Contribution of FDOPA PET to radiotherapy planning for advanced glioma

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Abstract. Despite radical treatment with surgery, radiotherapy and chemotherapy, advanced gliomas recur within months. Geographic misses in radiotherapy planning may play a role in this seemingly ineluctable recurrence. Planning is typically performed on post-contrast MRIs, which are known to underreport tumour volume relative to FDOPA PET scans. FDOPA PET fused with contrast enhanced MRI has demonstrated greater sensitivity and specificity than MRI alone. One sign of potential misses would be differences between gross target volumes (GTVs) defined using MRI alone and when fused with PET. This work examined whether such a discrepancy may occur. **Materials and Methods**: For six patients, a 75 minute PET scan using 3,4-dihydroxy-6-18F-fluoro-L-phynel-alanine (18F-FDOPA) was taken within 2 days of gadolinium enhanced MRI scans. In addition to standard radiotherapy planning by an experienced radiotherapy oncologist, a second gross target volume (GTV) was defined by an experienced nuclear medicine specialist for fused PET and MRI, while blinded to the radiotherapy plans. The volumes from standard radiotherapy planning were compared to the PET defined GTV. **Results**: The comparison indicated radiotherapy planning would change in several cases if FDOPA PET data was available. PET-defined contours were external to 95% prescribed dose for several patients. However, due to the radiotherapy margins, the discrepancies were relatively small in size and all received a dose of 50 Gray or more. **Conclusions**: Given the limited size of the discrepancies it is uncertain that geographic misses played a major role in patient outcome. Even so, the existence of discrepancies indicates that FDOPA PET could assist in better defining margins when planning radiotherapy for advanced glioma, which could be important for highly conformal radiotherapy plans.

1. Introduction

Despite radical treatment with surgery, radiotherapy and chemotherapy, advanced gliomas recur within months (2). Radiotherapy planning is performed on post-surgical contrast enhanced MRI (1) or CT. The contrast agent used in MRI is a marker for blood brain barrier breakdown. Active regions of tumours are enhanced because tumours damage or destroy the blood brain barrier. However, tissue disruption and reactive inflammation are not sufficient to damage the local blood vessels in all regions of active tumour. One example of this is on the "advancing fronts" at the tumour periphery where tumour cells, infiltrating along white matter tracts, are not yet of sufficient bulk to disrupt the blood brain barrier. For this reason MRI is well known to under-report tumour volumes (3)(4). Even so, the

use of PET for routine radiotherapy planning has only been explored relatively recently (5), and then mainly using FluoroDeoxyglucose (6). The planning of radiotherapy on a modality known to under-report tumour volumes raises the question of whether recurrence occurs because regions of active tumour cells may be missed in the planning of radiotherapy and hence do not receive the radiation dose necessary to kill them.

The aim of this study is to address whether radiotherapy planning would change given the availability of PET images. Such discrepancies could be indicative of potential geographic misses due to the lack of metabolic information, although this would need to be verified histologically. PET imaging was performed with 3,4-dihydroxy-6-18F-fluoro-L-phynel-alanine (18F-DOPA) PET four weeks after a post-surgery course of chemoradiotherapy. FDOPA rather than FDG was chosen because superior tumour-to-background ratios are obtained by FDOPA in the brain (3). FDOPA is avidly taken up by active tumour tissue along the amino acid transporters (3) and correlates well with the Ki-67 index (7). FDOPA has proven to be sensitive for detecting tumour (8).

2. Materials and methods

The six patients (5 males, age range 52 to 71 years) used in this study had a single primary brain tumour without metastases. The study was approved by the Ethics Committee for Royal Brisbane and Women's Hospital and all patients gave written informed consent to participate in the imaging study. In all patients the tumours were newly diagnosed. MRI analysis was used to diagnose glioblastoma-multiforme, which was confirmed by subsequent histopathological analysis.

Radiotherapy planning was performed using a MRI scan taken 24-48 hours after surgery, by an experienced radiation oncologist (Michael Fay). Gross, clinical and planned target volumes (respectively GTV, CTV, & PTV) were generated as was a dose plan. The PTV was generated by adding 5mm to the CTV but radiosensitive tissue was spared. The CTV was based on visible oedema combined with a 5mm margin where safe. Following a six-week course of chemoradiotherapy (external beam radiotherapy was given at 60Gy/30 fractions or 40Gy/15 fractions, with concurrent temozolomide) and a four week recovery period, patients received follow-up PET and MRI scans, taken within two days of each-other. MRI data was acquired on a 3T Siemens Trio employing a Magnetization-Prepared Rapid Acquisition Gradient-echo (MPRAGE) sequence with the following parameters (FOV 24x25.6x17.6 cm, TR/TE/TI 2300/2.26/900 ms, flip angle of 90, 1 mm isotropic resolution). Images were acquired before and after administration of contrast agent Gadovist, (Bayer HealthCare Pharmaceuticals).

18F-FDOPA was synthesised according to a previously reported procedure (9). PET imaging was performed using a Philips Gemini GXL scanner. A transmission CT scan was acquired first. Subsequently, an FDOPA bolus with a mean activity of 151MBq (range 138 to 164MBq) was administered intravenously and a 75-minute acquisition initiated. The images were reconstructed using ordered subset expectation maximisation with corrections for attenuation and scatter. The final volume has a matrix size of 128x128, consisting of 90 planes of 2x2x2mm3 voxels. The PET intensities were normalised to the cerebellum to enable reporting of Standardized Uptake Value Ratio (SUVR) values. MRI and PET images were fused using multi-scale mutual information rigid registration. The MRI taken immediately post-surgery was also fused to the post-therapy MRI, as was the CT used to plan the radiotherapy dose. The registration was propagated from the planning CT to the dose map.

In addition, an experienced nuclear medicine physician (Paul Thomas) manually contoured each tumour on the FDOPA PET image fused with post-contrast MR, while blinded to the radiotherapy plan. The overlap between the PET-defined volume and available volumes defined during conventional radiotherapy planning was computed. The overlap with the 95% of prescribed dose isocontour was also calculated. Note that the PET images used were taken 3 months after the post-surgery MRIs used for conventional radiotherapy planning.

3. Results

A summary of the results is shown in Table 1. The regions enclosed by the 95% of prescribed dose contours, referred to as the *therapeutic dose volumes* (TDV), range from 197-400ml in size. In two cases, the TDV completely encloses the CTV, and in the remaining four cases at most 2.4ml of the CTV is found outside the TDV. For the PET defined volumes the volumes ranged from 8 to 96ml, with regions of PET-defined volumes outside of their corresponding TDVs ranging from 0 to 2.2ml. The PET defined volumes outside of the conventionally defined volumes ranged from 2.4 to 84ml for GTVs and from 0 to 27ml for CTVs.

Table 1: Therapeutic, i.e. 95% of prescribed dose, therapeutic dose volume (TDV) compared to gross, clinical, & planned target volumes (GTV, CTV, PTV) and PET-derived volume. All units are in ml. Dashes indicate unavailable volumes.

	Radiotherapy Volumes			95% prescribed dose (TDV)				PET-defined volume					Comment
				Total	GTV	CTV	PTV	Total	Outside				
Pat.	GTV	CTV	PTV	Vol	outside of TDV			Vol	**GTV**	CTV	PTV	TDV	
1	-	-	194	278	-	-	3.7	54	-	-	3.4	0.4	G/CTV unavailable
2	14	142	231	313	0	0	1.8	96	**84**	27	9.5	2.2	
3	25	141	253	337	0.3	1.4	17	28	**22**	11	4.6	0.8	Near organ at risk
4	14	129	217	324	0	0	0.7	71	**57**	3.5	0.2	0	
5	-	196	317	400	-	0.3	14	53	-	1.9	0.2	0	GTV unavailable
6	27	107	186	197	0	2.4	30	8	**2.4**	0	0	0	

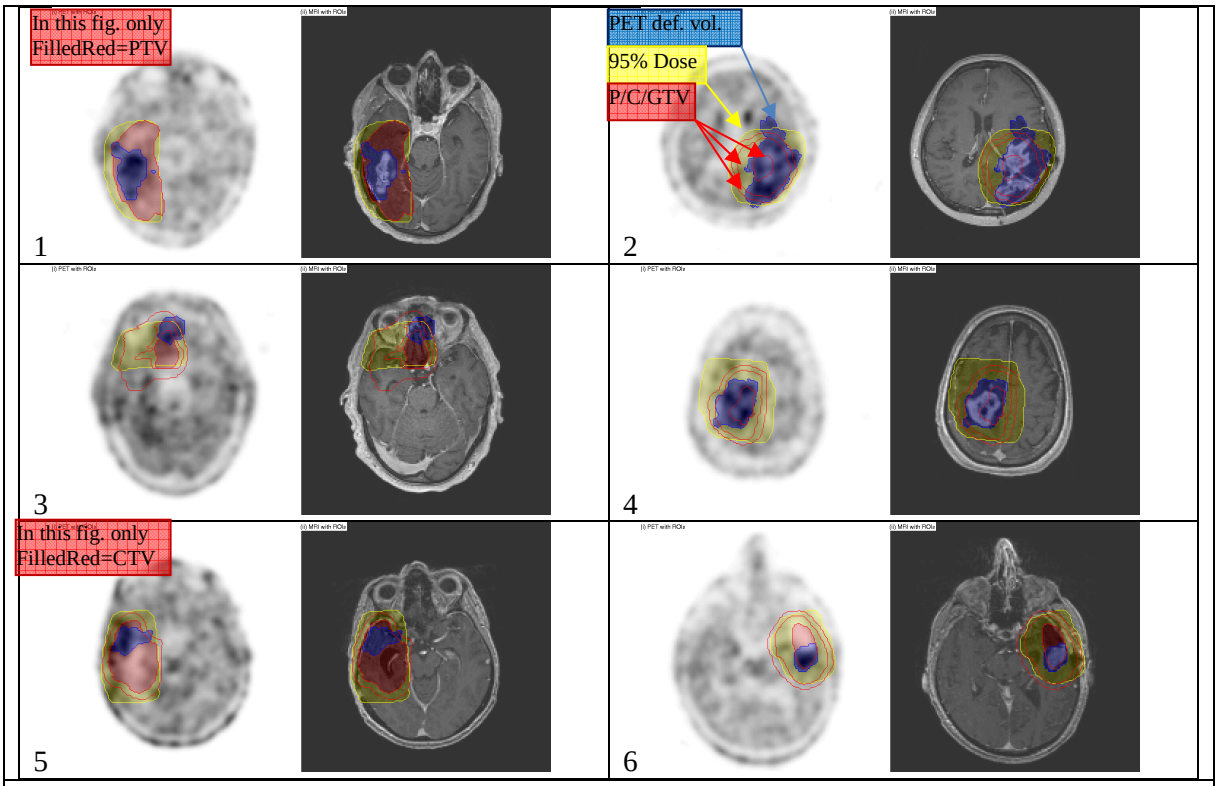

Fig. 1. Slices from each scan showing therapeutic dose volume (yellow), and PET defined volume (blue) for each patient. The clinical target volume is also shown (red). Patient numbers are on left.

Examples of one slice from each patient are shown in Fig. 1, where the therapeutic dose volume is shown in yellow, the GTV, CTV and PTV are shown in red, and the PET defined volume is shown in blue. For patient 1 only a PTV was available. For patient 5 the GTV was not available. The smallest available radiotherapy volume is filled. The contours of each volume are displayed on the PET image and the follow-up MRI (not the post-surgery MRI, as this shows same information as is contained in the contours).

4. Discussion

Arguably, the PET-derived contours probably are most equivalent to the definition for GTV, i.e. visible tumour. However PET images are highly sensitive and have some, limited, capability to detect infiltration that would not be visible on contrast enhanced MRI. So it may be fairer to make a comparison to the CTV. Although PET is sensitive to tumour compared to other modalities, microscopic infestation below a certain threshold is not visible to this modality either. Hence comparisons against both GTV and CTV are made. This implies that PET defined contours would also need margins to account for microscopic infiltration and patient motion. How large such margins would be is an open question that is beyond the scope of this work and no margin was applied to the PET volume in this work.

The volume of the PET-derived contours outside of the smallest available radiotherapy volume is 3.5ml or less for three patients (GTV for patient 6, CTV for patient 5, PTV for patient 1), indicating concordance between the MRI and PET images. However for three patients, the discrepancies ranged from 22 to 84 ml (all GTVs) indicating that the MRI scans substantially under-reported the tumour volume. These large discrepancies imply that the treatment plans would probably have been different if PET data had been available during radiotherapy planning. These values may seem large, but it is important to re-emphasise that the PET images were taken ~3 months after the post-surgery MRIs used for radiotherapy planning. And although chemo-radiotherapy was given in the intervening period, advanced glioma is known to be resistant to treatment and may have even progressed during treatment. Hence the one-to-one comparison results in Table 1 should be treated as indicative only.

On the other hand, Fig. 1 shows that although the GTVs from the follow-up and post-surgical MRIs would differ in some cases (Patients 1, 2 & 4) regions of PET uptake are seen some distance beyond the boundary of MRI enhancing tumour. This implies that the availability of PET would result in some GTVs increasing in size, and possibly commensurate increases in the CTV and PTV margins.

Despite the high PET activity beyond the bounds of both the post-surgery defined GTVs and the enhancement in follow-up MRI, all of the PET-defined volumes received relatively high doses of radiation. This is demonstrated by a comparison between the PET-defined volume and the 95% of prescribed dose contour (therapeutic dose volume). In three cases, the PET defined contours were entirely encompassed by the 95% of max isocontours. For the remaining patients, excluded PET-defined volumes ranged from 0.4 to 2.2ml. In comparison, the GTVs outside of the 95% max isocontour were zero in three cases and 0.3ml in one case, due to limitations imposed by avoiding organs at risk. Hence, the results indicate that radiotherapy plans could change in some cases, if PET were available.

Note however that all regions within the PET defined contours received a 50Gy radiation dose or more. Also, recurrence occurred in every case except patients 3 & 6. Hence it cannot be concluded from this data that a lack of metabolic information is a key reason for subsequent recurrence. Even if GTVs were enlarged, and given the palliative objective of treatment, it is unclear that every part of the GTV should receive a full dose of radiation when near organs at risk. An additional consideration is that treatment failure also stems from radio-resistance arising from local hypoxia and boosting the standard radiation dose to such regions to induce complete cell death to occur (10) (11), may not be practical in many regions near to radiosensitive tissue.

5. Conclusion

Large discrepancies between GTVs defined on MRI alone and contours defined using FDOPA PET in some cases, imply that the availability of FDOPA images could result in larger gross tumour volumes being generated for advanced glioma. However the large time-gap between the MRI used for planning and the PET scans mean these results are indicative only. Even with the opportunity for tumour growth granted by the gap between scans, all PET-defined regions received a 50Gy dose or more. It cannot be concluded that the lack of metabolic information during planning is a primary reason for later recurrence. Even so, the discrepancies between the margins of contrast enhancing MRI and high activity PET motivate for the use of PET during radiotherapy planning.

Acknowledgements

Substantial assistance was provided by the staff in various departments at the Royal Brisbane and Women's Hospital. Thank you. This research was supported by a Queensland Government Smart State NIRAP grant (MedTeQ) and the Australian National Health and Medical Research Council (NHMRC) grant number 631567.

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