Single photon emission computed tomography in long term survivors of adult brain tumours

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Abstract

Sixteen patients with primary brain tumours were examined on average eight years after treatment with surgery or whole brain irradiation using standard clinical assessment, CT, a neuropsychological test battery, and single photon emission CT (SPECT) with ^{99m}Tc -exametazime. Seventeen lesions were discovered on inspection of SPECT images, 11 with x-ray CT. Quantitative assessment of tracer uptake compared with 16 matched healthy volunteers was consistent with the presence of lesions. Measurement of uptake in brain regions of the hemisphere not containing the primary tumour still showed significant reductions in patients. This may be due to remote direct effects of the tumour or, more likely, to the whole brain irradiation received. Psychometric performance on most tests was significantly impaired in the patient group and was correlated with abnormalities of tracer uptake to relevant brain regions.

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Diffuse encephalopathy is common in long term survivors with malignant glioma.^{1 2 3} Its pathogenesis is unknown,⁴ but the clinical syndrome of dementia, spasticity and seizures associated with classical CT and MRI changes is well recognised.⁵ Both clinical disability and radiological abnormalities are seen more commonly in patients treated with whole brain irradiation; 50% show atrophy, ventricular dilatation, and periventricular white matter changes compared with 14% treated with focal radiation fields. CT is likely to underestimate the severity and the extent of changes compared with MRI.⁶ Pathological examination shows a mixture of astrocytosis, diffuse pallor, loss of brain substance, and gliosis.⁷ Vascular changes are common, affecting both small and medium arteries. The pathological hallmarks of radiation damage are small discrete foci of necrosis causing large scale blood-brain barrier disruption, initiating vasogenic oedema, demyelination and increased water content in the white matter, finally leading to necrosis, loss of brain substance, and atrophy.⁸

We have used the cerebral blood flow marker ^{99m}Tc -exametazime (hexamethyl-

propyleneamine oxime, HMPAO) to examine long term survivors with primary brain tumours.⁹ Abnormalities in the uptake of this tracer can be due to a variety of causes. Reductions may reflect a loss of cerebral tissue directly due to the tumour or to surgical resection, cell loss secondary to radiotherapy, or remote secondary reduction in metabolism due to the loss of input from destroyed areas; an increase in uptake may be due to the lack of inhibitory input. Single photon emission CT (SPECT), like PET,^{10 11 12} may detect such function-related changes in areas that appear normal in CT or MRI scans. We further examined the relationship between neuropsychological function and local tracer uptake. Traditional neuropsychology has been informed by structural brain lesions.¹³ SPECT may detect functional brain alterations at rest which are related to cognitive performance.¹⁴

The (weak and strong) hypotheses of this study were therefore the following.

Firstly, visual inspection of SPECT images will reveal the lesions seen on CT scans (weak), and will further reveal lesions not seen on CT scans (strong).

Secondly, semi-quantitative region of interest analysis will show a reduction of tracer uptake in areas affected by the tumour (weak), and will also show a reduction of tracer uptake in the hemispheres not affected by the tumour (strong).

Thirdly, neuropsychological performance will be correlated with regional tracer uptake.

Patients and methods

Sixteen patients with a primary brain tumour (nine female and seven male),^{9 15} were recalled and examined on average eight years (SD 4.9) after treatment with surgery and whole brain irradiation. These patients are virtually all the survivors of patients treated in Edinburgh from 1970 onwards. One patient refused to cooperate with the study and one patient had developed a recurrence of the tumour. Their mean age was 45 years (SD 8.2), with an average of 11.9 years of education (SD 3.2). Three patients belonged to social classes 1 or 2, eight to class 3, and five to classes 4 or 5. All patients were right handed. Further clinical details have been reported previously.¹⁵

A control group of healthy volunteers, matched by age, sex, education, and handedness was recruited from community sources. There were 10 female and six male controls,

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with a mean age of 43.6 years (SD 14.7), and, on average, 12.9 years (SD 3.3) of education. Seven controls belonged to social classes 1 or 2, six to class 3, and three to classes 4 or 5.

CLINICAL AND NEUROPSYCHOLOGICAL EXAMINATION

Informed consent was obtained from all subjects. Clinical examination (AG), neuropsychological assessment (KB and AC), CT and SPECT were carried out within one week of each other, during two or three separate appointments.

The national adult reading test (NART)¹⁵⁻¹⁷ was used to estimate the subjects' premorbid IQ. The subtests for similarities, comprehension, object assembly, and block design of the Wechsler adult intelligence scale—revised (WAIS-R)^{18,19} were selected to reflect current ability in verbal and non-verbal function. The Rey Osterrieth complex figure test²⁰ was used to investigate perceptual organisation and visual memory. The trail making test²¹ was used to identify patients who have difficulty in dealing with more than one input at a time, and in retaining the flexibility to make shifts in current activity. For the word fluency test, patients were asked to give as many words as they could, beginning with a given letter, within a fixed time period.²² Two administrations allowed for an easy letter (S) and a harder, less commonly occurring letter (J). Patients were also asked to generate words beginning with any letter, but belonging to a specific category (occupations). Deficits in this test are found in patients with dominant frontal lesions.²³ To facilitate comparison across the psychometric tests used, patients' performance was expressed as percentiles based on age corrected population norms. The hospital anxiety and depression (HAD) scale²⁴ was used to assess mood disturbance, which might impair performance during cognitive testing.

NEUROIMAGING

CT was performed using a GETCB/8000 scanner, high dose contrast and 7–8 mm contiguous slices through the whole brain. CT scans were reviewed separately by a neuro-radiologist (RS) and a neuro-oncologist (AG) who recorded and graded visible lesions on anatomical templates identical to those used for the data analysis of SPECT images (see below).

Patients and controls were imaged with a single slice multidetector dedicated head scanner (Multi X 810, Strichman Medical Equipment Inc., Boston, United States) after injection of 500 MBq of ^{99m}Tc-exametazime. The maximal in-slice resolution of the scanner is given as 7.5 mm (full width half maximum) by 15 mm slice thickness. The sensitivity of the instrument was measured as 520 counts per second per 1 kBq/ml in a head sized phantom.²⁵ About one million counts were acquired per slice over an acquisition time of 2–3 minutes. For the injection of the tracer, subjects were positioned comfortably on the imaging table with eyes patched and ears

unplugged. Environmental noise was kept to a minimum. The subject's head was placed in a moulded head rest, positioned with the help of two crossed light beams and fixed with two pressure pads over the zygomatic arches. Seven slices were acquired parallel to the orbital-meatal (OM) line at 1 cm intervals, starting approximately 2 cm above the OM line.

All visible lesions or reductions of uptake on SPECT images were recorded (KPE and ND), blind to the site of the tumour and previous therapy. Lesions across contiguous slices of the same cerebral lobe were counted as one. The number of visible lesions on SPECT and CT scans was compared using a one-tailed McNemar test, assuming that more lesions were detectable in SPECT images.

Templates outlining cortical lobar regions of interest in the seven brain slices were drawn from a standard brain atlas.²⁶ They were fitted to the respective image slices using the scanner software (SME version 2.66) by aligning the outline of the template with the 40% iso-contour line of the brain activity map. The inter-rater reliability of count density measures taken from regions of interest of similar size has previously been determined to be about 5%.²⁵ Tracer uptake was normalised to the average of count densities in occipito-calcarine cortex of slices 1–6. These regions of interest were unaffected by tumour pathology in all patients. In one patient, left optic atrophy and blindness had been present from the time of first referral, but this was not associated with any visible lesion in the occipital cortex. Regional count densities of patients were expressed as their deviation from the control mean in control SD units. A value of –2 would, therefore, indicate a tracer uptake comparable with the lower 2.5% of control values.

To examine changes remote from the primary tumour, count densities in the hemispheres not containing the tumour were compared with control values. Tracer uptake was compared between groups using one-tailed *t* tests, assuming that patients would show a reduction of tracer uptake compared with healthy controls. The relationship between abnormal tracer uptake and abnormal psychometric values was examined using Spearman's *ρ*. One-tailed significance values were again calculated, assuming that significant correlations were positive, that is, better psychometric performance was associated with higher regional tracer uptake.

Results

CLINICAL AND NEUROPSYCHOLOGICAL EXAMINATION

The clinical examination of the patients revealed a variety of abnormalities. Ataxia in six patients, tremor in two, psychomotor slowing in eight, and dementia in four were prevalent. Estimated premorbid IQ derived from scores of the NART suggested that all patients probably fell within the normal range.¹⁵ On current neuropsychological testing they performed well below average. For

Figure 1 Corresponding transaxial SPECT and CT slices. Patient 11 is a 44 year old man, examined eight years after biopsy of a left temporoparietal anaplastic astrocytoma, treated with 20 Gy in 12 fractions and 6 Gy in 12 fractions. He had seizures and alopecia. The left temporal lesion is seen in SPECT and CT scan; in addition there is reduced tracer uptake to posterior temporal cortex (arrow).

the similarities and comprehension subtests their average (median) score corresponded to the ninth percentile of an age matched control population, that is, 50% of the patients scored less than the bottom 9% of normative controls. For object assembly the patient median score was 12.5%, for block design 25%, for Rey copy 20.5%, for Rey recall 7.5%, for trails A 10%, for trails B 15%, for easy word fluency 28%, difficult word fluency 33%, and category word fluency 26%. Five patients achieved "case level" anxiety scores and four scored in the borderline range, namely 8–10, on the HAD scale. Three patients were significantly depressed and a further four scored in the borderline range for depression. Depression and anxiety scales were significantly associated with each other (Spearman's $\rho = 0.67$; $df = 14$; $p = 0.005$). Depression scores tended to be negatively associated with

performance in the cognitive tests, but only the correlation with block design reached significance ($\rho = -0.45$; $df = 14$; $p = 0.04$; before correction for multiple comparisons).

NEUROIMAGING

Selected examples of corresponding SPECT and CT slices are illustrated in figures 1 and 2. Eleven lesions could be detected by CT, whereas 17 appeared on SPECT scans. Seven lesions detected by SPECT were not visible on CT, whereas only one lesion seen on the CT scan was not detected by SPECT (McNemar test, $p < 0.04$, one-tailed).

Table 1 summarises uptake in different regions of interest in patients relative to controls. Mean uptake ratios were always lower in patients than in controls. Group differences were more pronounced in a number of frontal regions, reflecting the large

Figure 2 Patient 16 is a 36 year old woman, examined 15 years after partial excision of a left frontotemporal fibrillary astrocytoma, treated with 47.5 Gy in 20 fractions. She had left optic atrophy, temporal field loss in the right eye, recent memory impairment, and motor slowing. Reduction of tracer uptake to right posterior temporal cortex is just visible (arrow).

Table 1 Regional cerebral uptake of ^{99m}Tc -exametazime normalised to occipitocalcarine cortex of slices 1–6 expressed as the difference from the respective control mean in control standard deviation units; the corresponding percentile values can be derived from appropriate tables for Z scores. After comparing all regions in all 16 patients with controls, nine left hemispheres and 11 right hemispheres not affected by the primary tumour or the operation were selected in patients and compared with the 16 controls. Emboldened Z scores indicate significant group differences in *t* tests ($p < 0.05$, one-tailed)

Region of interest	Left		Right	
	All regions (n = 16)	Unaffected hemispheres only (n = 9)	All regions (n = 16)	Unaffected hemispheres only (n = 11)
Frontal 1	-0.15	0.58	-0.66	0.17
Frontal 2	-0.63	0.09	-1.25	0.31
Frontal 3	-1.83	-0.79	-1.49	-0.46
Frontal 4	-2.23	-1.25	-1.64	-0.43
Frontal 5	-1.82	-0.86	-1.19	-0.23
Frontal 6	-2.15	-1.35	-0.83	-0.3
Frontal 7	-2.28	-1.36	-0.73	-0.22
Temporal 1	-0.57	-0.99	-0.74	-0.33
Temporal 2	-0.61	-0.69	-0.65	-0.4
Temporal 3	-0.47	-0.72	-0.91	-0.75
Temporal 4	-0.3	-0.41	-0.66	-0.18
Parietal 5	-0.09	-0.37	-0.23	0.33
Parietal 6	-0.52	-0.57	-0.55	-0.13
Parietal 7	-0.47	-0.57	-0.73	-0.59

number of patients with a frontal lobe tumour (n = 9).

Even after excluding the hemisphere that was the site of the primary tumour, mean uptake remained lower in patients than in controls, although the difference between groups was reduced (table 1). Of the 56 *t* tests carried out, three (5%) would have been expected to be significant by chance alone, with a 95% confidence interval of 1 (1%) to 9 (15%), whereas 13 (23%) significant results were actually obtained.

CORRELATIONS BETWEEN REGIONAL TRACER UPTAKE AND NEUROPSYCHOLOGICAL TESTS

Table 2 gives the regional distribution of significant correlations. Scores in putative tests of frontal function such as the trails and verbal fluency tests were worse if uptake to frontal areas, particularly left, was reduced. Impaired performance on trails A and B was also associated with reduced parietal tracer uptake. Finally, there was an association between

Table 2 Spearman's ρ correlations between tracer uptake ratios and psychometric percentile scores; * $p < 0.05$, ** $p < 0.01$, one-tailed.

	Frontal							Temporal				Parietal		
	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Left:														
Comprehension												*	**	
Similarities														
Block design										*	*		*	
Object assembly												*	**	
Rey copy														
Rey recall														
Trails A				*	*								*	
Trails B			*	*	**	*						*	**	
Verbal fluency (CAT)					*									
Verbal fluency (I)	*	*	*	*	*			*	*					
Verbal fluency (S)												*	**	
Right:														
Comprehension														
Similarities														
Block design														
Object assembly														
Rey copy														
Rey recall														
Trails A							*							
Trails B												*	*	
Verbal fluency (CAT)														
Verbal fluency (I)	*	*			*	*	*							
Verbal fluency (S)														

reduced left parietal uptake and the comprehension, block design and object assembly subtests of the WAIS. Of 308 computed correlations, 33 (11%) were significant ($p < 0.05$). Fifteen (5%) significant correlations were expected by chance, with a 95% confidence interval from 8 (3%) to 25 (8%).

Discussion

All three hypotheses were supported by the data. We visually identified significantly more lesions in the SPECT scans than in the CT scans of the patients. The semiquantitative region of interest analysis comparing patients and matched healthy volunteers indicated reductions in uptake ratios in frontal and temporal hemispheres, in keeping with the presence of visible lesions in these areas. Moreover, after removing the hemispheres which originally contained the tumour from the comparison, uptake ratios were still reduced in some frontal and temporal regions. These distant changes can be explained by remote effects of the tumour and its removal, or more likely by radiation damage. The reference of regional count densities to occipital cortex values could have lead to an underestimation of the real reductions in tracer uptake—for example, if occipital cortex was itself affected by radiation, or as in the patient with unilateral optic atrophy. Unaffected left hemispheres appeared to have more severely reduced tracer uptake than the unaffected right hemispheres (table 1). If this effect is not spurious, that is, due to the sampling process, it could imply either that a primary tumour on the right has a greater effect on the contralateral hemisphere than a tumour on the left, or that the left hemisphere is more sensitive to radiation damage than the right.

Which general conclusions can be derived from the data? The retrospective nature of the study, the inhomogeneity of the patients' clinical and treatment history, and the small number do not allow for clinical predictions valid in other samples of survivors. SPECT with ^{99m}Tc -exametazime with the resolution used, however, allowed for the visualisation of lesions at least as well as CT. Particularly if used in a semi-quantitative fashion, it may also allow for the detection of remote and radiation damage. For the neuropsychologist, SPECT provides information about the presence of functioning brain tissue, which might be more relevant than purely the localisation of lesions in structural scans.

PET has been shown to be useful in assessing brain damage after irradiation,^{11 12} although it is likely to remain restricted to a few centres. SPECT is much more widely available and has the potential to answer questions about the effect of irradiation on the brain: Is there a dose related effect on tracer uptake? What is the natural history and progression of altered uptake? Future studies should investigate correlations of abnormalities in tracer uptake with differing radiation doses and with different tumour loci. The differentiation between recurrent tumour and

late radiation damage is not reliably possible with CT and MRI. Therefore, the use of SPECT in the follow up of patients, possibly combining exametazime with other tracers,²⁷ might prove informative. The high mortality in patients with a malignant brain tumour will limit the feasibility of true prospective studies. SPECT studies of retrospective series covering all survivors within a certain geographical area should continue to increase understanding of the course and the effects of late radiation induced brain damage.

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