Journal of Neuro-Oncology **22**: 269–273, 1994.

PET: Blood flow and oxygen consumption in brain tumors

K.L. Leenders
PET-Program, Paul Scherrer Institute, CH-5232 Villigen, Switzerland

Key words: positron emission tomography, brain tumors, blood flow, oxygen consumption

Summary

Tissue perfusion and cerebral energy metabolism in brain tumor patients are regionally abnormal, and certain patterns of pathological changes may be demonstrated in and around tumor tissue. Tumor CBF may vary widely between subjects, whereas oxygen extraction is almost always markedly reduced. This is in apparent contradiction with the tumor tissue oxygen tension data (see previous chapter): since these are low, an increase of OER would be expected. Still, as discussed above, oxygen consumption calculated from oxygen tension or PET data yield the same relative decreases (0.3) of tumor oxygen utilization compared to normal brain. This suggests that the characteristic pathological changes of tumor cell energy metabolism have diminished oxygen demand and changed the level of coupling between CBF and OER.

Since all published data on OER in tumor patients have been obtained by the steady state method, possibly resulting in an underestimation of OER, it will be mandatory to apply dynamic oxygen uptake measurements to circumvent this methodological problem and e.g. to make use of distribution volume of water to correct for tissue composition as has been reported in one paper studying patients with breast tumors.

Because of the conspicuous regional changes in tumor oxygen metabolism it is expected that effectivity of chemotherapeutic measures is directly reflected by characteristical adaptations of metabolism. Systematic studies in this context have not been reported to date. Whether oxygen metabolism changes would be more sensitive than just CBF measurements as indicator of treatment effectivity remains to be seen.

Introduction

Concerning the application of tracer methods to determine cerebral blood flow and oxygen metabolism in brain tumor patients only a few papers have been published during the early and mid eighties from a few centers. Since then no results on this topic have been published, except one methodological paper using computer simulation data [1] and one paper on breast tumors [2]. Still, the topic of oxygen uptake into tumor cells in relation to delivery of oxygen through blood is potentially of utmost importance to understand pathophysiology and therapy response. This question addresses not only radiosensitivity of tumors, but also the difference between chemotherapeutic substance presented by the blood and the actual tumor tissue concentration achieved. The discrepancies concerning this topic are not solved yet and are discussed from a microenvironmental point of view in the previous chapter and from a macroscopical PET point of view below.

According to published data in total only 132 brain tumor patients, including a large spectrum of pathology e.g. gliomas, secondaries, lymphomas and others, underwent blood flow or oxygen related PET scans (Table 1). These patients were investigated under various treatment conditions. This means that current knowledge of the complex issue surrounding pathophysiology of brain tumors is based on very little *in vivo* data.

Table 1. Literature on PET investigations in patients with brain tumours: blood flow (CBF) and oxygen (Oxy) related studies

Authors	Year	Type of PET scans*	n
Ito e.a. [4]	1982	CBF, Oxy	8
Rhodes e.a. [7]	1983	CBF, Oxy Glu	7
Leenders e.a. [3, 11]	1985, 1986	CBF, Oxy	10,1
Beaney e.a. [10]	1985, 1987	CBF, Oxy	14,11
Lammertsma e.a. [13]	1985	CBF, Oxy	21
Tyler e.a. [6]	1987	CBF,Oxy Glu	16
Mineura e.a. [8, 9]	1987, 1988	CBF,Oxy Glu	8
Ogawa e.a. [5]	1988	CBF,Oxy Glu	13
Hino e.a. [12]	1990	CBF,Oxy Glu	23
			132

* Some studies partly combined the [O-15] methods (CBF,Oxy) with [F-18]fluorodeoxyglucose (Glu) PET scans.

Methods

The term blood flow is used rather loosely in the field of biomedicine. Strictly speaking flow is expressed in units of volume per unit time (e.g. ml/min). What really is measured using PET is tissue perfusion: blood flow per unit volume of tissue (ml/min/100 ml). This term, because of tracer measurement conditions, relates to capillary tissue perfusion and is usually the variable of interest. A distinction needs to be made with blood velocity measurement in blood vessels, which sometimes is also referred to as 'blood flow'. Here, cerebral blood flow (CBF) is used in the sense of capillary tissue perfusion. Vascularity of tissue must also not be confused with 'perfusion': this term expresses the volume of vascular space in relation to total tissue or rather sample volume and is usually given as cerebral blood volume (CBV, % or ml blood per 100 ml tissue sample). Under normal circumstances CBF and CBV roughly correlate, but in tumor tissue this relationship is usually altered and sometimes markedly so.

The above mentioned studies have used compounds labeled with ^{15}O (a positron emitting isotope of ^{16}O) to quantify regional cerebral blood flow and oxygen metabolism. To assess brain tumor CBF the $H_2{}^{15}O$ technique in one of the various possible application modes has been employed. The fraction of oxygen delivered to tissue (oxygen extraction rate = OER (unitless or as fraction)) is derived from the regional cerebral $^{15}O_2$ uptake. The actual oxygen utilization (cerebral metabolic rate of oxygen consumption = $CMRO_2$ (ml/min/100 ml)) to define regional oxidative metabolism is derived from the OER, CBF and plasma oxygen concentration. See formula in Tables 2 and 3. Administration of ^{11}CO (carbon monoxide labelled with the positron emitter ^{11}C), which binds irreversibly to hemoglobine, has been used to measure cerebral intravascular blood space i.e. regional CBV. Apart from determining tumor vascularity, the CBV measurement is also necessary to correct the OER measurement for intravascular oxygen signal, since after a single passage of oxygen through the cerebral capillaries on average 60% of oxygen normally remains in the blood.

The complexities and assumptions of the various tracer methods can not be detailed here. The newer tracer methods using $H_2{}^{15}O$ or other substances all relate to rapid dynamic measurements, which allow calculation of additional entities like volume of distribution of water. The latter might be of interest in view of the large differences in tumor tissue heterogeneity. These techniques would also allow rapid sequential measurements and pave the way for studying immediate changes resulting from pharmacological or other challenges.

Baseline values in brain tumors

Representative values for CBF, OER, $CMRO_2$ and CBV are given in Table 2. The values are taken from

Table 2.

	Healthy control grey matter	Tumor contralateral grey matter	Tumor tissue	Tumor contralateral white matter	Healthy control white matter
CBF [ml/100 ml/min]	42.8 ± 8.4	39.6 ± 4.9	24.2 ± 14.8	22.7 ± 5.6	24.0 ± 4.3
CBV [ml/100 ml]	3.8 ± 0.5	4.1 ± 0.6	3.4 ± 1.3	2.5 ± 0.6	2.5 ± 0.3
CMRO2 [ml/100 ml/min]	3.0 ± 0.4	3.0 ± 0.4	1.0 ± 0.5	1.52 ± 0.4	1.6 ± 0.3
OER [%]	42.3 ± 7.4	43.3 ± 4.4	21.6 ± 3.8	38.8 ± 5.2	40.2 ± 7.0

Cerebral blood flow (CBF), blood volume (CBV), metabolic rate of oxygen (CMRO2) and oxygen extraction rate (OER) in brain tumor patients and healthy controls. CMRO2 = CBF × OER × art.[O2].
From reference [3].

[3] since in that paper the baseline values had been measured before any treatment was started. In cerebral gliomas and metastatic brain tumors a decrease in OER within all tumors, despite an adequate oxygen supply, is found [4–6]. Therefore on average $CMRO_2$ is markedly reduced when CBF is only moderately lower than normal. The tumor CBF values may cover a wide range between patients e.g. from 6 to 164 ml/min/100 ml (mean CBF values in healthy control brain ± 50 ml/min/100 ml). A reduction of the oxygen:glucose ratios and of the OER has been reported in gliomas despite the presence of an adequate oxygen supply [7, 5]. This is commonly attributed to increased anaerobic glycolysis in viable tumor cells and points to the possibility that pathologically altered changes of the tumor cells are responsible for the reduced OER despite sufficient blood supply.

The microenvironment considerations dealt with in the previous chapter contrast with the PET interpretations: there it is suggested that the oxygen supply is primarily reduced which then leads to the well documented low oxygen tension in tumor tissue. Theoretically this should result in increases of OER, e.g. from a normal value of 40% to maximally 100%, but by PET these are universally low (± 22%). On the other hand the OER measures using the steady state oxygen method have been questioned concerning their reliability on the basis of the large tissue heterogeneity in tumors [1]. These authors suggest that the to date available OER values are underestimations. However, the cited paper addressed this question only on the basis of computer simulations and compared particular extreme situations. Clearly, OER measurements need to be repeated using dynamic tracer uptake methods to verify this issue. Also arguing against a generally reduced blood supply to tumor cells is the fact that glucose consumption and extraction measured by PET are unchanged in tumor tissue when compared to normal brain [7]. Furthermore, the apparent effect of dexamethasone [3] leads to reduction of CBF and CBV compared to baseline values in brain tumor patients, both in contralateral healthy brain and in tumor tissue thereby increasing the OER. This suggests that on a macroscopical basis the vascular supply to tumor tissue is essentially intact.

In Table 3 is schematically indicated how oxygen utilization, CBF and OER are related in general terms.

1) If a primary vascular disease is present, OER may increase initially to compensate for reduced CBF in order to guarantee oxygen utilization since the tissue demands in that respect will be unchanged until cell damage start to present itself.
2) If primarily parenchymal brain tissue cell loss or diminished cell function occurs like in neurodegenerative brain diseases usually CBF responds proportionally and is reduced whereas OER remains essentially unchanged.

Table 3. Relationship between oxygen utilisation, blood flow and oxygen extraction in various disease conditions. For abbreviations see text

Condition	CMRO2 =	CBF ×	art.[O2] ×	OER
Vascular disease	±	↓	±	↑
Parenchymal pathology	↓	↓	±	±
Tumor tissue	↓	↓↑	±	↓

3) The situation in tumor tissue is more complex: oxygen utilization is always clearly reduced, OER usually markedly reduced, but CBF may vary widely from very low to high values. It therefore appears that the ordinary relationship of the formula in Table 3 does not hold in tumor tissue. As explanation may be suggested, apart from methodological considerations mentioned above, a characteristically altered tumor cell metabolism. In the presence of a maintained or increased number of viable cells in the sample volume, oxygen requirements are specifically low so that the coupling of CBF and OER is maintained at a lower level than normally. Naturally other features like shunting, greater intercapillary distances and large cell heterogeneity equally confound the picture.

Of interest is to compare the diffusional flux of oxygen in tissue using oxygen tension data on the one hand and the oxygen PET data on the other. An estimate of oxygen flux (m) can be obtained by the formula,

$$m = \frac{K \cdot A \cdot \Delta p}{\Delta x} = \frac{ml\ O_2}{min \cdot ml}$$

where K represents the diffusion constant of oxygen in tissue, A the capillary density, Δp tension difference between tissue and plasma, Δx the intercapillary distance. Direct calculation is not easy to perform without further specific experimental results, but relative values (m of tumor to m of normal brain) can be easily calculated, assuming that the diffusion of oxygen in normal tissue is similar in tumor tissue. The relative capillary density of tumor tissue to normal tissue can be estimated by dividing the respective CBF values. The values for intercapillary distances and oxygen tension differences are listed in Table 4.

Calculating m (tumor) over m (normal gray matter) gives the value 0.30 which compares very well with the value 0.33 obtained by the ratio CMRO2 (tumor) over CMRO2 (control). Thus the relative consumption of oxygen by tumor tissue compared to normal brain tissue, calculated via two fundamentally different methods, yield virtually the same value of 0.3. This supports the validity of the PET measures. The ratio OER (tumor) over OER (normal brain) is 0.51 suggesting a lesser decrease of OER in tumor tissue relative to the decrease of CMRO2.

Treatment effect

Only very few papers using the oxygen utilization PET methods to follow up metabolic tumor tissue response to treatment have been published.

Dexamethasone treatment in patients with gliomas and brain secondaries led to a decrease of CBF and CBV in tumor tissue and in the contralateral hemisphere, while the OER increased and the CMRO2 remained unchanged [3].

Table 4. Mean values from which relative oxygen diffusional flux have been calculated

	Normal brain	Tumor
Δx	50	250
Δp	30	75
CBF	0.50/0.20	0.30
OER	0.40	0.03–0.52
$CMRO_2$	3.5/1.5	0.60–1.30

Δx is the intercapillary distance.
Δp is the difference of oxygen tension between tissue and plasma.
Normal values of CBF and CMRO2 are given for grey and white matter.

Tumor radiation and chemotherapy induced a fall of CBF, $CMRO_2$ and CBV in patients with gliomas [5]. In contralateral grey matter, [8] found a slight increase of CBF and CBV within the first month after completion of radiation therapy. At a later stage (3 to 31 months), a reduction in CBF, CBV and OER was noted suggesting radiation-induced cell damage [8, 9].

It needs to be mentioned that brain tumors may influence remote brain tissue. In brain tumor patients before treatment a significant reduction in CBF and $CMRO_2$ was found in contralateral brain which in part was reverted by surgical decompression [10]. Focal increases of OER returned to normal after tumor removal in one case observation [11].

References

1. Lammertsma AA, Jones T: Low oxygen extraction fraction in tumours measured with the oxygen-15 steady state technique: effect of tissue heterogeneity. Br J Radiol 65: 697–700, 1992
2. Wilson CB, Lammertsma AA, McKenzie CG, Sikora K, Jones T: Measurement of blood flow and exchanging water space in breast tumors using positron emission tomography: A rapid and noninvasive dynamic method. Canc Res 52: 1592–1597, 1992
3. Leenders KL, Beaney RP, Brooks DJ, Lammertsma AA, Heather JD, McKenzie CG: Dexamethasone treatment of brain tumor patients: Effects on regional cerebral blood flow, blood volume, and oxygen utilization. Neurol 35: 1610–1616, 1985
4. Ito M, Lammertsma AA, Wise RJS, Bernardi S, Frackowiack RSJ, Heather JD, McKenzie GG, Thomas DGT, Jones T: Measurement of regional cerebral blood flow and oxygen utilization in patients with cerebral tumors using ^{15}O and positron emission tomography: Analytical techniques and preliminary results. Neuroradiol 23: 63–74, 1982
5. Ogawa T, Uemura K, Shishido F, Yamaguchi T, Murakami M, Inugami A, Kanno I, Sasaki H, Kato T, Hirata K, Kowada M, Mineura K, Yasuda T: Changes of cerebral blood flow, and oxygen and glucose metabolism following radiochemotherapy of gliomas: A PET study. J Comp Ass Tomogr 12: 290–297, 1988
6. Tyler JL, Diksic M, Villemure JG, Evans AC, Yamamoto YL, Feindel W: Metabolic and hemodynamic evaluation of gliomas using positron emission tomography. J Nucl Med 28: 1123–1133, 1987
7. Rhodes CG, Wise RJ, Gibbs JM, Frackowiak RS, Hatazawa J, Palmer AJ, Thomas DG, Jones T: *In vivo* disturbance of the oxidative metabolism of glucose in human cerebral gliomas. Ann Neurol 14: 614–626, 1983
8. Mineura K, Suda Y, Yasuda T, Kowada M, Ogawa T, Shishido F, Uemura K: Early and late stage positron emission tomography (PET) studies on the hemocirculation and metabolism of seemingly normal brain tissue in patients with gliomas following radiochemotherapy. Acta Neurochir (Wien) 93: 110–115, 1988
9. Mineura K, Yasuda T, Kowada M, Ogawa T, Shishido F, Uemura K: Positron emission tomographic evaluation of radiochemotherapeutic effect on regional cerebral hemocirculation and metabolism in patients with gliomas. J Neuro-Oncology 5: 277–285, 1987
10. Beaney RP, Brooks DJ, Leenders KL, Thomas DG, Jones T, Halnan KE: Blood flow and oxygen utilization in the contralateral cerebral cortex of patients with untreated intracranial tumors as studied by positron emission tomography, with observations on the effect of decompressive therapy. J Neurol Neurosurg Psych 48: 310–319, 1985
11. Leenders KL, Findley LJ, Cleeves L: PET before and after surgery for tumor-induced parkinsonism. Neurol 36: 1074–1078, 1986
12. Hino A, Imahori Y, Tenjin H, Mizukawa N, Ueda S, Hirakawa K, Nakahashi H: Metabolic and hemodynamic aspects of peritumoral low-density areas in human brain tumor. Neurosurg 26: 615–621, 1990
13. Lammertsma AA, Wise RJ, Cox TC, Thomas DG, Jones T: Measurement of blood flow, oxygen utilization, oxygen extraction ratio, and fractional blood volume in human brain tumours and surrounding oedematous tissue. Br J Radiol 58: 725–734, 1985

Address for offprints: K.L. Leenders, PET-Program, Paul Scherrer Institute, CH-5232 Villigen, Switzerland