Physics and Imaging in Radiation Oncology 6 (2018) 94–100

Contents lists available at ScienceDirect

Physics and Imaging in Radiation Oncology

journal homepage: www.elsevier.com/locate/phro

Original Research Article

Dosimetric impact of amino acid positron emission tomography imaging for target delineation in radiation treatment planning for high-grade gliomas

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ARTICLE INFO

Keywords:
^{18}F-DOPA PET
PET-guided radiation therapy
Planning study
Amino acid PET

ABSTRACT

Background and purpose: The amino-acid positron emission tomography (PET) tracer 3,4-dihydroxy-6-[^{18}F] fluoro-L-phenylalanine (^{18}F-DOPA) has increased sensitivity for detecting regions of biologically aggressive tumors compared to T1 contrast-enhanced (T1-CE) magnetic resonance imaging (MRI). We performed dosimetric evaluation of treatment plans prepared with and without inclusion of ^{18}F-DOPA-based biological target volume (BTV) evaluating its role in guiding radiotherapy of grade III/IV gliomas.

Materials and methods: Eight patients (five T1-CE, three non-contrast-enhancing [NCE]) were included in our study. MRI only-guided anatomic plans and MRI + ^{18}FDOPA-PET-guided biologic plans were prepared for each patient, and dosimetric data for target volumes and organs at risk (OAR) were compared. High-dose BTV_{60Gy} was defined as regions with tumor to normal brain (T/N) > 2.0, while low-dose BTV_{51Gy} was initially based on T/N > 1.3, but refined per Nuclear Medicine expert.

Results: For T1-CE tumors, planning target volumes (PTV) were larger than MRI-only anatomic target volumes. Despite increases in size of both gross target volumes and PTV, with volumetric-modulated arc therapy planning, no increase of dose to OAR was observed while maintaining similar target dose coverage. For NCE tumors, MRI + ^{18}F-DOPA PET biologic imaging identified a sub-region of the large, T2-FLAIR abnormal signal which may allow a smaller volume to receive the high dose (60 Gy) radiation.

Conclusions: For T1-CE tumors, PTVs were larger than MRI-only anatomic target volumes with no increase of dose to OARs. Therefore, MRI + ^{18}F-DOPA PET-based biologic treatment planning appears feasible in patients with high-grade gliomas.

1. Introduction

Evidence has emerged for a role of metabolic or biologic imaging in gliomas [1–4]. The amino-acid positron emission tomography (PET) tracer 3,4-dihydroxy-6-[^{18}F] fluoro-l-phenylalanine (^{18}F-DOPA) was found to have considerably increased sensitivity for detecting regions of biologically aggressive tumors compared to T1 contrast-enhanced (T1-CE) magnetic resonance imaging (MRI). In addition, T1-CE substantially underestimated the volume of the highly aggressive disease components [4]. Utilizing a derived threshold (uptake ratio of tumor to contralateral normal brain > 2.0), high uptake regions were identified outside of T1-CE in 8 of the 21 patients in our previous pilot study, including 3 non-contrast-enhanced (NCE) patients [4].

Ledezma et al. [5] also demonstrated that ^{18}F-DOPA uptake was increased in tumors that were NCE on MRI. Lee et al. [3] evaluated the site of glioblastoma failure in relation to pre-treatment ^{11}C-labeled methionine (^{11}C-MET) PET uptake, which was not used for radiotherapy (RT) targeting. Inadequate coverage of the high-risk region defined by ^{11}C-MET PET uptake was associated with an increased risk of regional recurrence, indicating that knowledge about high-risk regions outside the T1-CE region may be important in treatment planning.

These and other recent studies suggest that accurate delineation of brain tumors was improved by incorporating biologic imaging [6–8]. This is consistent with our previous work in which ^{18}F-DOPA uptake regions which showed aggressive, high-grade disease components extending as distant as 3.5 cm beyond the T1-CE region [4]. Because aggressive disease was reported beyond regions of T1-CE, it was expected that target volumes would be larger if biologic-based imaging was incorporated into treatment

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https://doi.org/10.1016/j.phro.2018.06.004
Received 2 November 2016; Received in revised form 4 June 2018; Accepted 6 June 2018

planning. Increased volume of uninvolved brain receiving RT has been associated with an increased risk of acute and late toxicity including fatigue, endocrine, and neurocognitive effects [9], therefore in preparation for a prospective phase II trial evaluating the role of ^{18}F-DOPA PET in guiding RT treatment in patients with high-grade gliomas, we sought to evaluate the effect of ^{18}F-DOPA PET biologic information on RT treatment planning. This study also describes a methodology for robust dosimetric evaluation of treatment plans with and without the inclusion of ^{18}F-DOPA PET biologic information.

2. Materials and methods

2.1. Patients and basic characteristics

This was a retrospective treatment planning study comparing treatment planning objectives in eight patients with high-grade glioma histology with and without the incorporation of ^{18}F-DOPA PET imaging. Because ^{18}F-DOPA is not FDA approved for clinical use, the patients had all previously enrolled in an ^{18}F-DOPA surgical planning pilot study at our institution. A total of 21 patients were enrolled on the pilot study [4], but only eight high-grade histology patients were for included in this study. Five patients had T1-CE, and three with grade III tumors did not (NCE). The pilot study was open to both newly diagnosed and recurrent patients with gliomas who were able to undergo both MRI with contrast and ^{18}F-DOPA PET scans. Basic patient characteristics have been summarized in Supplementary Table 1.

2.2. MRI and ^{18}F-DOPA PET/CT acquisition

All patients underwent intra- or pre-operative brain MRI and ^{18}F-DOPA PET/computed tomography (CT) (GE Healthcare Discovery 690, Waukesha, WI, USA) imaging. The pilot study and retrospective analysis of these results were both approved by the Institutional Review Board. Technical parameters of PET and MRI acquisition have been previously published [4]. The ^{18}F-DOPA PET biologic data corresponded to the pre-operative imaging, thus the helical CT image (pixel size 0.59 mm, slice thickness 2.0 mm), which was performed for attenuation correction of the PET data, served as our RT treatment planning CT. Acquired images were transferred to MIM Maestro (MIM Software, Inc., Cleveland, OH, USA) for PET uptake analysis for BTV volumes and MRI GTV volume delineation, and to the Eclipse Treatment Planning System (Varian Medical Systems Inc., Palo Alto, CA, USA) for subsequent GTV and PTV delineation and RT planning.

2.3. Target volumes and organ-at-risk definition

^{18}F-DOPA PET uptake was used for biological target volume (BTV) delineation. High-dose BTV_{60Gy} was defined as regions with T/N > 2.0, based on previously reported results of our pilot study with spatial-related histopathological correlations [4]. Low-dose BTV_{51Gy} was first contoured based on T/N > 1.3, but was modified in the clinical judgment of an experienced nuclear medicine physician.

T1-CE determined GTV_{60Gy}_MR. GTV_{51Gy}_MR was determined by T2-weighted-Fluid-Attenuated Inversion Recovery (T2-FLAIR) volume, with the exception of NCE tumors, in which GTV_{60}_MR was the entire T2-FLAIR. The MRI criteria used to define target volumes was based on the historical standard of care at our institution and the North Central Cancer Treatment Group [10]. Definitions of all gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV), and associated prescribed doses are summarized in Table 1.

We analyzed the discordant region between boost volume PTVs created utilizing MRI only, and MRI + ^{18}F-DOPA PET [11]. The brainstem, optic nerves, and chiasm were defined as high priority organs at risk (OAR), while the eyes, retinas, and both hippocampi were defined as low priority OAR [12]. Hippocampi were delineated based on the Radiation Therapy Oncology Group online contouring atlas.

2.4. Radiation treatment planning and dosimetric evaluation

Three patients with grade III tumors had NCE gliomas. For these patients, inclusion of PET biologic imaging and limiting the 60 Gy volume to the areas of highly aggressive disease components as determined by ^{18}F-DOPA PET, led to a substantial reduction of volume intended for boost doses of 60 Gy (Fig. 1). As shown in Fig. 2, for patients with T1-CE, including the ^{18}F-DOPA PET can lead to an increase in the 60 Gy volumes.

For all patients, two experimental treatment plans were created: one based solely on MRI only information and another which included both MRI and ^{18}FDOPA-PET biological target volume (BTV). Volumetric-modulated arc therapy (VMAT) planning was performed in all cases for the TrueBeam system (Varian Medical Systems Inc.). Dose prescription was specified as 51 Gy (1.7 Gy per fraction) to the PTV_{51Gy} and 60 Gy (2.0 Gy per fraction) in 30 fractions to the PTV_{60Gy} with a simultaneous integrated boost technique. For all plans, 95% of PTV_{60Gy} volume received 100% of the prescribed dose. All plans were also limited to < 0.5 cc received < 110% of the prescribed dose (66 Gy).

Two full 360° coplanar arcs and one sagittal non-coplanar half arc were arranged for all patients. Because of shape, size, and location of target volume, an additional sagittal half arc was added in one patient to meet all PTV dose coverage constraints. The same arrangement was used for both MRI only and MRI + PET biologic plans in this particular patient. Supplementary Table 2 shows the OAR dose constraints which were used to evaluate the plan quality for each patient, with and without the incorporation of ^{18}F-DOPA. Corresponding parameters from MRI only and MRI + PET biologic plans were compared for each patient.

Basic statistics were used to calculate percentages and averages. Treatment plans for each patient were compared separately. Because the T1-CE region is always included in high-dose target volume in treatment planning, we did not compare T1-CE to the high ^{18}F-DOPA uptake region (represented by T/N ratio > 2.0), but instead compared T1-CE to the union of T1-CE and the high ^{18}F-DOPA uptake region, which enabled direct incorporation into the evolution of corresponding CTVs and PTVs for creation of treatment plans. Because it is standard practice to include a margin for clinical and planning target volumes, we also evaluated the differences after volume expansions.

3. Results

3.1. Target volume comparisons

For all T1-CE patients, all volumetric changes in target volumes were less marked when expressed as PTV compared to GTV. BTV_{60Gy} volume ranged from being less than to 4.4 times larger compared to GTV_{60Gy}, whereas PTV_{60Gy} including MRI + PET ranged from being the same to 1.8 times larger compared to PTV_{60Gy} using MRI only (represented in Fig. 2, patient FDOPA 03). Between 6% and 36% of the BTV_{60Gy} and GTV_{60Gy}_MR volumes were overlapping, where FDOPA uptake was present (patient FDOPA01 did not have FDOPA uptake). Corresponding values for NCE patients were as follows: BTV_{60Gy} ranged from 48 to 202 times smaller than the GTV_{60Gy}_MR (comprised of the FLAIR MRI volume), while the resulting PTV_{60Gy} ranged from 3.2 to 72 times smaller (represented in Fig. 1 for patient FDOPA 05). Statistically speaking, all of the BTV_{60Gy} volume was contained within the GTV_{60Gy}_MR FLAIR signal abnormality. In the NCE subgroup of patients, no 51 Gy volumes were defined for MRI anatomic plans.