 0363-9762/17/0000–0000
DOI: 10.1097/RLU.0000000000001850

REFERENCES

1. Knisely JP, Rockwell S. Importance of hypoxia in the biology and treatment of brain tumors. *Neuroimaging Clin N Am*. 2002;12:525–536.
2. Teicher BA. Angiogenesis and cancer metastases: therapeutic approaches. *Crit Rev Oncol Hematol*. 1995;20:9–39.
3. Mapelli P, Incerti E, Fallanca F, et al. Concomitant lung cancer and gastrointestinal stromal tumor: first report of hypoxia imaging with ^{18}F-FAZA PET/CT. *Clin Nucl Med*. 2017;42:e349–e351.
4. Vajkoczy P, Menger MD. Vascular microenvironment in gliomas. *Cancer Treat Res*. 2004;117:249–262.
5. Vartanian A, Singh SK, Agnihotri S, et al. GBM's multifaceted landscape: highlighting regional and microenvironmental heterogeneity. *Neuro Oncol*. 2014;16:1167–1175.
6. Mapelli P, Incerti E, Bettinardi V, et al. Hypoxia ^{18}F-FAZA PET/CT imaging in lung cancer and high-grade glioma: open issues in clinical application. *Clin Transl Imaging*. 2017;5:389–397.
7. Lehtiö K, Eskola O, Viljanen T, et al. Imaging perfusion and hypoxia with PET to predict radiotherapy response in head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2004;59:971–982.
8. Souvatzoglou M, Grosu AL, Roper B, et al. Tumour hypoxia imaging with [^{18}F]FAZA PET in head and neck cancer patients: a pilot study. *Eur J Nucl Med Mol Imaging*. 2007;34:1566–1575.
9. Kinoshita T, Fujii H, Hayashi Y, et al. Prognostic significance of hypoxic PET using (18)F-FAZA and (62)Cu-ATSM in non–small-cell lung cancer. *Lung Cancer*. 2016;91:56–66.
10. Susheela SP, Revannasiddaiah S. Radiotherapy to volumes defined by metabolic imaging in gliomas: time to abandon monstrous margins? *Ann Transl Med*. 2016;4:55.

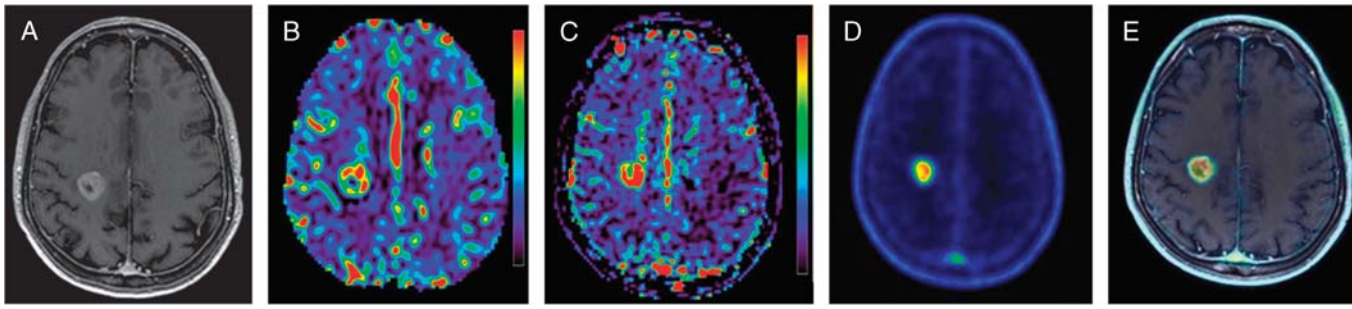

FIGURE 1. A 57-year-old man underwent brain MRI with dynamic susceptibility contrast and dynamic contrast-enhanced perfusion to confirm the diagnosis of a high-grade glioma. Gadolinium-enhanced T1 images (**A**) showed an irregular ring enhancing lesion in the right frontal lobe with high values of relative cerebral blood volume (rCBV; **B**) and fractional plasma volume (Vp; **C**), suggestive of high-grade glioma. The man signed an informed consent form for brain ^{18}F-FAZA PET/CT, which has been performed to identify tumor hypoxic regions, potentially more resistant to treatment. ^{18}F-FAZA PET (**D**) showed tracer uptake in the brain lesion, with a central photopenic area, possibly due to necrotic tissue. PET and MRI images have been coregistered (**E**) to delineate the most representative region to be sampled during stereotactic biopsy. Histological analysis confirmed a glioblastoma (World Health Organization grade IV) with *IDH1* mutation.

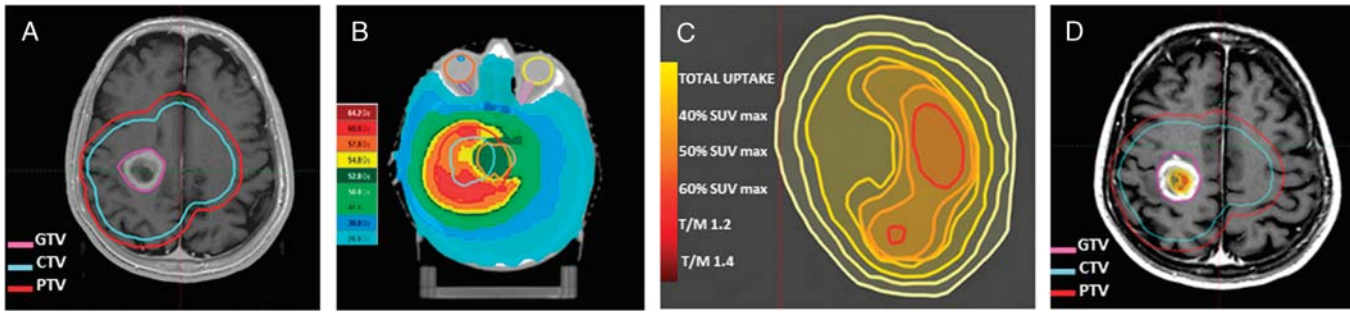

FIGURE 2. Radiotherapy target delineation was performed using contrast-enhanced T1+T2/FLAIR MRI sequences fused with CT planning (**A**). Gross tumor volume (GTV) was delineated on T1-weighted images; clinical target volume (CTV) was generated adding 20 mm to GTV, and planning target volume (PTV) was obtained adding an isotropic margin (5 mm) to CTV. Planning MRI was then matched with ^{18}F-FAZA PET/CT. Tomotherapy (60 Gy in 2Gy/fraction to PTV) was delivered in association with temozolomide (November 2016 to January 2017) (**B**). To investigate the feasibility of performing a radiation boost on hypoxic regions, 7 different biological volumes of interest (VOIs) have been delineated (**C**). The first VOI was manually drawn by an experienced nuclear medicine physician on the whole uptake area (biological target volume: BTV-1); 3 additional volumes have been automatically generated as 40%, 50% and 60% of SUVmax of BTV-1. Three additional BTVs have been generated as representative hypoxic regions based on tissue-to-muscle ratio. A VOI was drawn on neck muscle and tracer uptake was divided by mean values obtained from this VOI. Finally, 3 different thresholds (1.2, 1.3 and 1.4) have been applied to the resulting activity distribution. Simulated VOIs have been subsequently integrated to standard planning to compare different and/or complementary information provided by ^{18}F-FAZA PET/CT (**D**).

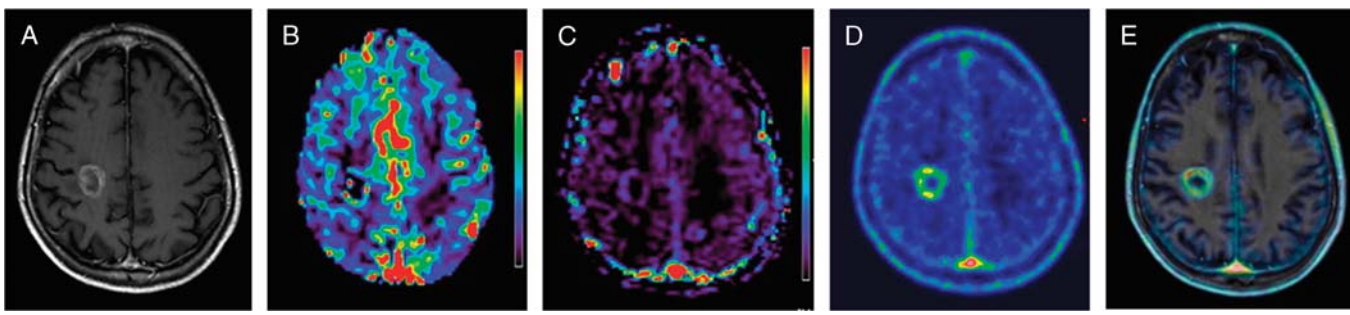

FIGURE 3. MRI and ^{18}F-FAZA PET/CT were performed after the end of treatment. MRI showed an increase of the necrotic area (**A**) with stability of rCBV (**B**) and Vp (**C**). Accordingly, ^{18}F-FAZA PET/CT showed a central photopenic area surrounded by radiotracer uptake (**D**). Both examinations and fused PET/MRI images (**E**) concordantly showed a partial response to treatment. Hypoxia reduces the sensitivity to ionizing radiation and interferes with many chemotherapy regimens, by hampering sufficient drug delivery.[1–3] High-grade gliomas are highly vascularized, although having a functional inefficient microcirculation compared with normal brain.[4,5] Hypoxia assessment with a non-invasive imaging modality such as ^{18}F-FAZA PET/CT may be able to identify tumor areas with the highest grade, thus accurately guiding stereotactic biopsy.[6] The biological information provided by ^{18}F-FAZA PET/CT could be used for dose painting with dose escalation on the most hypoxic tumor regions.[7–10]