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A RELOCATABLE HEAD FRAME FOR THE GEOMETRIC CORRELATION OF BRAIN IMAGES AND THEIR INTEGRATION WITH STEREOTACTIC PROCEDURES

by

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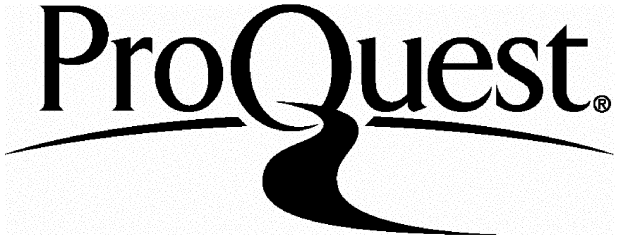

To my wife and children

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ABSTRACT

Brain images from Computerised Tomography (CT), Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopy (MRS), and Positron Emission Tomography (PET), contain complementary anatomical and physiological information. The precise geometric correlation of these different imaging modalities and their integration with stereotactically guided procedures is of critical importance for neurological research, diagnosis and treatment.

Classical stereotactic surgery has required an invasive method of fixation to the head which has been a definite constraint on the frequency with which a frame may be applied for multiple imaging and guided procedures. The problem of integrating multiple brain images with stereotactic procedures has been solved by the development of a stereotactic frame which can be rigidly fixed to the head non-invasively and which is accurately relocatable. Brain images are spatially matched with reference to the frame in a 3D computer matrix and can be displayed in any combination or form.

The system has been tested and applied in a number of clinical settings including lesion biopsy and correlation of histology with image data, functional thalamotomy, serial follow up of gliomas and focused irradiation of brain tumours and arterio-venous malformations.

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CHAPTER 1

INTRODUCTION

THE PROBLEM

HISTORICAL BACKGROUND

1. Brain Imaging
2. Correlation of multiple brain images
3. Integration of multiple brain images with stereotactic procedures

OBJECTIVES OF THE PROJECT

THE PROBLEM

Brain images from X-ray Computerised Tomography (CT), Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopy (MRS), Positron Emission Tomography (PET), and Single Photon Emission Tomography (SPECT) contain complimentary anatomical and physiological information. The precise geometric correlation of these different imaging modalities and their integration with stereotactic guided procedures is of critical importance for neurological research, diagnosis and treatment. At present there is no practical method for such integration.

HISTORICAL BACKGROUND

1. Brain Imaging

X-Rays

The discovery of X-Rays by Roentgen in 1895 heralded a new era in the practice of medicine. The value of being able to 'see into the body' in a painless and non destructive way was immediately appreciated and rapidly utilised in many fields. As early as the end of the nineteenth century Rontgengrams of the skull had been obtained, and attempts to demonstrate or localise brain tumours had been made. Church (1899) for instance described a case in which Xrays showed what appeared to be a nodular tumour. At necroscopy a tumour of the same appearance was found.

In 1896 the Swedish physician Stenbeck (1900) obtained lateral and antero-posterior views of the skull of a patient with gunshot wounds to the head. With these combined views a bullet was localised to the occipital region and successfully removed at surgery. This case was reported by Henschen (1897) at a congress in Moscow and was probably the first case in which an intracranial lesion was exactly localised with Xrays and treated successfully by surgery.

The Rontgenographic appearance of the skull as well as some changes produced by intracranial tumours were known by the second decade of the twentieth century. However a review by Heuer and Dandy (1916) revealed that of one hundred consecutive brain tumours proved at operation the tumour was distinguishable on radiographs in only six cases. An additional nine had been detected because of bone destruction.

Ventriculography

Although air had been observed in the cranium following fractures (Luckett 1913), the use of air as a contrast medium for examination of the intracranial spaces was not suggested until 1918. Dandy, successfully introduced air directly into the human ventricular system and later via lumbar puncture without ill effect. In his report Dandy (1918) concluded that ' from the data obtainable from the combination of intraventricular and intraspinous injections, it is difficult to see how intracranial tumours can escape location.'

Air ventriculography subsequently became widely used. The distortion and displacement produced in the ventricular system by expanding or atrophic lesions allowed conclusions to be drawn about the site and size of intracranial lesions. In addition, the identification of the anterior and posterior commissures of the third ventricle provided internal landmarks to aid target localisation for functional neurosurgical procedures (Talairach et al. 1957). The technique was not without serious complications and there were a number of early fatalities. Despite Dandys confidant predictions of its diagnostic value a review of the literature by Grant (1925) revealed that among 392 patients examined by ventriculography a correct diagnosis was obtained in only 124.

In order to improve radiodiagnostic definition lipid soluble (Sicard and Forestier 1922) and later water

soluble contrast media (Kandel and Chebotaryova 1972) were introduced for ventriculography, but again they were not without complication and did not significantly contribute to the specificity or sensitivity of neurological diagnosis.

Angiography

The Portuguese neurologist Moniz (1927), proposed the introduction of contrast agents either intravenously or by mouth by which the brain could become directly visible on the roentgenogram. After experiments using different contrast agents injected intravenously into dogs and then into human subjects (who were either insane or had grave neurological disturbances) he successfully obtained views of the cerebral vessels with sodium iodide. In 1936 Loman and Myerson (1936) reported the use of direct carotid puncture to introduce contrast into the cerebral circulation. Subsequently selective and highly selective angiographic techniques were developed (Lindgren 1956).

Cerebral angiography was initially employed in much the same way as ventriculography in that the displacement of vessels or abnormal vasculature would indicate the anatomical site of a cerebral lesion. The initial lack of safe contrast materials however limited its use to patients in whom pneumography did not give definite information regarding the presence of an expanding lesion. Nowadays with safer contrast agents it is primarily reserved for those patients suspected of having vascular malformations and occasionally as a pre operative method for mapping the vascular relations and supply of tumours.

Radio isotopes

Moore et al. (1950) reported the use of radioisotopes to detect intracranial tumours. They used I^{131} which is a negatively charged gamma-emitter that will not normally cross the blood brain barrier. When the blood brain barrier is breached as occurs in the presence of a tumour the isotope accumulates within it. By injecting I^{131} intravenously and applying a geiger counter over the head a tumour could therefore be crudely localised.

During the latter part of the 1950's and the 1960's scintillation counters and gamma-cameras were developed and short lived isotopes such as ^{99m}Tc and ^{113m}In were introduced. The technique for measuring regional blood flow using gaseous ^{133}Xe was also developed. The images produced by these latter methods however had poor spatial resolution and a high false negative rate for detecting tumours (Isherwood and Testa 1984).

Computerised Tomography

Not until the 1970's did diagnostic imaging again witness an epoch-making development of similar magnitude to Roentgen's discovery. The evolution of modern computers coupled with the development of a mathematical solution to image construction using a quantitative tomographic technique (Hounsfield 1973 and 1980) sparked a literal revolution in medical imaging. Within the decade several new imaging modalities were brought into clinical practice, including Xray Computed Tomography (Ambrose 1973),

Magnetic Resonance Imaging (Hawkes et al 1980), Magnetic Resonance Spectroscopy (Matson and Weiner 1988), Positron Emission Tomography (Phelps et al 1975) and Single Photon Emission Tomography (Kuhl et al 1976).

Although they differ somewhat in their energy forms, equipment and computational approaches, they have in common the capability to produce non-invasively accurate 2 dimensional representations of 3D structures or functional processes within the brain.

Each imaging method delivers electromagnetic energy (eg. Xrays, gamma rays or radio-waves) at dose levels sufficient to penetrate the tissues without directly affecting the tissue function. It is the differential absorbtion and scatter pattern produced by the volume of tissue being examined which is carried in the transmitted beam and recorded by appropriate detectors that facilitates the formation of an image. The energy received at each detector is measured and digitised, mathematical estimates are computed and the three dimensional distribution of the different energy / tissue interactions displayed as a series of two dimensional slices composed of a matrix of pixels (or picture elements).

The pixel intensity or image brightness of a CT scan reflects the incident energy of the Xray beam and the electron density of the tissue it traverses.

In MRI, pixel intensity is a quantification of the density of the mobile hydrogen nuclei modified by their local physical and chemical environment. The method involves the detection of emitted electromagnetic energy from the hydrogen nuclei that are excited by incident radio waves in the presence of a preconditioning strong and uniform, external magnetic field.

The distribution and concentration of other paramagnetic elements can be detected and displayed in a similar manner using high field strength MRI ($\geq$ 1.5 Teslar). Using appropriate phase encoding Magnetic Resonance Spectra from phosphorous (^{31}P), Carbon (^{13}C), Fluorine (^{19}F) and protons (^{1}H) can be obtained and displayed as spectroscopic images. However these other elements produce less signal per atom and are found in much lower concentrations than is hydrogen. The lower signal intensity of elements such as phosphorous necessitates the sampling of a larger volume for a longer time than is needed for routine brain imaging techniques. The larger voxels displayed with spectroscopic imaging ($\sim$ $1cm^3$) therefore give poor anatomic resolution. Despite this it is possible to obtain coarse metabolic images of phosphocreatine, ATP, inorganic phosphate, pH, phospholipids and lactate. With computer reconstruction it is also possible to obtain the MR spectra from selected regions of interest. An alternative technique of obtaining MR spectra is to use the method of image-localised single volume MRS in which spectra from ^{31}P or ^{1}H are obtained from specific volumes of interest selected from an MRI image. This is presently the most accurate method of obtaining quantitative MRS data from human subjects as there is relatively little contamination from adjacent regions

but of course this information is not presented as an image.
In Single Photon Emission Computed Tomography (SPECT) the pixel intensity reflects the energy emitted from inhaled or injected gamma-emitting radioisotopes or radiopharmaceuticals in the tissue under examination.

Positron emission tomography makes use of short lived isotopes that emit positrons. When these are annihilated by colliding with electrons they give rise to high energy gamma rays which are emitted at 180° to each other. A ring of crystal detectors connected to an electronic coincidence circuit is used to register only rays detected simultaneously at points opposite to one another. Using mathematical techniques similar to those employed in xray CT, emission events are recorded from many angles of view and the two dimensional distribution and magnitude of the gamma radiation is computed.

These imaging methods can each provide unique information about the structure under consideration. The advantages and limitations of each modality depend on the particular medical or biological information sought. CT and MRI images of the brain clearly determine anatomic and morphological features but provide little functional information. MRS, PET and SPECT on the other hand display elements of brain function and metabolism which can be quantified in vivo but delineate anatomy poorly.

Structural Imaging

The advantage of CT over MRI in neuroimaging is that CT will demonstrate cortical bone that is poorly seen on MRI. The freedom from bone artifact on MR images, however makes MR more useful in demonstrating tumours in the middle and posterior cranial fossae and enplaque dural lesions.

It is possible to identify a tumour type with a high degree of confidence on both CT and MR images. CT is better than MR in demonstrating those tumours containing calcification, but the characteristic variation in T_1 and T_2 relaxation times gives MR greater specificity in identifying a number of other tumour types. For example neoplasms such as those containing hydrogenated triglycerides or haemorrhage have short T_1 relaxation times whereas the solid cholesterol in many epidermoids give a very long T_1 relaxation time (Hadley and Paterson 1989). Metastases tend to have a short T_2 relaxation time on MR.

The high contrast differences of most tumours caused by increased T_1 and T_2 relaxation times give MR an increased sensitivity compared to CT. This is particularly so in identifying low grade gliomas. A disadvantage of MR imaging tumours is that extensive peritumoural oedema produces a similar increase in T_1 and T_2 signal to that of the tumour mass which can make it difficult to separate the two processes. The intravenous injection of the MR contrast agent Gadolinuim (GdDTPA)[1] will assist in identifying the margin

[1](Magnevist[R] Schering Health Care, UK)

between solid tumour and oedematous brain in those tumours with neovascularity in much the same way as contrast enhanced CT (Earnest and Kelly 1988).

MR has now become an alternative to CT for the investigation of nearly all intracranial disorders (Bradley and Bydder 1990). It is superior to CT in the assessment of hydrocephalus (Guthrie and Davis 1989) and demyelination (Ormerod et al. 1987),and will readily distinguish aneurysms, AVM's, benign cysts and fatty lesions from tumours which can often be difficult using CT alone.

MR has a further advantage over CT in that it provides information about the patency of the extra cranial and major intracranial vessels. Rapidly flowing blood is seen as a 'flow void' on MR images, and with appropriate sequencing projectional angiograms may be produced. This three dimensional assessment of cerebral vessels is on the brink of competing with conventional angiography (Masaryk et al 1989).

Functional Imaging

Magnetic Resonance Spectroscopy has been used primarily as a research tool in the study of normal and abnormal brain function. (^{31}P) MRS detects phosphate containing compounds including Phosphocreatinine (PCr), Adenosine Triphosphate (ATP), Inorganic Phosphate (Pi), Phosphomonoester (PME), and Phosphodiester (PDE). In addition the chemical shift of inorganic phosphate can be used to quantify tissue pH. (^{31}P) therefore provides information concerning tissue energy metabolism and phospholipid metabolism. Proton (^{1}H) MRS detects the protons in tissue metabolites such as the amino acids lactate, N-acetyl aspartate,aspartic acid and choline. (^{13}C) MRS can be used to monitor metabolic pathways and (^{19}F) MRS can be used to measure concentrations of fluoride - containing drugs.

Ischaemia and infarction have been associated with diminished concentrations of PCr and ATP and an increase in the break down products of Pi. The ischaemic area around infarcted brain shows high lactic acid concentrations (Berkelbach Van der Sprenkel et al. 1988). Phosphorous spectroscopy has been used to demonstrate that in patients with temporal lobe epilepsy the pH of the affected lobe is alkaline compared to the normal pH of 7.0. Such findings occur even when there is no significant abnormality seen on MRI (Hubesch et al. 1989)

Brain tumours are associated with increased intracellular pH (Hubesch et al. 1990). The amino acid N-acetylaspartate which is abundant in neural tissue has been shown to be reduced in brain tumours, in addition there may be increased peaks for aspartic acid and choline (an important component of phospholipid metabolism). Specific alterations in the concentrations of these metabolites may make it possible to accurately diagnose the type and grade of a brain tumour. (Bruhn et al. 1989, Gill et al. 1989, 1990).

The applications of PET and SPECT in brain research and diagnosis are ever increasing. The rate limiting

step with both modalities is primarily the development of suitable radio labelled compounds. Positron emitting isotopes include ^{15}O, ^{11}C, ^{18}F, ^{13}N and $^{75/76}Br$. Their short half lives generally necessitate an on-line cyclotron for the PET method. In contrast SPECT allows the use of a wider variety of radionuclides and labelled compounds with longer half lives where an on-line cyclotron is not a prerequisite.
The most important advantage of PET compared to SPECT is the ability to correct for loss of signal due to tissue attenuation of the emitted gamma rays. This has meant that SPECT remains primarily a qualitative imaging technique, whereas PET will provide quantitive imaging of regional function and biochemistry within the brain using tracer kinetic modelling. The considerable expense of the PET technique has however confined its use to a few specialised centres and therefore limits its general diagnostic application.

SPECT has had its greatest application in mapping regional cerebral blood flow and perfusion. These can be quantified using freely diffusible agents such as the inert gasses ^{133}Xe and ^{81m}Kr. Alternatively tracers such as ^{123}I N-isopropyl-p-iodoamphetamine (IMP) and Hexamethylpropyleneamine oxime (HMPAO) can be used. These are extracted in proportion to flow and then trapped in cerebral tissues providing an essentially static distribution during the scanning procedure.
Using these methods variations in regional blood flow in the brain in response to various physical and medical stimuli have been studied (Lassen et al. 1978). Blood flow changes in various disease states such as stroke, epilepsy, tumours and trauma have also been assessed. (Bonte et al. 1982, Raynaud et al. 1987, Bushnell et al. 1989).
A number of labelled tracers have been used in SPECT imaging to identify and define binding to neurotransmitter receptors (Drayer et al. 1982). As more research in the area of brain function continues and biochemical details regarding neurotransmitters are discovered, more of the receptor sites of the estimated 100 to 200 neurotransmitters will become likely candidates for imaging using suitably labled agents. This will provide not only a better understanding of normal brain function but will enable specific abnormalities and biochemical imbalances in disease to be evaluated non invasively.

To date most PET studies have been directed towards elucidation of normal and pathologic physiology and have been performed in a research environment. PET has been used extensively to map regional changes in cerebral blood flow brought about by specific tasks or manipulations using flow tracers such as oxygen^{15} labelled water or [^{13}N]ammonia. These techniques facilitate functional mapping of the human cortex (Reivich 1982) and have been applied to the study of biochemical and psychiatric disorders (Reiman et al. 1984).
PET will provide quantitative images of the density and / or affinity of several important post-synaptic receptors (Dopamine D_1 and D_2 receptors, central and peripheral type of benzodiazepine binding sites, serotonin, 5HT, U opiate and muscarinic receptors). It can also be used to investigate the presynaptic dopamine reuptake sites and the activity of key enzymes of the catecholamine system (Wagner et al. 1983).
In addition to the investigation of neurological and mental diseases, this approach is being increasingly used during drug therapy to measure the occupancy of a given receptor in the brain.

With increasing experience it has become apparent that PET studies are useful not only in understanding normal function and pathological functional changes but also in diagnosis, prognostication and treatment planning as part of the clinical evaluation of individual patients.

In most diseases chemical changes occur prior to anatomic changes. PET can detect functional abnormalities before anatomic changes have occurred, as for example in epilepsy (Engel et al. 1982). Focal abnormalities may be identified with PET when CT and MRI show no abnormality and even when EEG data are unable to identify a unique focus. PET scans obtained in patients with partial seizures demonstrate zones of hypometabolism in 70% during the interictal period using 18 Fluro-2-deoxyglucose (FDG), (Kuhl et al. 1980). PET is also capable of detecting carriers of the Huntingdons gene before the disease presents clinically, (Kuhl et al. 1982). More recently it has been suggested that Parkinson disease and Alzheimer disease may also be detected preclinically by changes in the pattern of resting cerebral metabolism, (McGeer et al. 1986).

A further area where PET has provided important clinical information is in patients with Gliomas. The evaluation of glucose metabolism in brain tumours using FDG has been used extensively in diagnosis and management. PET-FDG is able to distinguish high grade malignant gliomas (III & IV) from slower growing, low grade tumours (I & II), (Di Chiro 1986). PET-FDG can differentiate necrosis due to treatment (radiotherapy or chemotherapy) from recurrent tumour when CT and MRI are unable to differentiate between them, (Di Chiro et al. 1987).

The assessment of tumoral protein synthesis has been attempted with a number of amino acids. ^{11}C-Methionine is taken up by high and low grade gliomas and will define the extent of viable tumour more precisely than CT and MR scanning (Mosskin et al. 1989). However its mechanism of uptake appears to be related mainly to its capillary transport rather than to increased amino acid requirements for protein synthesis.

More recently it has been possible to image peripheral benzodiazepine receptors using ^{11}C-ligands, (Junck et al. 1989). These may be involved in regulation of glial cell proliferation. Tumour cells proliferation may theoretically be quantified in vivo by the use of [^{11}C]-thymidine which is currently being assessed.

2. Correlation of multiple brain images

At the present time many patients undergo more than one type of brain imaging during their diagnostic work up. This is because a combination of images will often describe an abnormality more fully than the images obtained with any single modality. In addition patients with progressive neurological disorders or undergoing treatment will be monitored by repeating images using the same modality. These images from different studies are generally correlated qualitatively in the mind of the physician or surgeon reviewing them. However the image data from CT, MRI, MRS, PET and SPECT are in digital form and it is therefore possible to correlate these data quantitatively by computer.

The ability to precisely match this complimentary information and display it in a desired combination and form is of the utmost importance for neurological research, diagnosis, treatment planning and monitoring. Such quantitative correlation will for example facilitate the study of basic structure / function relationships in normal subjects and in those with physiological or behavioral disturbances. Epileptic foci localised with PET or SPECT may be correlated with CT or MR images and allow accurate surgical planning. The correlation of CT with MR imaging would be useful in defining CT detected skeletal lesions or calcifications in the context of an MR depiction of soft tissue anatomy. This combination would also be useful in radiotherapy planning where MRI may best demonstrate the anatomy of the target lesion, but where CT is needed to provide a map of the radiation attenuation coefficient so that dose distributions can be calculated.

Functional images of brain tumours using PET or MRS may provide the most accurate information as to the tumour type, grade and extent of spread. PET will also differentiate radionecrosis from recurrent tumour. When these images are correlated precisely with CT or MRI this information can be placed in its anatomical context for accurate treatment planning or monitoring. The correlation of PET or SPECT studies with MR or CT would be useful in planning and evaluating tumour therapy using radiolabelled monoclonal antibodies.

The precise matching of serial images using the same modality will enable a chosen parameter to be measured repeatedly at the same location in the brain and so allow truly objective comparison. This would be of value in monitoring tumour growth or metabolism in response to therapy, but could of course be applied to quantitative monitoring of a large number of progressive neurological diseases such as multiple sclerosis, Parkinsons disease, or Alzheimers disease. A potential future application would be in monitoring the viability of grafted neural tissue using PET imaging where areas of new innervation could be precisely defined anatomically.

Routine clinical imaging studies are not (and often can not be) performed with rigorous attention to reproducible patient positioning. Even under ideal conditions using crossed laser alignment with surface landmarks on the head, repositioning accuracy at best approaches 5 mm. Correlations at this level of accuracy are not of sufficient value to motivate their use. The potential advantages from using all of the available information in multiple imaging studies are therefore not realised. Image correlation with a three dimensional accuracy to within the voxel size of the matched image with the lowest spacial resolution should in my view be regarded as the gold standard. Examples of the voxel sizes for the different imaging modalities are 0.5 x 0.5 x 1.5 mm for CT, 1 x 1 x 3 mm for MRI, 10 x 10 x 10 mm for MRS, 4 x 4 x 7 mm for PET and 10 x 10 x 10 mm for SPECT. Thus correlation of CT with CT images should idealy be achieved to within 1-2 mm, CT with MRI to within 3mm etc.

To achieve geometric correlation of multiple brain images with this level of accuracy, any technique must take into account the position of the patients head during different studies and variability between imagers in their form of data collection. Image data from the different modalities will vary in the axial slice thickness, intersection gap, section number, matrix size and pixel size. In addition the data from different imagers will vary in their computer formats and so will generally require reformatting prior to being entered into a suitable computer programme for correlation and display.

IMAGE CORRELATION METHODS

Methods by which multiple brain images may be correlated fall into two groups and are shown in (fig 1). In the first group the patients head is precisely repositioned in each imager and data collected from a defined base line. This ensures that the image volumes are aligned without variation in rotation or translation.

When the image data is reformatted so that it can be read by an appropriate computer algorithm, coordinate transformation requires only the rescaling of the image sets. Rescaling involves the adjustment of pixel size and reslicing of the image volumes to match a selected 'primary image'.

In the second group, patients heads are randomly positioned in each imager and so when the image sets are reformatted and processed by the computer, coordinate transformation requires the ability to scale, rotate and translate image volumes in three dimensions.

Geometric correlation of images in this instance depends upon matching anatomical or applied reference points visible on all the image sets to the 3D coordinates of those same reference points on a selected 'primary image'. When each image set has been manipulated into the desired 3D orientation then it is resliced to match the primary set.

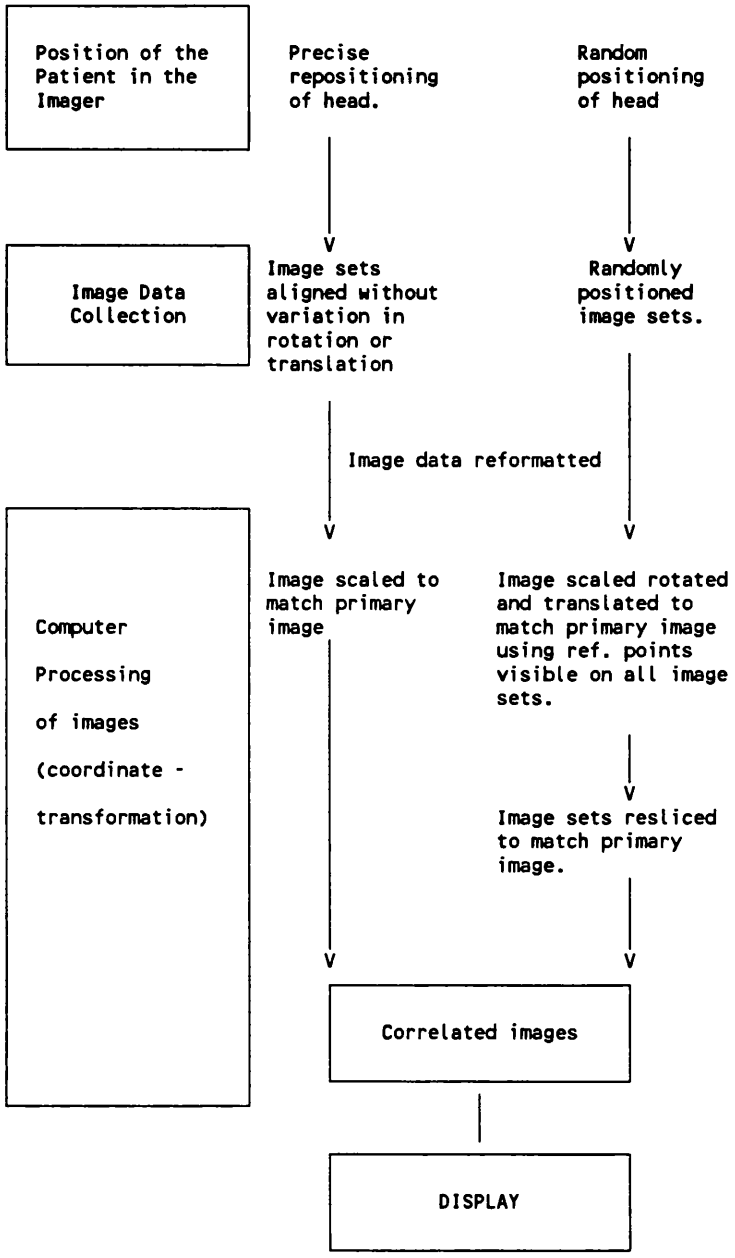


Figure 1. Methods of correlating multiple brain images

Examples of these two principle methods are reviewed below.

1. PRECISE REPOSITIONING OF THE HEAD IN IMAGERS

Calibrated crossed lasers mounted on the gantry of each of the described biomedical imagers are routinely used to define the position in space and the isocentre of the imaging plane. Precise repositioning of the head in the imaging plane can be achieved by aligning the crossed lasers to anatomical or applied reference

points on the head. Alternatively the head can be reproducibly fixed to the scanner couch using a head holder which is repositioned using the crossed laser system.

i. The use of anatomical reference points

As mentioned previously surface landmarks on the head such as the outer canthi and external auditory meati can not be defined with sufficient accuracy to allow precise realignment with a crossed laser system. However, Conner et al. (1975), Du Boulay et al. (1978) and Conti et al. (1982), have described **video subtraction systems** which will effectively match thousands of reference points on the external surface of the head and enable the head to be repositioned with a high degree of accuracy. The systems employ a wall or floor mounted video camera which bears a fixed relationship to the imager and is used to record an image of the patients head when they are correctly positioned.

When the patient returns for a comparable scan the head position is adjusted to its former location using a television picture which displays a static negative image of the former head position superimposed on the dynamic positive image of the patients head. When the two images cancel by subtraction then the head is in the same position as before.

Total cancellation of the two images may not be possible because of differences in hairstyling or minor alterations in facial expression, but despite this the system is claimed to have a repositioning accuracy in the order of $\pm$ 1mm. This degree of accuracy is however likely to decrease when images are separated by a period of time since surface contours of the face will alter. This is particularly so when patient are undergoing treatment such as steroid medication.

Although this method has been described for comparison of repeated images from the same imaging modality (CT or PET) it would be theoretically possible to use the method to compare images from different modalities. By using a headrest that was interchangeable between the different imagers and positioning it exactly in each imager using crossed lasers the position of the video camera mounting in each imaging facility could be adjusted to have an identical relationship to the positioned head rest. The position of a patients head in the head rest in one imager could then be compared with that in another using video subtraction.

ii. The use of applied reference points

The use of reference points or lines **marked on the skin** to reproducibly align the head with crossed laser system is generally unsatisfactory due to movement of the skin over the skull with changes of facial expression. Skin marking is also unsuitable for long term follow up studies. Vogl et al. (1989) described the use of skin marking to define the base line imaging plane on patient heads but were able to more accurately adjust and correct the orientation of the head by the use of a curved spirit level that was stuck to the forehead and zeroed in each imager. With this system a geometric correlation between CT and SPECT images was achieved with an accuracy of between one and two millimetres. Because the skin marks and spirit level must remain on the patient continuously to allow comparison of images, the technique is

obviously unsuitable for comparing images separated by a prolonged period.

To overcome the disadvantages of marking the skin Miura et al. (1988) and Meltzer et al. (1990) have used patient specific **face masks** formed from thermoplastic material. The heat softened material is applied over the forehead, orbital margins and bridge of the nose and sets when it cools. Reference marks are made on the mask for cross laser alignment. In addition a radio-opaque reference system is stuck to the mask which facilitates the identification of the slice position.
Miura et al. have used this system to correlate images from CT and PET. V-shaped tubes fitted on each side of the mask acted as the image localiser system and were filled with ^{68}Ge - line sources for PET localisation, and steel wires for CT localisation. Using two video cameras, hard copy of the slice matched CT and PET images were then scaled with reference to the radio-opaque reference points using an appropriate zoom. The images could then be superimposed by mixing the images and displaying them on a television screen. The accuracy of this correlation was < 2mm in slice positioning and $< 1^{\circ}$ in slice angle.
Meltzer et al. used a series of fluid filled tubes visible on MR as a localising system on the mask. From a sagittal MR image a plane of interest (eg. parallel with a line joining the anterior and posterior commissures) was planned and defined by its relationship to the localising device. The plane of interest was marked on the mask and coplanar images taken after cross laser alignment. CT, MR, and PET images were correlated using this technique. Phantom studies demonstrated than accuracy and reproducibility of imaging plane selection of within 1mm and 1°.

An alternative head repositioning method in which a reference system is located on the head has been described by Kingsley et al. (1990). This employs a **relocation device** comprising a small mirror and a spirit level attached to a mouth piece containing a patient specific dental impression. By zeroing the horizontal spirit level and correcting the head position so that a beam of light reflected from the vertically positioned mirror strikes the same target, head repositioning with no significant flexion, extension or canting can be achieved. Head repositioning in the scanner is then dependant upon moving the couch to the desired starting position with reference to gantry mounted lasers.This system has been described for use with repeated CT imaging and has been shown to have a repositioning accuracy of within 1mm with cooperative patients. It would however be possible to match images from other modalities using an identical set up. A shortcoming of this repositioning method is that it requires a high degree of patient compliance and would not be suitable for children, confused, drowsy or anaesthetized patients because it is dependant on them biting on the mouth piece of the relocation device and keeping their head still.

With all the methods described above some form of head restraint is required during image acquisition, even for the most cooperative patients. For however accurately the head can be positioned at the beginning of each study, any movement that subsequently occurs will increase the error in image correlation.

Conventional head rests are U-shaped and despite padding and velcro bands they will not adequately immobilise the head. This is particularly so for PET studies where the image acquisition time may be up to 2 hours. Head immobilisation in conventional head rests is assisted by the use of a deflatable bean bag which is moulded around the head and then evacuated. This method has been described by a number of groups including Kingsley et al. (1990). Although it minimises movement it does not prevent it because the bag contracts away from the head. A variety of head holders which also provide the means of head repositioning have been described and are outlined below.

iii. The use of head fixation devices

To achieve accurate head repositioning and fixation in a variety of imagers a head holder should ideally hold the head rigidly and yet comfortably in a desired and precisely reproducible position. It should be well tolerated by patients for the full duration of each imaging procedure . The head holder should be able to accept the full range of head sizes and be simple to apply and remove. Its repositioning accuracy should be maintained over many months or years for follow up studies. There should be fixation points on the holder for rigid attachment to a variety of scanner couches and it should have reference markers on it for cross laser alignment. Finally it should be constructed of materials that cause no artefact on biomedical images. The following head fixation devices fulfil these criteria to a variable degree.

Moulded head rest

Kearfott et al. (1984) have described a head holder in the form of a patient specific head rest. This is made by pouring polyurethane resin and catalyst between an injection moulded polystyrene shell and a protective latex sheet. The patients head is placed in the form while the resin expands and sets. The large surface area of contact of the mould with the patients head provides comfortable restraint. When fixed to a scanner couch and used in conjunction with a crossed laser system it will give a repositioning accuracy in the region of 2mm. The accuracy of this system however is limited because the mould does not hold the head with sufficient rigidity and is constructed of a material that is itself compressible and easily deformed. The head can slide in the mould and the scalp can slide over the skull. In addition any changes in the patients hair style between repositionings will further add to the inaccuracies of the system.

Moulded head / face masks

Head fixation using moulds of the head and face have been developed by Fox et al. (1985) and Lyman et al. (1989). Fox employs an acrylic hemicylinder attached to the scanner couch which is padded with shape assuming foam. Patients are then positioned in the head holder and immobilised by applying a pre made face mask formed of thermoplastic material that is fastened to the head holder by hinged arms with quick release clasps. A localiser system attached to the head fixation device consisting of an acrylic plate containing steel wires is used to define the position of the head in the scanner using crossed laser system. The radio-opaque wires also enable the scan slice position to be transferred to a lateral skull Xray.

The accuracy of head repositioning using this system is said to be high but has not been quantified in this paper. The head holder was designed primarily for repeated PET studies and for indirect correlation of PET images with reference brain slices in a stereotactic atlas.

The AC-PC line which is the reference plane for a number of stereotactic atlases has been shown to bear a close relationship to the glabella-inion line (Takase et al. 1977, Tokunga et al. 1977) which can be identified on a lateral skull radiographs. The likely position of the AC-PC line can therefore be calculated and drawn on a lateral skull radiograph allowing the direct transfer of PET coordinates to the stereotactic atlas.

This method of indirect correlation between an image and a stereotactic atlas could be applied to other imaging modalities and therefore facilitate comparison between images. However, the method assumes 'normal' anatomy and does not take account of inter subject variability or structural abnormalities and is therefore of limited value

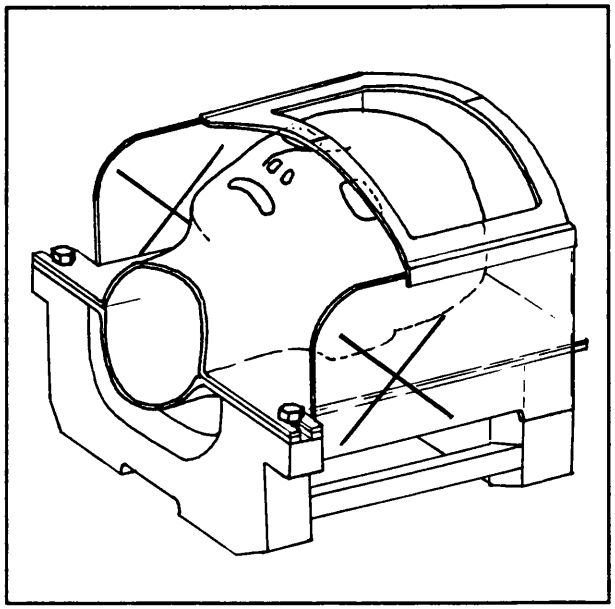


Figure 2 Lymans head fixation device

The head fixation device developed by Lyman et al. (fig.2), comprises a mask of the head which is made in two halves from a thermoplastic that is modelled around the patient while in its softened form. Holes are made in the face mask half for the eyes, mouth and nostrils. The head mask is secured within a cylindrical Lucite frame to which side plates are attached, each containing radio-opaque reference markers made of copper wire in the form of a cross set at 45° to the vertical. These reference markers or fiducials, are visible on radiographs and CT and are interchangeable with plates containing plastic beads filled with olive oil that can be visualised on MRI images.

The frame is by definition a stereotactic frame in that a 3D coordinate system may be established within it with reference to the fiducials. Measurements in the AP (or y) direction, the lateral (or x) direction and the vertical (or z) direction are made from the mid point between the two laterally positioned fiducial crosses. Three dimensional image coordinates are established with reference to the positions of the fiducial markers visualised on each image.

The head fixation device can be secured to a variety of biomedical imagers or to a radio-surgery couch using separate interfacing adapters. Image correlation is achieved by fixing the head in a defined position in each imager using cross laser alignment. The image data is reformatted and placed in a computer for coordinate transformation between the images. This requires the rescaling of images and the matching of slice positions which is accomplished with reference to the fiducials visible on the images. The system also allows the transfer of coordinates between cerebral angiograms and CT or MR images. The head frame was

designed for heavy charged particle radiosurgery using multiple images for the planning procedure. The authors claim that they are able to reposition the head with an accuracy of approximately 1mm in each of the three orthogonal planes.

Moulded Helmet

Greitz et al. (1980), Kingsley et al. (1980) and Bergström et al. (1981) describe a head fixation device, 'The Fixter system' (fig. 3) which comprises a base plate that is secured to the head with aluminium bars that are incorporated into a patient specific plastic helmet. The helmet is formed by wrapping a fibre glass based bandage (Lightcast II, 3M Company) around the patients head. Two limbs of the helmet project downwards to meet in front of the mouth and are secured to a cast made from orthodontic resin which has been moulded to fit the patients incisors. The helmet is hardened by exposing it to ultraviolet light.

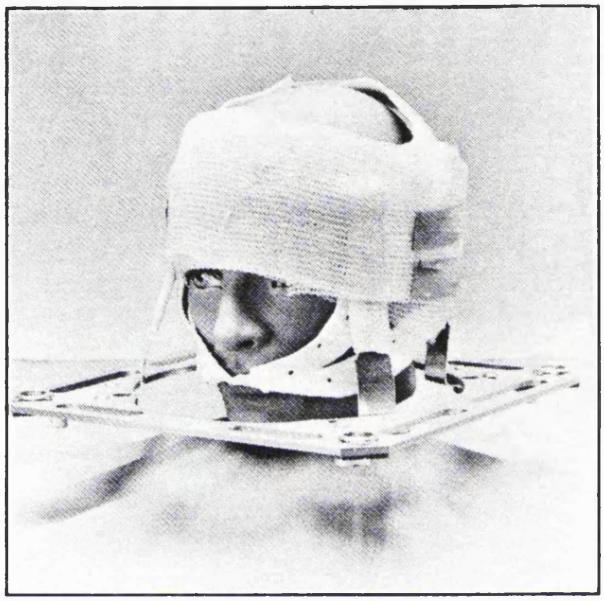


Figure 3 **The Fixter system** (Illustration by courtesy of Fixter Instruments AB, Stockholm, Sweden)

The base plate with its aluminium rods is then placed in the desired position over the patients head and then the bars are fixed to the helmet by wrapping more Lightcast round them. The baseplate can be secured to a variety of imagers using specially designed brackets. Image correlation is achieved with reference to a stereotactic localisation frame that is attached to the surface of the base plate during image acquisition. The localiser frame consists of six rods formed into two N-shapes positioned on each side of the head. The four corner posts define the AP and lateral coordinates on an axial slice and the oblique rods (set at 45° to the vertical) are used to calculate the vertical position of the target above the frames reference plane.

The frame has been used to transpose positions between CT scans and cerebral angiograms and to correlate CT images with PET images.

The helmet is removed by cutting it in two while it is positioned on the head and then removing the two halves, each with their retained aluminium bars. The helmet can subsequently be repositioned by assembling the two halves around the head and binding them together with more Lightcast bandage. Movement of the helmet over the head is of the order of 2-3mm in any measured plane and relocation is accurate to within 3-6mm.

The system was developed for correlating multiple neurological images and integrating these with stereotactic surgical procedures. When the surgical target has been chosen access to the skull requires that a section of the helmet is cut away.

As a device for correlating multiple brain images its primary shortcoming is its poor accuracy of relocation and lack of absolute stability on the head when in position. This lack of stability is due to scalp and hair interposition between the helmet and the skull. The scalp and hair are compressible and the scalp will slide over the skull. Although the impression of the incisor teeth forms a fixed point of location relative to the skull, the helmet will tend to pivot around this point. A further disadvantage of this system is that each patients helmet has to be stored between follow up scans or repeated procedures. For routine use with a large number of patients a considerable amount of storage space would be required. The rather cumbersome nature of the device and method has prevented its widespread adoption.

Head Restraining Pads

Mazziota et al. (1982) developed a head holding system as a means of correlating functional PET images with structural data obtained from skull radiographs and Xray CT images. This is in the form of an acrylic cylinder into which the head is placed.Head immobilisation is then achieved by tightening cushioned, adjustable pads down on the subjects maxilla and forehead bilaterally. The head gear can be fixed to a CT or PET couch and is aligned using a crossed laser system. The patient is transferred between these imagers with the device attached to the head. When the patient is immobilised in the head holder the only movements of the head are produced by the skin sliding over the bony surface of the forehead and maxilla. The possible extent of such movements are not quantified in the publication.

The head holder appears to be suitable for its designed purpose of correlating isolated PET images with CT or Xray radiographs that are performed consecutively with the device continuously attached to the head. It is however unsuitable for repeated head fixations over an extended period because no means is provided for recording the positions of the headrest or immobilisation pads.

Fixation to external auditory meati and nasion

A relocatable reference frame or 'Stereoadapter'(fig. 4) has been developed by Laitinen et al. (1985) which is constructed from light weight aluminium alloy and armed plastic. It is located on the head by means of two ear plugs and a nasion support. The adapter can be fitted to different sized heads by adjusting the length of the bowed connecting arms between the ear plugs and nasion support, using four calibrated cogwheels. By resetting the cogwheels to their previously recorded positions accurate relocation is possible. The radio-opaque reference system comprises two inverted triangular frames set on each side of the head to which the ear plugs are secured. Each triangle contains four transverse rods. A connector plate joins the bases of the triangular frames over the vertex and a rod passing anteriorly from the plate to the nasion support provides additional stability and a mid line radio-opaque reference line. A rigid band strapped against the occiput finally immobilises the adapter on the patients head. The adapter which was developed for Xray CT guided stereotaxis, is made compatible with MRI by attaching fluid filled tubes to the frame and could be made compatible with PET by attaching tubes containing radionuclides to the frame to serve

as reference markers.

For immobilisation of the patient on each scanner table a fixed plastic plate with a small cushion is used. The adapter is fixed to the plate by a multi-joint locking component. The binaural axis of the adapter is forced into a horizontal position, and the head is then positioned around the binaural axis until the transverse arms on the triangular frames are vertical, or parallel with the axial imaging slices. The adapter is then locked to the plate.

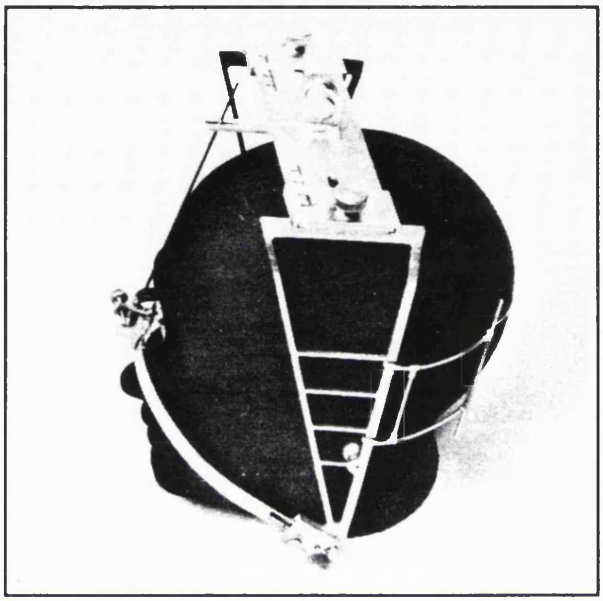


Figure 4 **The Laitinen Stereo adapter** (Illustration courtesy of Beverly Surgical Instruments, Montpellier France)

When the images have been acquired the 3 dimensional coordinates of any region of interest are measured directly from the images with reference to the localiser frame, whose rods are seen as dots on the axial images. Using this method coordinates can be transferred between different images and although not described, computer correlation of multiple images would be possible. The Stereoadapter has been used for target localisation for functional and non functional neurosurgery and stereotactic irradiation of AVM's and tumours.

Its accuracy of relocation has been assessed by Delannes et al. (1991) Ten patient were submitted to 5 serial CT scans with the Stereoadapter repositioned each time. The basal artery trunk at the prepontine cistern was chosen as a constant anatomical structure that could be identified on the scans and its displacement relative to the frame was measured in the three orthogonal planes. The average range of displacement for the 50 set ups were $x = 1.8$mm, $y = 1.5$mm and $z = 1.9$mm. The average 3D range $\sqrt{(x^2+y^2+z^2)}$ is therefore 3mm.

The paper does not state the maximum recorded displacement of the target for any individual which is more useful information. It is also of note that the basal artery trunk is positioned between the external auditory meati where one would expect the least displacement of a target relative to the frame.

Another short coming of the system is that the springy nature of the frames material will not allow for rigid fixation of the head. In addition firm pressure on the external auditory meati and nasion upon which the immobilisation is dependant is uncomfortable and would not be tolerated for prolonged procedures such as PET scanning.

Another device that uses the external auditory meati and nasion for non invasive head fixation has been developed by Hitchcock (1988). This device, the Stereotactic-Computerised Tomography Interface Device (SCID) is a rectangular aluminium base frame with a graduated nasion rest and ear plugs. Localiser plates

containing N-shaped fiducials are attached laterally and project above the frame.

The device is fixed to the scanner table and the patients head positioned within the SCID and adjusted by sorbo supports behind the occiput to permit the ear plugs to be placed snugly in the meati. The nasion rest is then placed snugly on the nasion and the degree of advancement is noted on the nasion and ear bars. The CT table is then adjusted so that its crossed lasers intersect the horizontal zeros of the SCID. Target coordinates are then established with reference to the localiser plates. Repeat fixation is achieved by repositioning the patient at a later date in the manner described and inserting the ear plugs and nasion bar to their prerecorded depths.

The system has been used primarily for CT target localisation prior to stereotactic procedures. However with modification the device would be suitable for correlating multiple imaging modalities and matching repeated studies. Its accuracy of relocation is in the region of 2-3mm and has the advantage over the Stereoadapter of providing more rigid fixation. In common with the Stereoadapter it has the disadvantage that the degree of head immobilisation it provides and the accuracy of its relocation are proportional to the pressure applied on the ear plugs and nasion support which have to be limited due to patient discomfort.

Dental fixation

A head fixation method using a patient specific dental impression was described by New et al. (1975). This was in the early days of CT imaging where movement of the patient during the imaging procedure would cause significant image artefact due to the long acquisition time required for each axial slice.

A vinyl resin was used as a dental impression material which when softened in hot water was applied to a dental plate and then pressed against the upper teeth to take an impression. When the vinyl resin cooled it set to form a hard impression. Prior to imaging, the patient was positioned on the scanner table with the dental impression held tightly between the teeth. A bar projecting from the dental plate was then connected to a lockable snake-arm which was mounted on the scanner gantry.

The position of the impression was then fixed for the duration of the scan by locking the snake-arm.

This system was shown to significantly reduce movement artefact with routine CT imaging. As there was no means of defining the position of the dental impression in space the system was only applicable for head fixation for a single image acquisition.

Invasive skull fixation

Undoubtedly the most assured method of head fixation within a scanner is to invasively fix the skull within a stereotactic head ring which in turn is bolted to the scanner couch. Skull fixation within a stereotactic frame may be achieved by driving metal pins into the outer table of the calvarium or by inserting carbon fibre rods into pre made holes under local or general anaesthesia.

Coordinate transformations from CT images to stereotactic frames using this method are widely described. Koslow & Abele (1980), Birg & Mundinger (1982) and Mundinger and Birg (1984) achieve coordinate transformation directly from the CT scanner software by positioning the frame in the centre of the scanner

so that the (x,y) coordinates of each coincide. By taking images parallel to the frame the z axis corresponds to the increment of the scanner table movement.

Other authors including Bergstrom & Greitz (1976), Boethius et al. (1980), Leksell & Jernberg (1980), Gleason et al. (1978), Makay et al. (1982), Montagno and Nashold (1985) and Sheldon et al. (1980) have in addition to head fixation via a stereotactic frame employed localizer systems or fiducials attached to it (fig 5). These are generally in the form of oblique and vertical rods made of radio-opaque material that are seen as points on an axial image. The (x.y) coordinates of a target can then be determined from its relationship to the vertical rods and its z coordinate is determined by the relative displacement of the oblique rods. The use of fiducials therefore enables coordinate transformation from any image independently of the mechanical coincidences of two coordinate systems and independent of the precision of incrementation of the scanner table.

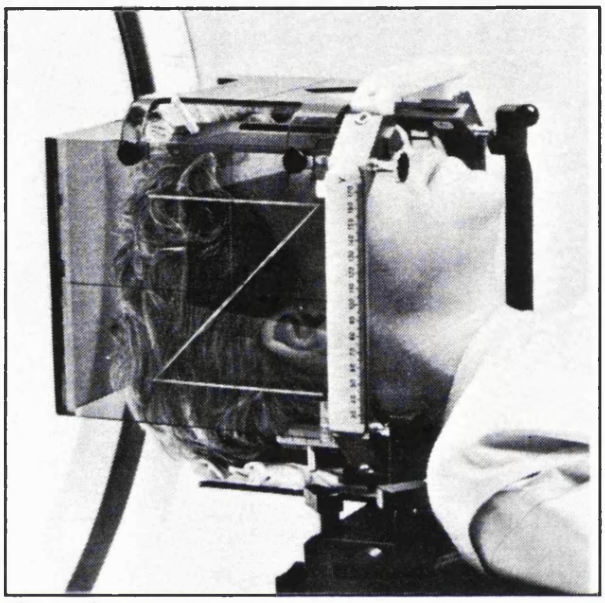


Figure 5 **CT compatable Leskell frame**
(Illustration courtesy of Elekta Instruments Inc. Stockholm Sweden)

This two dimensional solution to the problem of three dimensional coordinate transformation is achieved by registering variations in translation between the imager and frames coordinate systems but does not take account of variation in rotation. The latter being prevented by rigid head fixation to the scanner table. The accuracy in the determination of any CT defined target using these systems has been shown to be within 1mm.

Following the introduction of MR imaging into clinical practice MRI directed stereotactic techniques were quickly developed to exploit the increased sensitivity that these images provided. In particular the ability to define and therefore biopsy cerebral lesions that are not clearly visualised on CT.

A number of CT compatible stereotactic frames that require fixation within an imager for coordinate determination have now been modified for MRI compatibility and include the Leksell frame (Leksell et al. 1985), the OBT frame (Olivier et al. 1985) and the Reichert Mundinger frame (Sturm et al. 1983). To allow the use of strong magnetic fields and to prevent closed conduction loops that will cause image artefact due to eddy current formation the frames are constructed of non ferrous materials. These include anodised aluminium (with or without interposing insulators) and a variety of plastics or composite materials. The fiducial systems for MR are of similar geometry to those of CT but have the addition of reference rods positioned above the vertex to allow coordinate transformation from sagittal and coronal imaging planes. The fiducials are generally constructed of plastic tubes filled with fluid such as vegetable oil or copper

sulphate solution which are visible on MR.
Stereotactic MR imaging is performed by attaching the frame to the MR table and taking images parallel to the frame and / or perpendicular to it in the sagittal or coronal planes. The (x,y,z) coordinates of a chosen target point can be determined according to the same principles described previously for CT. Accuracy is improved if a targets coordinates are determined in all three imaging planes.
Since these frames are compatible with both CT and MR imaging patients can undergo both types of imaging in sequence after simply changing the attached fiducial systems. The images may then be directly compared because the axial scan planes are taken at identical angles. Computer correlation and display of the matched images in a desired form is then feasible.

The accuracy with which CT and MR images may be matched using this method is limited primarily by distortions inherent in the MR images and by the voxel sizes of MR images which are larger than CT. MR image distortions are due to inhomogeities in the main magnetic field and to non linearity of orthogonal field gradients. They are the result of eddy currents that are produced during the image sequence and have been shown to be greatest in the coronal and sagittal imaging sequences, (Wyper et al. 1987). Schad et al. (1987)[1] have described a method for measuring and correcting these geometrical distortions using phantoms placed within a stereotactic guidance system. Errors in the x,y plane are assessed from a 2 dimensional phantom displaying a pincushion arrangement. The measured distortions can be corrected by calculations based on modelling the distortions as a fourth order 2 dimensional polynomial.
Errors in the z coordinate are then determined from a '3D phantom' which will display displacements due to warp and tilt of the image plane and are corrected by adjustment of the gradient shimming currents. Using this method the errors in all three axes may be reduced from 5 to 1-2mm which is the limit of resolution.
Fiducial systems have been developed for stereotactic PET imaging which can be fixed to the Reichart - Mundinger frame (Schad et al. 1987)[2] and to the Fixter system (Bergstrom et al. 1981). Both stereotactic frames can be fixed to the skull invasively using pins or rods, however, the prolonged image acquisition time inherent in the PET method and the need to transfer patients to special installations has generally made this method unsuitable. The authors therefore advocate and describe the use of moulded helmets to non invasively fix the stereotactic frame to the head.

Although the method of invasive skull fixation has the important advantage of achieving the greatest accuracy of image correlation it is unpleasant for the patient and is only appropriate to use where stereotactic surgical procedures or radiosurgery are to be performed from the correlated images. Even in these circumstances all the diagnostic images must be acquired the images correlated and the planning and treatment performed with the frame continuously fixed to the patients head.
In routine clinical practice this can be difficult to achieve in a reasonable time and may result in the patient suffering many hours of discomfort in the frame or unnecessarily prolonged general anaesthesia.

2. RANDOM POSITIONING OF THE HEAD IN IMAGERS

When a series of images are taken of a patient without regard to head position, then image correlation can be achieved by computer matching anatomical or applied reference points.

i. The use of anatomical reference points

Surface contours of the head

A retrospective technique for quantitative 3D image correlation of CT, PET,and MR images of the brain using a surface matching computer algorithm has been developed by Levin et al. (1988), and Pelizzari et al. (1989). The process of image correlation begins by outlining the contours of the head, including the scalp, as seen on serial slices of each scan. Using appropriate windowing, the surface contours of the scalp can be identified on CT and MR images. For PET images, the external surface of the head is defined from transmission images. 3D models of the surface to be matched are then created for each image set. Pairs of image sets are matched by translating, rotating, and scaling one image set termed the 'hat' to optimally match the second image set, termed the 'head'. The computer algorithm used a non-linear, least squares search procedure to perform automated coordinate transformation that minimised the mean distance between the 'hat' and 'head' surfaces. The residual mis-matching between the two surface models was found to be in the order of 1 - 2 pixel sizes in phantom studies. The computer software enables matched image slices to be displayed simultaneously. Furthermore, it allows superimposition of images so as to create hybrid images of, for example, MR and PET that will display functional abnormalities depicted by PET in their anatomical context as defined by MR. The authors claim that the significant advantage of this method is that it allows retrospective correlation using data acquired during routine clinical practice. This should be qualified, however, because the accuracy of the method is dependent on acquiring high resolution images throughout the head volume with narrow slice separations, so that the scalp surface may be optimally defined. In routine clinical practice CT images, for example, are generally acquired with slice separations of 10mm or 5mm, and narrower slice separations are usually confined to the area of interest to limit brain irradiation. For MR there is no such limitation, although the spatial resolution of the images is less ($\approx$2mm). The greatest limitation in this method is correlation of images involving PET. The poor spatial resolution of PET images with pixel sizes $\geq$4.5mm and slice thicknesses of .7 - 1.5cm., make surface definition difficult and unreliable.

Bony landmarks on the skull.

The skull is clearly depicted on x-ray CT but not on MRI,MRS, PET or SPECT images. The use of bony landmarks alone is therefore of no value in correlating multiple imaging modalities. Correlation of repeated

CT images by matching the positions of individual bony landmarks such as the clinoid processes crista gali etc., is difficult on axial CT slices, and so they have not been used alone as a reliable means of image correlation. Repeated CT images could, however, be correlated using the 'head in hat' method, as previously described, by using the surface contours of the skull rather than the scalp to match paired images.

Landmarks in the brain.

A method of retrospectively correlating multiple-brain images using internal cerebral landmarks has been described by Maguire et al (1985). Using up to ten landmarks identifiable on CT, MR and PET images, computer correlation was achieved with a mathematical matching algorithm. However, difficulty in identifying the precise location of individual brain landmarks, especially on poor resolution PET images resulted in correlation errors of several millimetres. More accurate image correlation of structural (e.g., CT and MR), and functional images (PET and SPECT), has been achieved by Pietrzyk et al. (1990), using the surface contours of the brain to provide multiple 'landmarks'. Brain contours are enhanced using appropriate filtering and multiple slices are displayed in all 3-dimensions. Image correlation is achieved by eye, using an interactive computer programme which will allow the brain contours from one imaging modality to be superimposed on reference images from another modality. A matching accuracy of within 4mm of translation and 3°s of rotation has been demonstrated for correlation of MR and PET using this method. In addition to the limited accuracy, this process of correlation is time consuming and requires an operator with expertise in neuro-anatomy to appropriately match the images.

ii. The use of applied reference points:

Fixed to the external surface of the head.

Radio-opaque markers bonded temporarily to the scalp are unsatisfactory for precise image correlation due to scalp movement and are obviously not suitable for matching images from long term follow up studies. These problems have to some extent been overcome by Wilson and Mountz (1989), who developed a reference frame that can be non-invasively relocated on the head, using the external auditory meati as the prime site of location. From the reference frame the image plane orientation (angle) and image plane level can be derived from axial images. The reference frame (fig. 6) is configured as two equilateral triangles made of nylon bars set on each side of the head. Each triangle has a vertical segment perpendicular to the base and extending to the apex. Continuous 1mm diameter tubing lines the bars of both triangles and is filled with radio opaque contrast media. Ear-plugs attached to the base of the triangles fit snugly into the external auditory meati and provide a pivot point around which the base of the reference triangles can be adjusted. The ear-plugs are, in addition, attached to a nylon band that passes over the patient's vertex and is continuous with an elasticated chin-strap. These cooperate to hold the ear-plugs and thus the reference

frame firmly in position.

Prior to imaging the frame is adjusted so that the anterior portion of the base of each triangle is aligned with the lateral canthus (i.e., the base is positioned along the canthomeatal line). The reference tubing is filled with an appropriate contrast media, which for CT is an iodine based contrast agent; for MR is nickel chloride solution, and for PET a solution of radionuclide tracer. On each axial image slice the contrast/tracer filled tubing is intersected at six positions that are seen as six dots. The angle of the image plane is determined from the ratio of the distance between the anterior and middle dots to the distance between the middle and posterior dots. The level of the image plane is determined by the distance between the anterior and posterior dots after angle correction. Using the information that the reference system provides, multiple contiguous image planes can be matched. Head rotation is corrected for prior to image reconstruction by alignment of the dots (and images), to lie in the vertical direction. The images are then rescaled to the same pixel size.

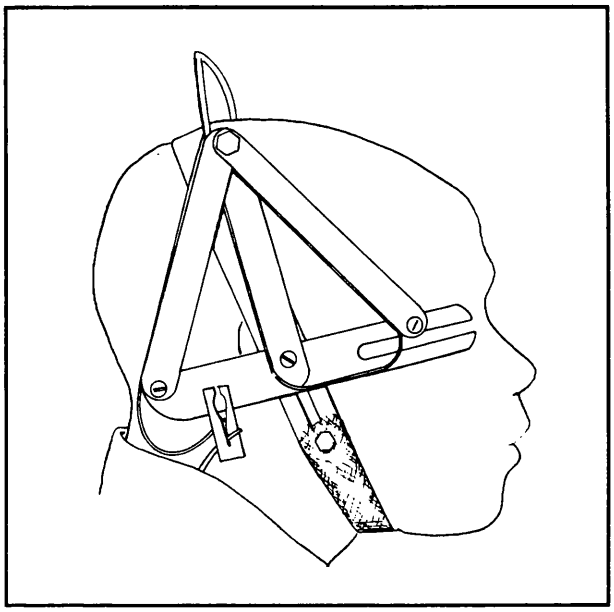


Figure 6 Wilsons Relocatable Reference System

The head frame has been used by the authors to correlate functional PET images with anatomical MR images. They tested the reproducibility of the frames placement on fifteen subjects by measuring the displacement of markers on the frame with respect to ink marks drawn on the test subjects heads. The average relocation error in the X Y and X dimensions were found to be 1.6, 1.6 and 1.5mm respectively, with an average 3D misplacement error of 2.7mm.

The accuracy of the reference system is also dependent on the accuracy of defining the position of each dot on the screen, using a cursor. The dot position selection was found to differ by no more than a 1 ± 1 pixel. Further sources of error in localisation are due to the small inter dot distances as the triangles converge towards the vertex and from movement of the subject's head during the scan.

Implanted in the skull.

Colombo et al. (1982) describes a method for transposing CT data into stereotactic space by implanting three reference points into the skull which are identifiable on CT image slices and radiographs. The reference points are lead balls set in acrylic screws which are screwed into the patients skull. They are a semi-permanent fixture, and while in position allow the stereotactic space to be exactly redefined.

The coordinates of a target are determined by taking contiguous CT slices through the head and recording the position of each reference ball and the desired target in terms of X and Y coordinates on the appropriate slice, using a cursor. As the slice separations are known, movement in the Z axis is defined, and the relationship between the target and the reference balls can be determined.

The system was developed for transposing image data into a stereotactic head frame for surgical procedures. This is achieved by fixing a conventional stereotactic frame to the head and measuring the relationship between the reference balls and the frame, from AP and lateral radiographs. A similar method was described previously by Seutens and Gybels (1979).

It would be feasible to correlate repeated CT images using implanted reference points as described, but as there is no universal marker that is visible on CT, MR, PET and SPECT, correlation with other modalities would not be possible. In addition, the use of such an invasive technique is not acceptable for image correlation alone and would only be appropriate where stereotactic procedures were contemplated.

Stereotactic frame fixed to skull

Accurate 3D correlation of multiple images with freedom of constraints regarding the orientation of the patients head in each scanner is best achieved by rigid fixation of a reference system or systems to the skull via a stereotactic frame. The methods of fixing a stereotactic frame to the skull with pins or rods has previously been described. The reference systems for this method, unlike those where head fixation is employed, must provide a true three dimensional solution to the problem of coordinate transformation.

Several such stereotactic localiser systems have been developed for coordinate transformation from CT images (Brown 1979, 1980, Dubois et al. 1982, Goerss et al.1982, Perry et al. 1980 and Dervin & Miles 1989). These take the form of a series oblique and vertical rods set around the frame, between 6 and 9 in number (fig.7). They are made of radio-opaque material such as carbon fibre which will not cause streak artifacts on CT images and are seen as a series of dots or ellipses on each axial image. The relative spacing of these reference points seen on an image allows calculation of the plane of the image relative to the stereotactic frame. Once the plane is defined any point on the image plane may be transformed into the stereotactic coordinate system. A computer programme is used to perform this

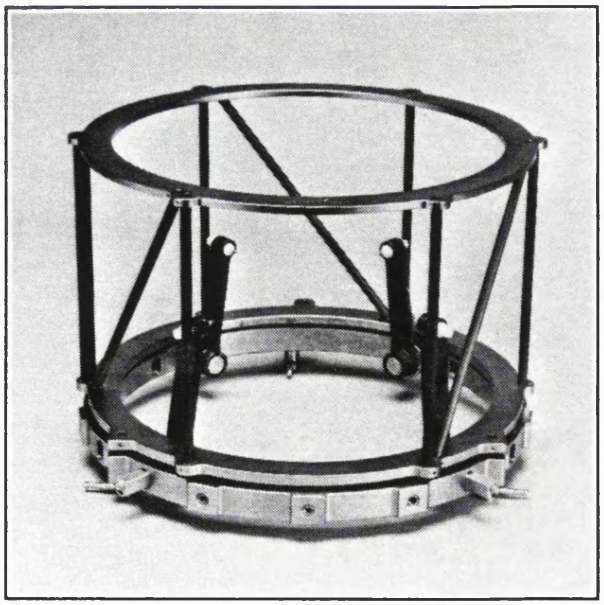


Figure 7 The BRW Stereotactic Frame

transformation.

The Brown Roberts Wells stereotactic frame (BRW),(Radionics Inc. Burlington Mass.), and the Kelly Goerss frame (Stereotactic Medical Systems Inc. New Hartford, NY13413) are commercially available systems and have an accuracy of target point determination using CT of between 1 and 2mm. Both systems have been modified to accommodate MR imaging.
The MR compatable BRW system employs a smaller head ring which fits in standard MRI coils and is constructed of anodised aluminium that is split to contain an insulated section thereby preventing eddy current formation. The MRI localiser consists of a box with open walls holding polycarbonate tubes filled with petroleum jelly on five faces. This configuration allows BRW coordinates to be calculated from axial, coronal and sagittal MR images because 3 sets of N shaped rods are seen in section on each image. The system has been tested using a phantom and T_1 and T_2 weighted images. Using 5mm scan slices targets were localised to a 5mm cube in three combined planes. (Heilbrun et al. 1987).
The Kelly Goerss frame has been adapted for MRI imaging by constructing the base ring from molybdenum disulphide (a non conductor) and using a multiplanar localisation system of similar construction to the BRW - MRI localiser. The localiser system is also capable of target determination within one MRI voxel (Kall et al. 1985).

Computer software packages have been developed for the BRW and the Kelly Goerss systems which will correlate CT and MR images by matching the stereotactic volumes in a common 3D computer matrix. In both systems this is aided by automated computer recognition of fiducial points on each image slice and the placement of that slice into its correct orientation in the 3D matrix. Matched axial, coronal or sagittal views or rendered 3D volumes can then be digitised simultaneously or superimposed. In addition the stereotactic coordinates of any point on an image can be automatically identified.

The BRW system also has provision for stereotactic PET or SPECT imaging. The localiser system for these modalities is of identical geometry to the CT localiser with the exception that the carbon fibre rods are hollow and accept radioactive line sources which are inserted during image acquisition. The stereotactic coordinates of chosen targets are determined from the images using the same computer software as for CT. The invasive nature of the frames fixation to the skull has however precluded its use for these types of imaging which are generally experimental.

As discussed previously invasive skull fixation is only applicable where stereotactic biopsy or therapeutic procedures are to be planned from the images. The method is not suitable for correlating images spaced over time.

EVALUATION OF THE METHODS OF MULTIMODALITY IMAGE CORRELATION

When evaluating the accuracy of the different methods of image correlation it must be appreciated that the geometric discrepancies between matched image pairs can only be measured to within the voxel size of the image with the lowest spatial resolution. Voxel size is a function of the pixel size and slice thickness. These vary considerably from system to system even of the same modality type. Representative examples of pixel size are $0.5mm^2$ for CT, $1mm^2$ for MR, $5mm^2$ for PET and $10mm^2$ for SPECT). Examples of slice thickness are 1.5mm for CT, 3mm for MRI, 7mm for PET and 10mm for SPECT. The spatial resolution of each imager is to a large extent governed by the physical parameters and sensitivity of its detector system. So that by reducing the voxel size in reconstructed images the signal to noise ratio will decrease with loss of image sensitivity. Likewise increasing the voxel size will increase image sensitivity but reduce spatial resolution.

Any computer manipulation of raw image data ie. by rotating, translating and reslicing it will degrade the spatial and contrast resolution of the image due to partial volume averaging. It is apparent then that the methods of multiple image correlation where the head is randomly positioned in each imager and which depend on such computer manipulations will be subject to greater matching error and loss of resolution. This is particularly so where images with large voxel sizes such as PET, SPECT and MRS are manipulated for geometric correlation. In these instances the degradation that can occur in the matched images can be so marked as to severely limit their usefulness.

Despite the practical disadvantages of precise head repositioning methods with their often elaborate set up procedures and the need to fix specialised head holders into each scanner they provide a more accurate means of image correlation with maintenance of image quality. Such methods require meticulous attention to detail and careful calibration of imaging hardware to minimise error. Any miscalibration of the gantry mounted cross laser systems, upon which the head repositioning methods are dependant, can lead to significant errors in coordinate transformation.

With scanners in regular clinical use, loss of laser alignment is not uncommon, and routine calibration with accurate phantom studies is essential prior to image acquisition. Even with correctly calibrated cross-lasers, accurate alignment with reference markers on a head holder can be hampered by poor tolerances in the fine adjustment of gantry angle and/or couch movement.

Errors in the method can also be introduced when acquiring CT data. This is because slice positioning is dependent on the mechanical advancement of the couch. Inaccuracies in couch movements which are either intrinsic to the scanner or due to wear in the drive mechanism will produce errors in direct coordinate determination, and misplacement of the slice position in the image matching computer matrix. Further error in coordinate determination may occur if the isocentric and parallel relationship between the head holder and the scanning plane is not maintained during couch advancement. This can be due to the sagging

of the couch under load, differential wear on the couch bearings, or due to the axis of couch advancement not being truly coincident with that of the gantry. This latter problem is not uncommon and results from imprecise alignment of the couch and gantry units during their installation.

These errors can be measured and to a greater extent corrected by attaching a stereotactic fiducial system to the head holder. This is best achieved by scanning through the top and bottom of the reference system with the patient in position and ensuring that the x,y coordinates of the vertical rods are maintained. If not then the frame position is mechanically adjusted. The slice separations can be determined from the relationship of obliquely positioned rods to the vertical as seen in section on the image.

For correlating images from multiple modalities the fiducial system is used to ensure correct placement of the image volumes into the image matching computer matrix. It should be noted however that coordinate transformation from fiducials alone will introduce small errors due to inaccuracies in centring the cursor on each fiducial (Zamorano et al. 1987).

The pre-requisite for accurate image correlation is not only that the head can be precisely repositioned in each imager, but that no movement occurs during image acquisition. This can only be ensured by invasively fixing the skull within a stereotactic frame which in turn is bolted to the scanner couch. By these means, and after correcting for image distortions in MR images, multi-modality image correlation can be achieved to within 1 - 2mm (Schad et al. 1987)[2]. This level of accuracy can be confirmed from matched CT and MR images which have spatial resolutions of this order of magnitude. With images that have larger spatial resolutions this accuracy of correlation has to be assumed by virtue of the method. Spatial resolution is optimised within matched image volumes by acquiring all images with the narrowest possible slice thicknesses and separations. This however, may considerably prolong the scanning time, and in the case of CT may expose the patient to unnecessarily large doses of ionising radiation. In functional imaging (e.g., PET, SPECT, and MRS), the longer scanning times necessary to improve spatial and contrast resolution are outweighed by the need to perform fast scanning procedures sequentially to measure dynamic changes. There are, therefore, trade-offs in the performance and application of imaging systems so that maximum resolution in the spatial, contrast (sensitivity), and time dimensions is not simultaneously achievable.

Although invasive fixation of a stereotactic frame to the skull will provide the most accurate means of image correlation, it is of course only acceptable where stereotactic procedures are to be performed from the combined data. The method is also not suitable for long term follow-up studies. The degree to which accuracy can be compromised in the choice of alternative methods of fixation depends very much on what information the clinician wishes to gain from the matched images. For example, the method of computer matching multiple images by the 'head in hat' method (Levin et al. 1988, Pelizzari et al. 1989), may

provide perfectly adequate data for quantitatively monitoring tumour growth using high resolution CT and/or MR images. The method does not require elaborate set-up procedures or head holders, and can be applied retrospectively on routinely acquired images from any scanner. Where a higher degree of accuracy is required, and particularly for correlations with functional images, head fixation using a stereotactic frame which can be reproducibly mounted on the head by a noninvasive means is the best alternative (Greitz et al. 1980 and Laitinen 1985).

To gain insight and understanding of pathological processes and structure/function relationships in the brain from correlated images, multidimensional display methods are essential. Tomography provides clear unambiguous views of two dimensional sections through the brain, using images which, by definition, contain no three dimensional information. Often it is difficult to interpret isolated tomographic images if an appreciation of three dimensional shapes and spatial relationships is required. The most common method used to resolve this dilemma is to scan and display a 'stack' of parallel tomographic images side by side on a multiformat film, or on a screen. This necessitates mentally reconstructing a representation of the structure of interest and its relationships, which is often both difficult and highly subjective.

Modern software programmes are now capable of depth encoding stacked two dimensional slices to achieve displayed images with a perception of the three dimensional shape and the relationships of various structures. Volumes or other regions of interest can be defined by contours, by density, or by shaded surface display with a fixed light source to give a realistic three dimensional surface rendering. The sophistication of these programmes is almost boundless; volumes can be coloured, cut in any desired plane, rotated around any axis, transposed from one image to another or viewed through semitransparent representations of their surrounding structures. These three dimensional display methods will give a rapid and efficient presentation of shape information, and allow quantitative comparison between the different modalities.

There are however, important factors to consider when measuring and comparing volumes on different images that can markedly affect the accuracy of quantitative comparison. These are the window settings on the displayed images and the voxel sizes of each image. The apparent diameter of an object will change with different window settings, increasing as the window centre approaches the background density. This is due to partial volume effects and occurs especially when evaluating spheres. Size estimates made with the window centre midway between the background and object density are most accurate. Volumes are calculated by adding the cross-sectional areas and multiplying by the slice thickness. The accuracy of volume determination therefore differs considerably between the different imaging modalities, especially where small volumes are involved. For example, if a 3mm sphere is imaged by CT the volume determination can be as little as 10% with appropriate window setting (or up to 30% with inappropriate window setting). For PET with large voxel sizes (e.g., 4 X 4 X 7mm), the minimum error in volume

determination of the sphere will be 800%, i.e., if it lies entirely within one voxel. If the sphere lies at the junction of 4 voxels, the error in volume determination may be as much as 6,400%.

Improved accuracy of image correlation will only come with reductions in the spatial resolution of each imager. This will require further miniaturisation of radiation detectors with adequate energy discrimination and signal to noise characteristics. Although there are continuing advances in this direction, an 'ideal' 3D imaging system that will provide, simultaneously and rapidly, all of the advantages and eliminate all of the limitations of the different imaging modalities is still in the realm of science fiction.

3. Integration of Multiple Brain Images with Stereotactic Procedures

STEREOTACTIC TECHNIQUE: Background.

Stereotaxis means a spatial (i.e., 3-dimensional) arrangement, that is:- the fixing of any point in space by the use of mathematical principles. The application of these principles to the study of the brain is credited to Victor Horsley and Robert Clarke in 1906 (Horsley & Clarke 1908). They were attempting to establish structure/function relationships in the cerebellum by making lesions in various tracts and nuclei, and observing the effects in experimental animals. The placement of a lesion generating electrode into a desired neuroanatomical target using a blind free-hand method is extremely unreliable, and this led Clarke to conceive of and develop the stereotactic methodology. He used the external auditory meati and orbital margins as external cranial landmarks from which to define the position of neuroanatomical structures with relative consistency (in the same animal species), using a 3-dimensional (cartesian) coordinate system. This he achieved by fixing a reference frame to the head isocentrically with, and in the plane of, the external cranial landmarks from which measurements could be made. The frame then acted as a platform from which an electrode could be guided to the selected target coordinates to make a lesion. By using this stereotactic method Clarke was able to produce functional maps of sections of the brain of the cat and monkey. He also anticipated the therapeutic possibilities of applying his instrument in humans. In particular, he thought his instrument could be used to implant radium for the treatment of brain tumours, or to relieve pain by coagulating tracts within the brain through a small burr hole (Clarke 1921).

A E Mussen, a physiologist who collaborated with Horsley and Clarke, designed the first stereotactic instrument for use in humans in 1918, but was unable to convince a neurological surgeon to use the device, (Pickard et al. 1983).The stereotactic method for subcortical localisation was not used on humans until the late 1940's, by which time contrast ventriculography was well established which allowed intracranial landmarks to be identified. From these, the position of specific nuclei and tracts could be established with greater accuracy than by the use of cranial landmarks. In addition there had been considerable advances in experimental neurophysiology, and the effects of different ablations and destruction of parts of the brain were known and had been applied to humans with otherwise intractable functional syndromes. The possibilities of using stereotactic localisation and guided procedures to treat functional disorders, as an alternative to open procedures with gross tissue destruction and undesirable post-operative sequelae, was realised by several groups who developed instruments and techniques in close succession.

The first human stereotactic operation was performed by Spiegel and Wycis in 1947, in which they made a lesion in the dorsomedial nucleus of the thalamus as an alternative to the open psychosurgical procedure

of pre-frontal lobotomy. Their original stereotactic frame was fixed to the head with plaster, (Spiegel et al. 1947), but was subsequently modified to include rigid skull fixation with pins to limit movement error (Spiegel et al. 1951). Later they produced the first atlas of the human brain for use in stereotactic surgery (Spiegel & Wycis 1952). This used the posterior commissure which can be identified on ventriculography, as a single intracerebral reference point in combination with several external cranial references.

These developments opened the way to treat other functional disorders such as intractable pain, epilepsy, and movement disorders by applying the same method. In the 20 years that followed the introduction of human stereotaxy (1947 - 1967), stereotactic functional neurosurgery flourished in centres throughout the world, and with this came advances in instrumentation and in the mapping of deep brain structures.

Talairach developed a stereotactic frame in 1949 (Talairach et al. 1949), and introduced the concept of teleradiography to minimise errors due to parallax and magnification. He produced an atlas that related the position of subcortical structures to the anterior and posterior commissures of the 3rd ventricle. (Talairach et al 1957). The use of these completely intracerebral reference points minimised errors introduced by the combined use of intracerebral and cranial landmarks. Talairach et al. (1967)introduced the combined use of ventriculography and angiography in stereotaxy for the placement of electrodes and for biopsy of brain tumours. In addition Talairach and Bancaud (1973) developed methods for localising epileptic foci in patients with temporal lobe seizures using multiple stereotactically implanted chronic depth electrodes.

In 1949 Lars Leksell developed a highly versatile stereotactic frame using the principle of a target centred arc (Leksell 1949). (fig. 8) Two years later he introduced the method of stereotactic radiosurgery for making lesions in functional targets Leksell (1951). By this method highly collimated beams of ionising radiation are delivered from multiple angles to the stereotactically defined target. The resultant dose gradient is extremely steep at the target site and produces a sharply circumscribed lesion of a prescribed diameter. The tissue adjacent to the target volume receives very little radiation. The first cases treated with stereotactic radio-surgery were patients with chronic-obsessive-compulsive states (Leksell et al.1955) subsequently the technique was applied to the treatment of patients with other functional disorders including a variety of psychoneuroses and intractable pain. The results of stereotactic functional

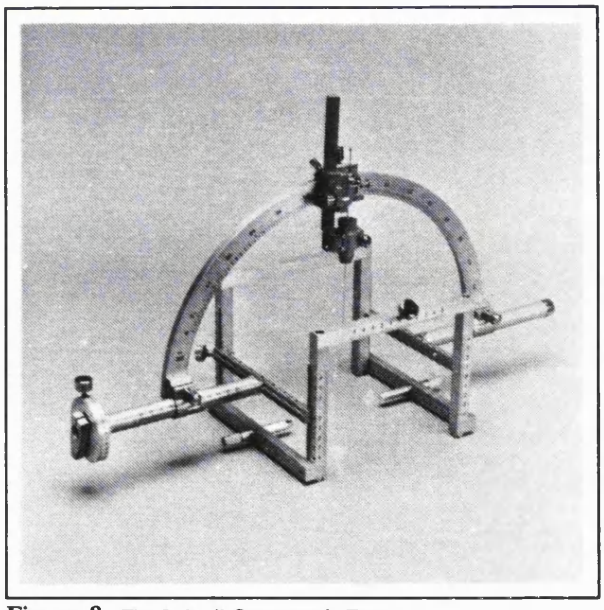


Figure 8 The Leksell Stereotactic Frame

procedures demonstrated that they were safer than open approaches with a mortality of 2% (Riechart 1962) as compared with 10% for open procedures (Meyers 1942). In addition the morbidity from stereotactic procedures was less with better post operative motor function than those having open procedures. These results proved to be the most satisfactory in Parkinsons disease and in the various pain syndromes. Nevertheless the introduction of dopamine drugs for the treatment of Parkinsonism by Cotzias et al. (1969) brought about a dramatic reduction in the number of stereotactic procedures performed and interest in the method waned.

The introduction of CT in the mid 1970's allowed direct visualisation of intracranial structures and lesions in a precise three dimensional data base. It was quickly realised that CT could be integrated with the stereotactic technique and that biopsy of small, deep and previously in accessible lesions would be possible. Several existing stereotactic frames were modified for CT compatibility (Boethius et al. 1980) and new systems were designed specifically for CT guided procedures (Koslow & Abele 1981, Perry et al. 1980, Mundinger et al. 1978, Brown 1979). To facilitate the continued use of traditional methods of target determination using ventriculography and angiography, for functional indications and the localisation of vessels,special floor stands and / or localiser plates were developed for the newer CT based systems (Heilbrun et al 1982, Bergstrom et al. 1986, Vandermeulen et al. 1987). These developments brought about a renaissance in stereotactic surgery and the development of many new techniques.

The ability of high resolution CT scanners to create multiplanar reformatted images has made it possible to accurately localise the anterior and posterior commissures on mid sagittal reconstructions of the 3rd ventricle. This has made it possible to perform functional stereotactic procedures without the need for conventional ventriculography (Lunsford & Martinez 1984, Laitinen, et al. 1985, Latchaw et al 1985). Computer resident stereotactic atlases have been created which can be scaled to superimpose with CT defined landmarks. Individual thalamic nuclei may then be selected by a cursor on the display console and stereotactic target coordinates calculated (Kall et al. 1985).

Further advances in functional neurosurgery include the stereotactic implantation of deep brain electrodes for chronic pain relief by transcutaneous electrical stimulation (Young et al. 1985), and the transplantation of foetal or autologous dopaminergic tissue into the striatum using stereotactic techniques in an attempt to ameliorate Parkinsonian symptoms (Backlund et al. 1985, Hichcock 1988).

The greatest advances that have followed the introduction of CT guided stereotaxis are for non-functional indications, primarily in the diagnosis and treatment of tumours. The accurate histological diagnosis of brain tumours is essential to determine prognosis and plan appropriate treatment but perhaps of equal importance is to prevent the possibility of in appropriate treatment. (Hoffman et al. 1980). CT directed stereotactic biopsy of deep seated, multiple, diffuse or small tumours has now become routine clinical practice in many

centres. This is due to the low complication rate and high diagnostic yield associated with the technique. In reported series mortality rates are less than 1%, morbidity between 1 and 4% and diagnostic yield between 96% and 98% (Lunsford et al. 1986, Apuzzo et al. 1987, Kelly et al. 1984, Thomas and Nouby 1989).
Stereotactic biopsy of brain stem lesions is also feasible with equally low mortality rates and high diagnostic yield (Ostertag et al. 1980, Albright et al. 1983).

A number of stereotactic procedures have been developed which are of direct therapeutic value in the management of tumours. Cystic gliomas, craniopharyngiomas and colloid cysts may be aspirated stereotactically or have in-dwelling catheters inserted for repeated aspiration. The injection of beta-emitting isotopes into craniopharyngiomas will additionally prevent or inhibit cyst recurrence. With a stereotactically guided endoscope excision of 3rd ventricular cysts is also possible.

The technique of stereotactically implanted interstitial brachytherapy predated the development of CT by 20 years (Talairach et al. 1955, Boyesen and Campbell 1955). The ability to accurately define tumour volumes and shapes from CT data increased interest in this form of therapy. Precisely placed radionuclide sources (eg ^{125}I or ^{192}Ir) create an isodose distribution that conforms to the CT defined 3D shape of the tumour. By this means high doses of radiation are delivered to the defined tumour volume alone. The method provides satisfactory palliation for high grade gliomas but is most effective with well demarcated low grade gliomas (Gutin et al. 1981).

The treatment of brain tumours using Leksell's method of stereotactic radiosurgery also became feasible after the introduction of CT. The 'Gamma Knife' (Leksell 1971), developed in Stockholm, delivers focused radiation from 200 radially positioned Cobalt ^{60} sources that are housed in a shielded unit. The stereotactically defined tumour volume to be treated is placed at the point of beam intersection and the size of the treatment volume varied by the exchange of collimator helmets.
The method has been used to treat intracranial tumours that are generally non malignant and small including pituitary tumours, craniopharyngiomas, pineal tumours, meningiomas and acoustic neuromas.

The results of treatment for these conditions appear to be very encouraging (Leksell D.G. 1987) but await controlled trials. The considerable capital cost of 'Gamma Knife' units, of which only a handful exist world wide, has encouraged the development of an alternative method of delivering stereotactic irradiation using conventional linear accelerators (Betti and Derichinski 1983, Colombo et al. 1985). This is achieved by positioning the stereotactically defined volume at the isocentre of the collimated linear accelerator beam and by a combination of couch and gantry movements irradiating the volume in a series of non-coplanar arcs. Trials of this method for treating a wide range of tumours are currently in progress.

The CT directed stereotactic method is particularly useful in localising superficial cortical lesions which can be resected by conventional means through small craniotomies. In addition instruments have been developed which will allow the guided extirpation of deep intracranial lesions. (Kelly & Alker 1980, Sheldon et al. 1980). The method of resecting deep intracranial lesions described by Kelly requires the interpolation of the tumour volume from digitised tumour boundaries in a 3D computer matrix. The tumour volume is then sliced by the computer orthogonally to a specified stereotactic approach angle avoiding critical areas. Using a trephine craniotomy a cortical incision is made and a cylindrical retractor inserted to create a shaft through the brain to the tumour. The surgeon monitors the position of the retractor in relationship to the reformatted planar tumour boundaries on an operating room graphics monitor. By graduated advancement of the retractor the new relationship of the tumour boundaries can be monitored to allow complete guided resection. Kelly employs an operating microscope and an interactive carbon dioxide laser to achieve tumour resection with minimal trauma to the surrounding brain tissue. The technique is suitable for the total excision of small, deeply situated, metastases and benign lesions where the boundaries tend to be regular and well defined.The situation is different with intrinsic lesions, especially infiltrative ones; when there is great difficulty in identifying the true tumour limits by CT or intraoperatively.

Further stereotactic methods directed towards the adjuvant therapy of brain neoplasms after cytoreduction are presently under investigation. These include photo-irradiation of dye sensitised tumours with laser light delivered through stereotactically implanted glass fibres; stereotactically directed radio frequency hyperthermia by magnetic loop induction and the local infusion of cytotoxic agents into stereotactically localised lesions.

As with intra cranial tumours, CT directed stereotaxy has an important role in the diagnosis and treatment of intracranial; infection. Evacuation or biopsy of infectious material for bacteriological investigation is easily accomplished with stereotactic localisation. This minimally invasive method is of increasing importance with the advent of Acquired Immune Deficiency Syndrome. Deep seated brain abscesses are most effectively treated by stereotactic aspiration and this also allows the instillation of antibiotics into the cavity; (Wise & Gleason 1979).

With angiographic localisation selected vascular lesions have been managed by stereotactic techniques. Stereotactic radiosurgery is most effectively applied to the treatment of small arteriovenous malformations which can not be handled by microsurgery (Steiner et al. 1974). It is possible to apply clips to the necks of aneurysms and to feeding vessels of AVM's (Kandel and Peresedov 1980). Procedures for the intraluminal thrombosis of intracranial aneurysms by the stereotactic injection of ferroacrylate solution has been described by Alksne et al. (1967) and by the insertion of fine copper wire coils by Mullan (1969).

Deep seated primary haematomas associated with a decreased level of consciousness have been successfully

treated with stereotactic aspiration when conventional surgery would be hazardous. This method has been particularly useful in the treatment of primary brain stem haematomas due to cryptic AVM's (Beaty & Zervas 1983) and to treat hypertensive brain haemorrhage of the basal ganglia; (Matsumoto and Hondo 1984). In primary lobar haematoma stereotactic aspiration gives comparable results to microsurgical techniques and so the indication is only relative.

Finally CT based stereotaxy can be applied to the treatment of acquired obstructive hydrocephalus or late onset acqueductal stenosis by stereotactic 3rd ventriculostomy. This is achieved by creating a communication between the third ventricle and the interpeduncular cistern using a stereotactically directed leukotome (Kelly 1990).

Following the introduction of MR imaging into clinical practice a number of CT based stereotactic systems were adapted for MR compatibility (see previously). These systems have been used primarily for non functional stereotactic procedures to exploit MR's increased sensitivity in detecting the presence of neoplasms not visible, or poorly visible on CT and to achieve a better understanding of the significance of the images; (Thomas et al. 1986, Lunsford et al. 1986). Biopsy targets are generally selected from T_1 weighted images due to the difficulty in distinguishing tumour from surrounding oedema on T_2 weighted images. Although T_1 images may show well circumscribed lesions when no lesion is visible on CT they tend to be non-specific in terms of histopathological typing. At present, if a lesion is visible on both CT and MR, contrast enhanced CT has the advantage of displaying inhomogineities and areas of probable necrosis within the tumour which aids target selection to achieve diagnostic tissue. With low grade malignancies MRI appears to be better than CT at defining a tumour boundary. With the advent of spatial reconstruction by computer and subsequent stereotactic excision or radio surgery, cure of these lesions may be feasible (Laster et al. 1984).

The application of MRI directed stereotaxy for functional procedures has considerable potential advantages over standard radiographic techniques including computerised tomography. Among these are the clear contrast of grey white matter which allows direct visualisation of important functional targets such as the amygdala and hippocampus in 3 planes (axial, coronal and sagittal). This facilitates direct target selection from MR images for deep electrode placement in the investigation of epilepsy without dependence on indirect referencing and may obviate the need for ventriculography in certain functional procedures such as stereotactic cingulotomy and amygdalotomy (Maxwell et al.1987). In addition MR can be used to accurately define the site and extent of radiofrequency lesions (Leksell et al. 1985) or corpus callosum section allowing correlation with seizure and behavioral outcome (Maxwell et al. 1987). Never the less an accuracy of target definition comparable to ventriculography or CT has not yet been demonstrated (Leksell et al. 1985, Villemure et al. 1987) and until spatial resolution and image distortions improve, the use of MRI alone will not be accepted.

As the spatial resolution and sensitivity of Digital Subtraction Angiography (DSA) has improved it has replaced conventional stereotactic angiography (using the same localisation methods) in a number of centres. (Olivier et al. 1985, Kelly 1984). Although the spacial resolution of DSA ($\pm$1mm) is worse than conventional angiography there are considerable advantages to the stereotactician in having the information in digitised form. It can be incorporated into a computer data base containing other images for treatment planning of vascular lesions for trajectory simulation to avoid vessels. Since DSA presents projections rather than the volumetric information provided by stacked computer tomographic images it can not be geometrically correlated with these in the same way. However, with combined AP and lateral projections coordinates established from DSA images can be transposed to other images taken under the same stereotactic conditions.

The development of functional imaging methods with PET, SPECT and MRS now permit quantitative 3D in vivo measurements of local haemodynamics, metabolism, biochemistry and pharmacokinetics in the human brain. This has provided a strong impetus to incorporate this complementary information into the stereotactic database to provide a better understanding of structure / function relationships in the brain and because of the considerable advantages such information may have in planning both functional and non-functional stereotactic procedures.

STEREOTACTIC TECHNIQUES EMPLOYING MULTIPLE BRAIN IMAGES

The capacity to integrate multiple brain images with stereotactic procedures has important application in brain research and in all aspects of stereotactic neurosurgery.

Material taken from stereotactic biopsy can be examined histologically, biochemically or by radioimmunassay or alternatively put into cell culture for in vivo experimentation. Thus the ability to take biopsy material from a region of interest selected from any image using the stereotactic method allows both functional and structural pathological change to be exactly correlated with the display screen intensities seen on any biomedical imager. Such correlations are of critical importance in the interpretation of brain images and in understanding the nature of pathological processes in the brain.

When primary brain tumours are imaged with CT, MRI or PET each imaging modality will show a different apparent tumour boundary. A knowledge of the relationship between the histological boundaries and the apparent tumour boundaries as depicted on images from the different modalities is essential for the optimum treatment of brain neoplasms, whether by guided surgical resection or radiotherapy. This relationship can be established with serial stereotactic biopsy planned from correlated images. Several such studies have been undertaken. Histology obtained from serial stereotactic biopsy in patients with supra tentorial gliomas have been compared with findings on CT and MR images (Lunsford et al. 1986, Kelly et al. 1987),CT and PET imaging (Mosskin et al. 1985), and CT, MR and PET imaging (Mosskin et al. 1989). The general conclusions that can be drawn from these studies are as follows:

MRI is the most sensitive method for detecting gliomas and T_2 weighted images are best at delineating the extent of isolated tumour cell spread, although isolated cells have been shown to extend beyond this area. MRI is poor at differentiating the solid component of tumours from surrounding infiltrated and oedematous tissue. Gadolinium enhancement of T_1 weighted images correlate with areas of neovascularity rather than with tumour proper.

Contrast enhanced CT will define the edge of the solid component of highly vascular malignant gliomas, but in less vascular and low grade gliomas it is poor at defining the boundary. It is also poor at defining the extent of spread of isolated tumour cells.

PET using "C-methionine as a tracer seems to outline the homogenous viable tumour tissue better than CT and MR in most cases, which makes it the imaging method of choice for planning biopsy, surgical resection or radiotherapy. Grading of gliomas is accomplished most efficiently by the combination of PET using ^{18}F-flurodeoxyglucose (FDG) and contrast enhanced CT. Areas of higher grade within inhomogeneous gliomas can also be identified with this combination of images (Targeting these areas for biopsy can prevent down grading of a tumour and selection of inappropriate treatment).

These findings point to the need for using the correlated information from multiple imaging modalities to most accurately and effectively plan stereotactic tumour biopsy, resection or radical radio-therapy. This particularly applies to treatment planning for low grade lesions which are potentially curable.

For stereotactic biopsy of lesions in close proximity to major vessels, the use of stereotactic angiography (or DSA) in combination with CT and MRI is advisable so that trajectories may be safely planned. Inadvertent rupture of a vessel during the passage of a probe is the greatest cause of morbidity and mortality in stereotactic biopsy. Stereotactic correlation of angiographic data with CT is also of importance in planning the treatment of AVMs with stereotactic radiosurgery, where CT is needed to provide a map of the radiation attenuation coefficient, so that dose distributions can be calculated.

When planning functional neurosurgical procedures it is often necessary to combine information from a variety of imaging modalities to accurately locate and safely reach functional targets. Stereotactic PET scans are capable of identifying epileptic foci when no lesion is visible on CT or MRI, and even when surface EEG data are unable to identify a unique focus. Anatomical localisation of PET defined epileptic foci for stereotactic implantation of recording or lesion generating electrodes, requires geometric correlation with CT or MRI performed under the same stereotactic conditions. In addition, the use of stereotactic angiography is advisable to plan trajectories with the avoidance of vessels. The ability of stereotactic PET imaging to localise functional targets in combination with images that will define their anatomical relationships is likely to have a major impact on all aspects of functional neurosurgery in the future. This would apply to the treatment of chronic pain, motor disorders, and psychological disorders in addition to epilepsy.

Most modern stereotactic systems are capable of collating image information from multiple modalities and allow coordinate transposition between images to plan procedures. In recent years special computer software programmes have been developed that are fully integrated with the stereotactic hardware, and provide rapid semi-automated image correlation thereby reducing transposition errors that are prone to occur with the more laborious manual methods. These programmes tend to be user friendly and highly interactive, and facilitate comprehensive volumetric treatment planning of a multitude of stereotactic procedures. An example of one such system is that developed at the Mayo Clinic (Kall 1987), which facilitates treatment planning and interactive surgery using CT, MRI and DSA data.

The sophistication of such computer interactive stereotactic systems continues to evolve with advances in computer technology and microelectronics to the extent that in the foreseeable future, robots could replace the stereotactic neurosurgeon for many guided procedures. Nevertheless, for such systems to exploit the information from multiple imaging modalities head fixation in a stereotactic frame during image acquisition remains a pre-requisite for accurate image correlation and treatment planning.

Invasive methods of head fixation in a stereotactic frame using pins driven into the outer table of the skull causes patient discomfort, and confines the time available for image acquisition and treatment planning to the immediate pre-procedural period. This would generally exclude PET scanning as an imaging option

where the acquisition time may be several hours, or require transferring the patient from his hospital to a PET facility some distance away. Methods for relocating a stereotactic frame using invasive fixation (i.e., relocatable rods in the outer table of the skull) will allow some spacing between investigations and the procedure over a few days. However, it is unpleasant to have the frame fixed once by this method let alone several times. The alternative method of non-invasive relocation is most desirable in that multimodality image acquisition, complex treatment planning and stereotactic procedures can be spaced over time at the convenience of the clinician. The method also opens up the possibility of repeating stereotactic procedures without the need for repeated imaging and treatment planning between episodes. This has particular application to the treatment of intracranial lesions with fractionated stereotactic irradiation. In addition to these advantages, the ability to repeatedly establish the same stereotactic coordinates on multiple and repeated brain images has important application in objectively monitoring pathological change and response to treatment, and in basic brain research to establish structure/function relationships.

As previously discussed, although several methods have been developed for the non-invasive relocation of a stereotactic frame, none has provided sufficient accuracy of relocation and rigidity of head fixation, combined with good patient tolerance to make it generally acceptable for these applications.

OBJECTIVES OF THE PROJECT

The prime objective of the project is to develop a practical method of geometrically correlating multimodality brain images which can be integrated with stereotactic procedures and applied in both clinical and research settings.

The intended means of accomplishing this is to develop a relocatable stereotactic frame which can be non invasively fixed to the head for multimodality image acquisition and to correlate multiple images in a 3 dimensional computer matrix with reference to applied fiducials. For stereotactic procedures the frame will act as a platform from which to guide instruments to targets selected from the image information.

Considerations in the design of the head frame are that it should meet the following 'ideal' criteria:-

1. The method of non invasive fixation to the head should be well tolerated by the patients.
2. The frame should be rigidly fixed with respect to the skull to minimise movement during investigative and therapeutic procedures.
3 Repeated fixations over an extended period (ie many months) should be highly reproducible with a 3 dimensional repositioning error not exceeding 2mm.
4. The design of the frame should be such that it will accommodate the full range of head sizes and can be fixed to the head in any desired orientation.
5. The frame should be compatible with existing stereotactic equipment so that operative procedures can be performed.
6. It should be constructed of lightweight and rigid materials that will cause no artefact on the various biomedical imagers, including X-ray Computer Tomography, Angiography, Magnetic Resonance Imaging and Positron Emission Tomography.
7. Fixation of the frame to the head should be uncomplicated and swift.

CHAPTER 2

THE DESIGN OF A PROTOTYPE FRAME

Description of prototype frame

Method of patient fixation

Discussion

DESIGN OF PROTOTYPE FRAME

Description of prototype frame

The prototype frame (figs.9&10) consists of a base plate on which conventional stereotactic equipment may be mounted. This is located on the head in a desired position by means of a 'localiser' unit, which employs a dental impression of the upper jaw, and an adjustable head rest which contains a moulded occipital pad. The frame is rigidly fixed in position by an upward force provided by straps which pass over the head.

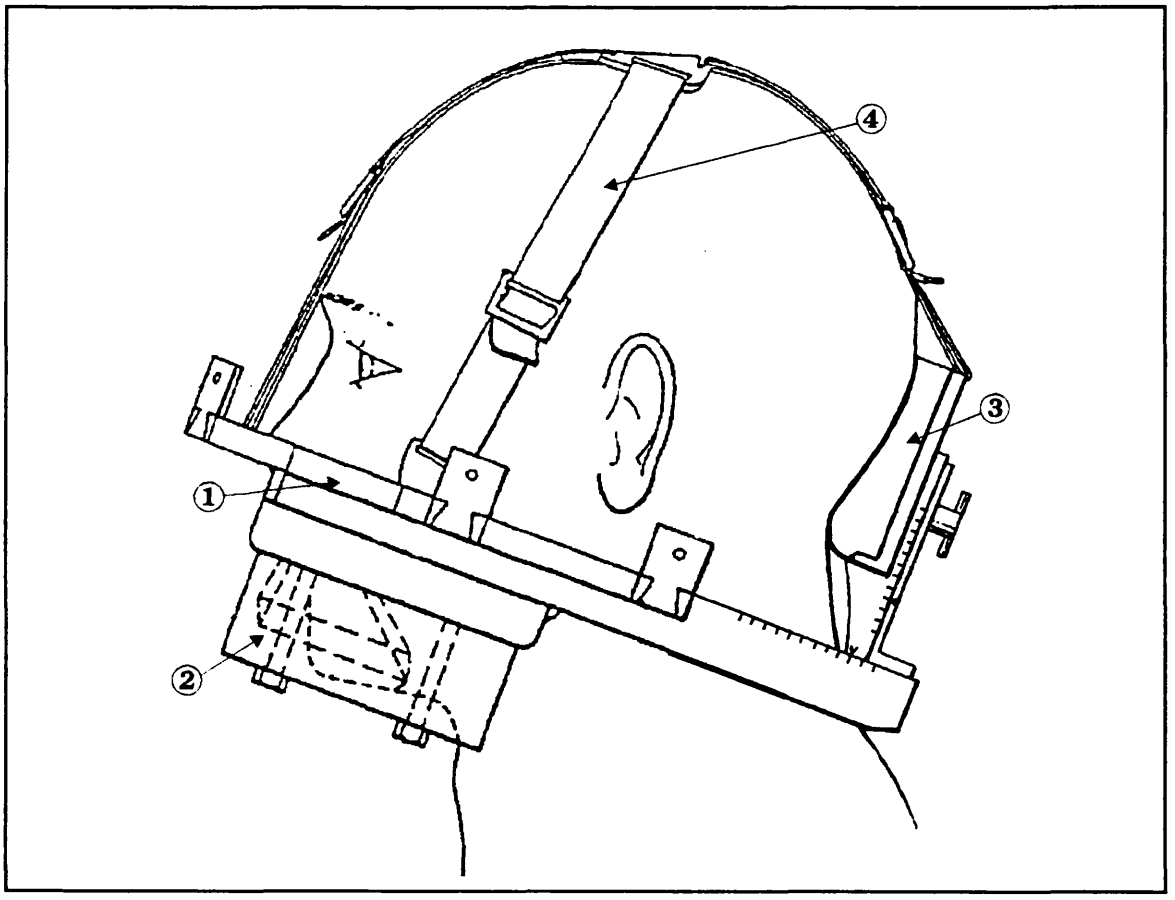


Figure 9 Lateral view of prototype frame

1. Base plate
2. Localiser unit
3. Head rest
4. Straps

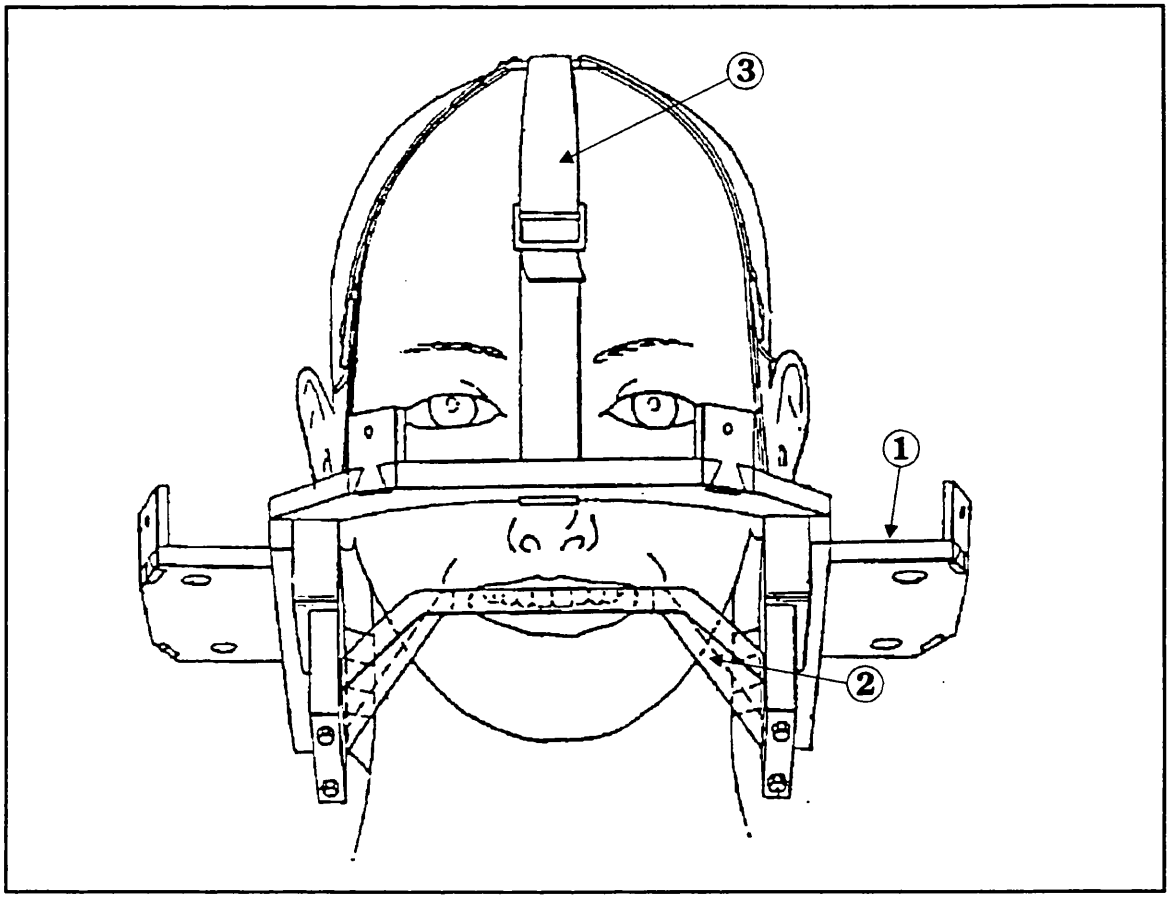
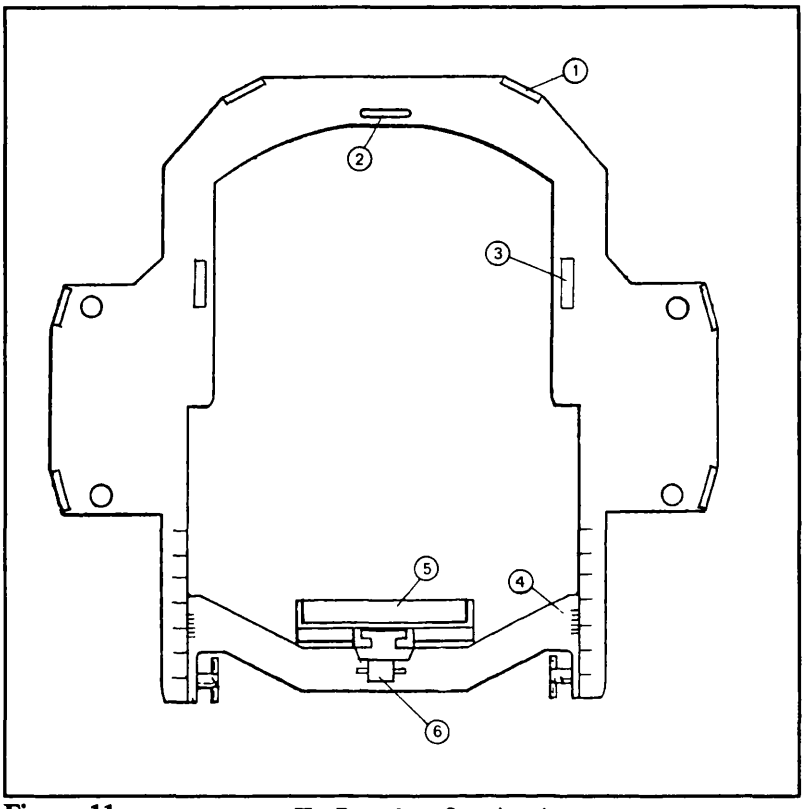


Figure 10 Anterior view of prototype frame

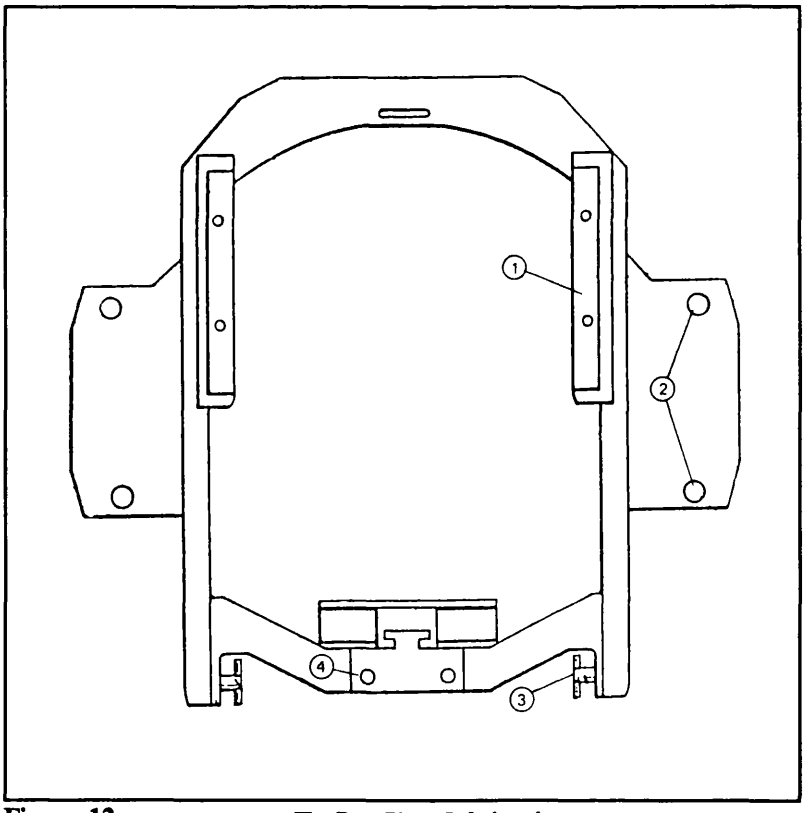
1. Base plate
2. Localiser unit
3. Straps

The baseplate (figs. 11 & 12) comprises a U shaped platform between the limbs of which is positioned an adjustable bracket carrying the head rest. The base plate in combination with the head rest bracket therefore forms a closed annular frame. It has laterally placed wings accommodating fixation holes so that it may be fixed within biomedical imagers or on to an operating table via an appropriate holder.The base plate was designed to accommodate fixation of the Brown Roberts Wells (BRW) stereotactic system. By exploiting existing screw holes in the BRW ring it can be fixed to the base plate with self centring conical screws via appropriately positioned lugs. The base plate is made of an epoxy based composite material containing finely woven cotton fabric, Tufnol 6F/45 (Tufnol Ltd. Birmingham).



1. Lug for locating BRW head ring
2. Anterior strap fixation point
3. Lateral strap fixation point
4. AP slide vernier
5. Head rest tray
6. T-clamp for head rest (vertical adjustment)

Figure 11 The Base plate: Superior view



1. Retaining box for positioning plate
2. Fixation holes for interface bracket
3. T-clamp for AP slide
4. Attachment of head rest post to adjustable bracket

Figure 12 The Base Plate: Inferior view

The Localiser unit (fig.13) comprises a dental piece fixed between two positioning plates. These components are provided as individual pieces made of acrylic ("Perspex" - Polymethylmethacrylate polymer). They are assembled and bonded together at the time of patient fixation and become specific to that individual. The positioning plates project vertically downwards from opposite sides of the base plate to which they are secured with bolts. They are retained in open boxes integral with the inferior surface of the base plate.

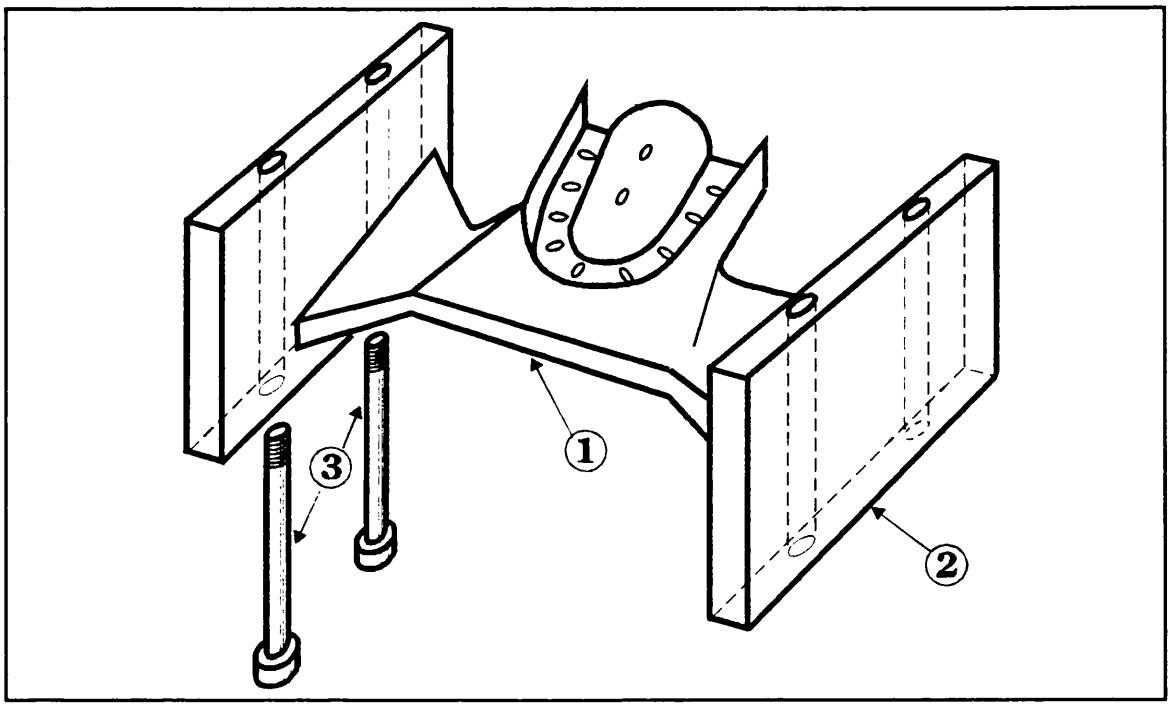


Figure 13: The Localiser Unit

1. Dental piece
2. Positioning plate
3 Securing bolts

The Dental piece is a dental tray which is integral with a bridge shaped supporting element. The dental tray is essentially a U shaped trough with a central dome shaped palatal section. Three sizes of dental tray have been found to be suitable to accommodate the full range of adult upper jaw sizes. They have multiple perforations which facilitate the locking in of the dental impression material. In addition they have built up sections positioned half way along their undersides, one on each side of the occlusal surface. The anterior half of the dental tray is incorporated into a flat central portion of the supporting element with which it is coplanar. Side portions of the supporting element extend downwards at an angle of 45 degrees from the central portion. They also extend rearwardly and are triangular in shape. The lateral edges of these side portions are long, and provide a large surface area of contact for bonding to the positioning plates.
The supporting element is constructed so that it's flat central portion is at an angle of 20° relative to its lateral edges, which are inclined upwards and anteriorly.

The head rest (Fig.14) is in the form of a tray into which a mouldable material is loaded at the time of patient fixation. It is carried on a bracket which is positioned between the U-shaped limbs of the base plate. The bracket slides between the limbs in T-slots and can be locked in a desired position with T-clamps. This antero-posterior position is registered on a Vernier scale. The head rest is connected to the bracket by an upwardly extending post along which it can be slid vertically and fixed at desired positions with a T-clamp. The vertical position is also registered on a Vernier Scale.

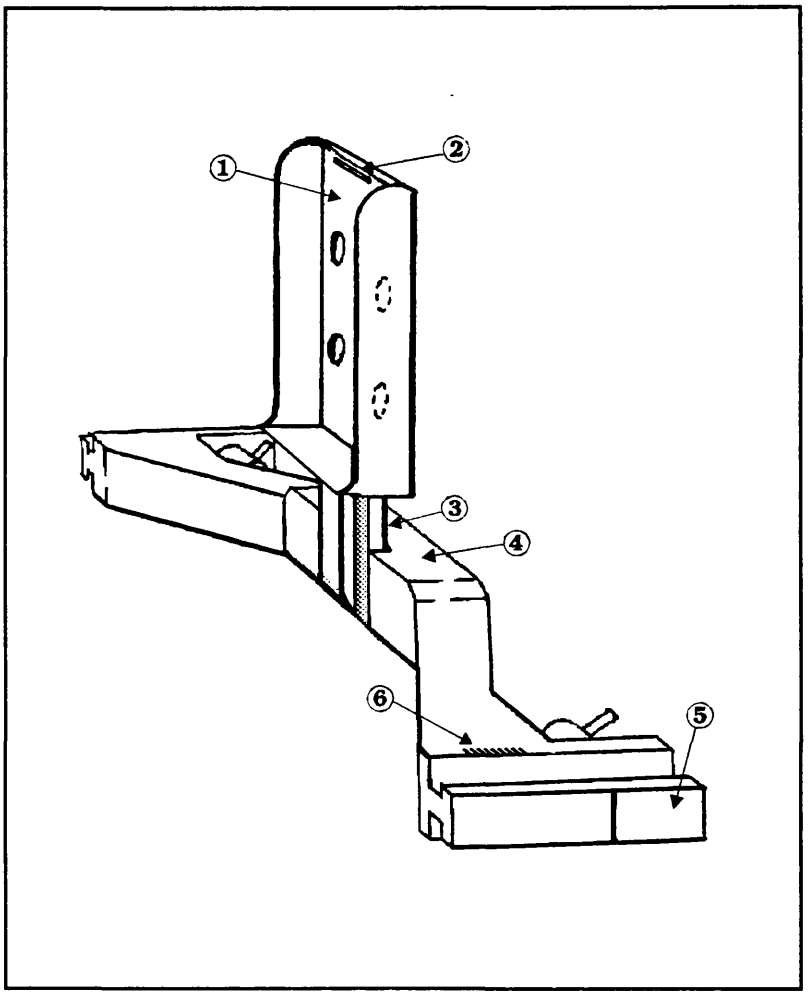


Figure 14. The head rest.

1. Head rest tray.
2. Fixation point for posterior strap
3. Vertical slide with Vernier scale.
4. Head rest bracket.
5. T-clamp - engages in limbs of base plate.
6. Vernier Scale, for AP adjustment

Four adjustable straps are attached to the frame (Figs. 9 & 10). One strap passing from the top of the head rest meets a second passing from the front of the base plate at a central connecting element. A further pair of straps pass from the connecting element, one to the right and one to the left side of the frame where they are attached to the base plate immediately above the centres of fixation for the localiser unit. The straps are made of woven nylon and the buckles of plastic.

Method of patient fixation

Fixation of the head is preceded by a full explanation of the procedure to the patient. The upper dentition is examined and a dental piece with an appropriate sized dental tray selected. The patient locates the tray on the upper jaw and bites on the built up sections on the under side of the dental tray (Fig.15), which engage with the lower premolar teeth.

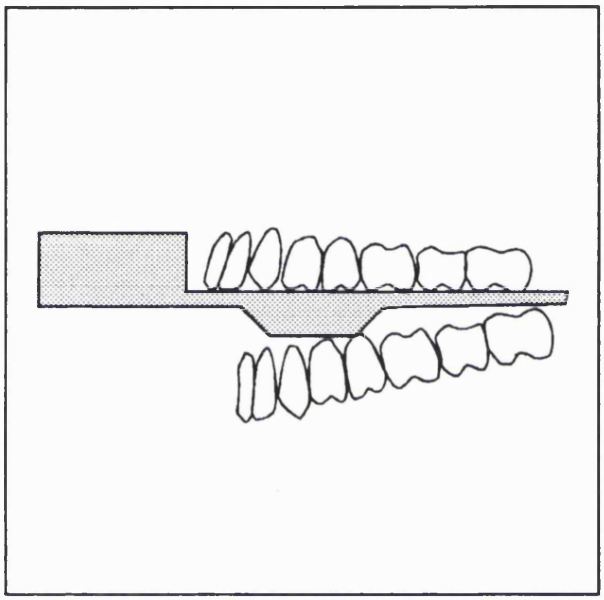


Figure 15

Patient biting on dental piece.(seen in section)

The built up section on the under side of the dental tray ensures even distribution of the occlusal force on the upper jaw.

Having checked the size, fit, and occlusion, the tray is removed from the mouth and a layer of an Acrylic impression material in a pre-set state is placed into it. The impression material used (PEM) contains polyethylmethylmethacrylate powder and a monomer of tetrahydrofurfurylmethylmethacylate with 2.5% volume/volume NNdimethylparatoluidene (Patel 1987, Braden et al. 1976). Three volumes of polymer are mixed with each volume of monomer. This is a non-irritant low exotherm mixture which polymerises and sets hard in several minutes with negligible shrinkage. When the impression material reaches a plastic state the dental tray is repositioned in the mouth and the patient bites, squeezing the impression material around the upper teeth and/or palate. When the impression material reaches an elastic rubbery state, before the final set, the tray is removed from the mouth. The process of removal clears the material away from the undercut areas around the teeth, allowing it to be subsequently repositioned, (fig. 16). When the impression material has set hard, which takes 2 - 3 minutes, drill holes are made through the infromedial edges of the tray in the region of the premolar teeth (Fig.17). The dental impression is next repositioned and the aforementioned holes now act as viewing ports which allow the clinician to see that the occlusal surfaces of the teeth have fully engaged with it. This is checked using a dental mirror.

The base plate with attached 'positioning plates' is next placed around the patients head and into the desired

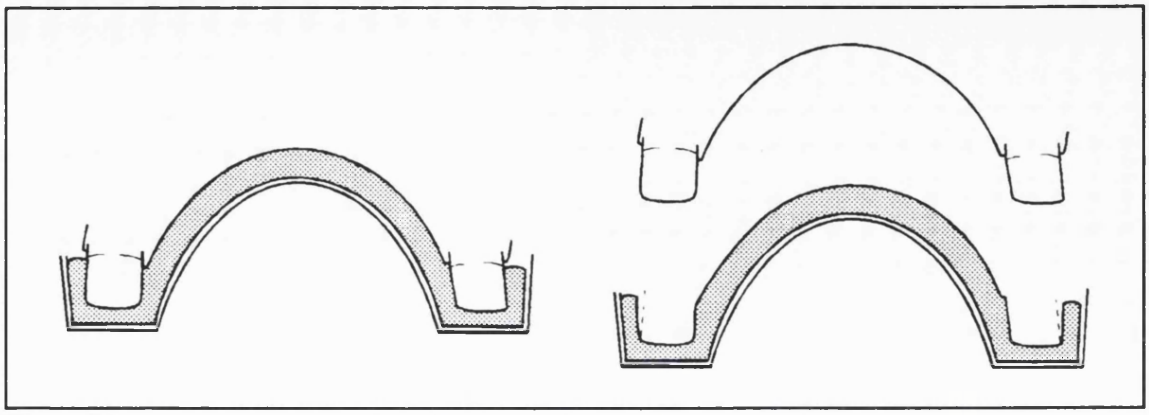


Figure 16 Forming a dental impression with automatic clearance of the undercuts of the teeth

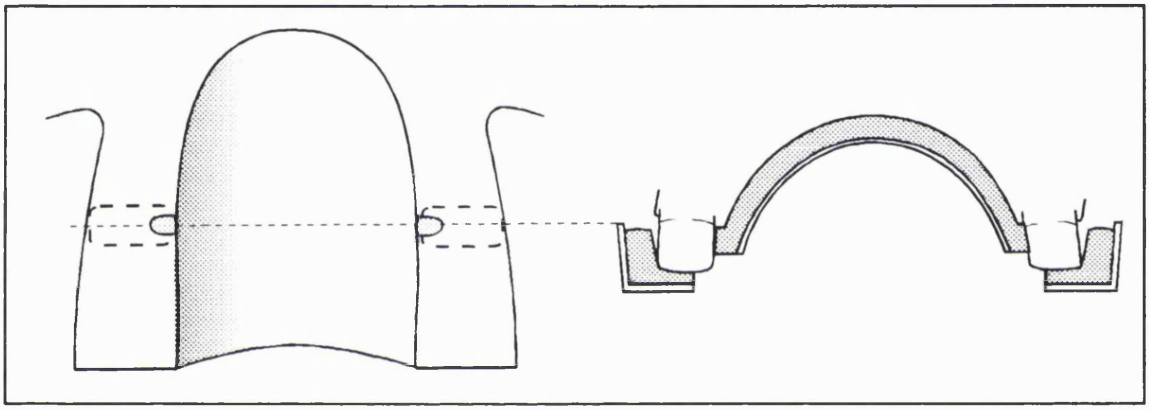


Figure 17 Inferior aspect showing holes X section

position. Positional adjustment of the base plate may be critical if the BRW Stereotactic frame is to be mounted on it. This is because the working space within the BRW frame (defined by its base ring, four head fixation posts and the stereoguide arc) is small. Positioning of the base plate in these circumstances is assisted by fixing to it a BRW Positioning Arc (Fig.18). This is a lightweight Perspex device, designed by the author which defines the BRW working space.

When the base plate is appropriately placed, the medial surfaces of the attached positioning plates have been brought into contact with the lateral edges of the supporting element which projects from the angles of the mouth. Their points of contact are marked on the positioning plates. The base plate and dental piece are then removed. The dental piece is now bonded to the positioning plates at this marked position, using a cold cure methylmethacrylate cement (Palapress clear. Kultzer GmbH. Wehrheim. Germany).

The acrylic cement is mixed with 3 parts polymer to 1 part monomer (volume/volume), and applied to the contact surfaces. The cement polymerises and sets in a few minutes. The frame is repositioned around the head and the patient bites on the dental impression. The head rest tray is loaded with a mouldable vinyl polysiloxane (Panasil^{R},Kettenback,D-6345, Eschenburg I.W. Germany). This is formed by mixing equal volumes of a base paste and a hardener paste into a malleable putty which will set into a dimensionally

stable hard rubber. The head rest is compressed against the lower rear portion of the patients head thereby forming an intimate mould which sets hard within 2 - 3 minutes.

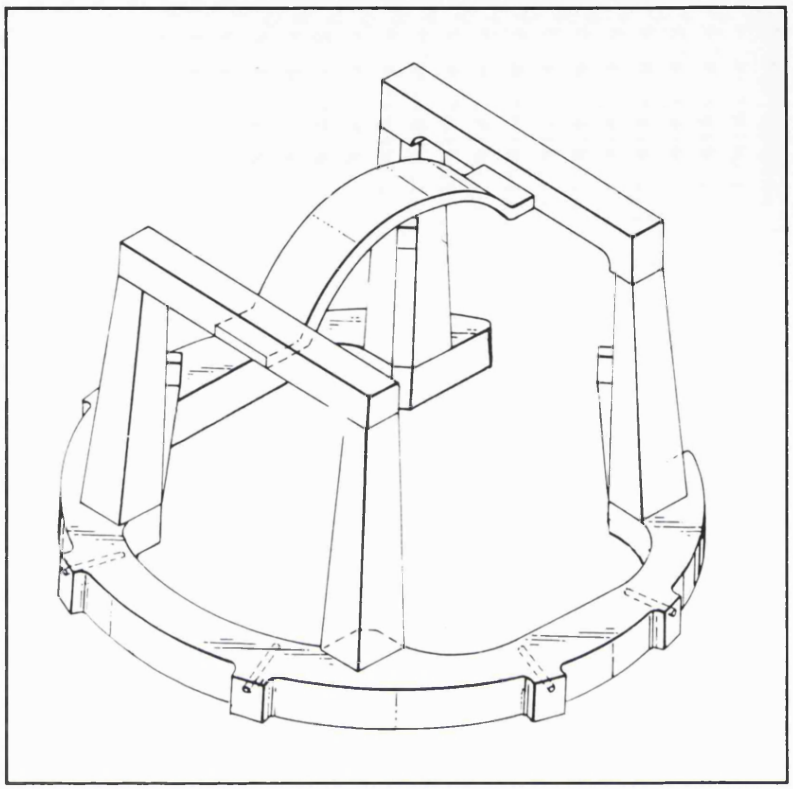


Figure 18
BRW Positioning Arc

A layer of polythene film (cling film) laid between the putty and the back of the head prevents the hair being caught up in the putty. The T-clamps on the head rest bracket and the vertical posts are locked and their positions, which are indicated on the Vernier scales, are recorded. These AP and vertical positions are marked with the patients name on the localiser unit. The straps are now connected to their respective buckles and the central connector positioned over the bregma. When firmly tightened the straps hold the Relocatable Frame rigidly in position. The patient no longer needs to bite on the impression and is free to talk. Stereotactic localisation devices or other instrumentation may now be secured to the base plate for imaging or treatment.

When the Relocatable Frame is removed from the head, the localiser unit may be detached from the base plate. This unit is small and easily stored and permanently records the unique relationship between the base plate and a given patients head. The patient specific moulded occipital pad is also detachable from the head rest tray, and this is stored with the localiser unit.

Relocation of the frame on the head is achieved by securing the patients localiser unit to the base plate. The patient then bites on the impression. The head rest containing this occipital pad is then adjusted to the previously recorded position and the straps are tightened.

Discussion

1. CHOICE OF MATERIALS FOR CONSTRUCTING THE FRAME

For the purpose of multiple imaging and guided procedures the frame should be constructed of materials that are light weight, durable, resistant to distortion and cause no artefact on biomedical images. Because the frame was designed in the form of a baseplate onto which conventional sterotactic instruments could be mounted it was not an absolute requirement that the materials should tolerate high temperature steam sterilization as the frame would be out of the sterile field during operative procedures.

Although metals can be machined to fine tolerances, are durable and resistant to distortion they have the disadvantage of being good electrical conductors. When placed in the magnetic field of an MRI scanner eddy currents will be induced within them. This is particularly so when the material is in the form of a ring. The eddy currents result in loss or distortion of the MRI image and generate heat within the conductor. Higher density metals in the imaging plane of a CT scanner may cause streak artefact, and when in a PET or SPECT scanner can absorb emitted gamma rays and again cause loss of signal and image artefact. Despite these disadvantages a number of 'MRI' compatible stereotactic frames such as the BRW, Leksell and OBT frames have been constructed from aluminium. When the aluminium is anodised and an insulated section is placed in the ring, major eddy currents are prevented. Never the less, smaller eddy currents will occur and when imaging close to such frames MRI images will be distorted or signal lost (Peters et al. 1987). The use of anodised aluminium is therefore a compromise solution; The advantages of its low density, durability, resistance to distortion and the fact that it can be machined to fine tolerances are balanced against local image artefact on MRI. It is of note that in many cases the ring is set low on the head and therefore the local eddy effects of small eddy currents will not significantly contribute to image artefact in the field of view. The low density aluminium is such that it does not generally cause streak artifacts on CT images.

My intention was to use the relocatable frame in a variety of biomedical imagers including high field strength (1.5 Tesla) MR spectroscopy. In these circumstances I felt that the frame should be constructed from a non conducting material to ensure that it would cause no image artefact. Non-conducting materials that would be suitable include a variety of plastics and composite materials. The material chosen to construct the base plate and head rest support was a composite material made of finely woven linen in an epoxy resin base - Tufnol grade 6F/45 (Tufnol Ltd. Birmingham). The fabric reinforcement increases the stiffness and durability of the material and it can be machined to fine limits. Tufnol is radiolucent as well as non - conducting and is also suitable for steam sterilization. In comparison with aluminium it is more difficult to machine as it is prone to chip, it is less durable and is less resistant to mechanical distortion.

I felt that these disadvantages were outweighed by the advantage of ensuring artefact free images. Mechanical distortions of the frame would also be minimised by the effective splinting of the base plate when the BRW base ring is fixed to its superior surface.

The components of the localiser unit and the head rest were constructed from the acrylic material "Perspex". (Perspex is the registered trade mark for a thermoplastic resin of polymethyl-methacrylate). The advantages of using Perspex are that it is a transparent, lightweight and stiff material that is radiolucent and non conducting and therefore causes no artifact on biomedical images. It can be machined on conventional lathes and milling machines or worked with simple hand tools. Its great advantage is that it can be easily moulded into complex three dimensional shapes. On heating the material to 160-170°C it becomes thermoplastic and can be bent or moulded to a desired shape which is fixed when the material cools to below 90°C. Acrylic components can be bonded together with cold cure acrylic cement which forms a chemical union between the components giving the joint considerable strength. Additions may be made to an acrylic structure by adding cold cure acrylic to a surface and building it up. Its prime disadvantage is that it is brittle and crazes with time or when exposed to ionizing radiation.

The locking nuts for the head rest slides, the bolts for connecting the localiser unit to the baseplate and the tabs for connecting the straps to the baseplate were machined from Polyoxymethylene (Acetal, Omari Plastics. Unit 2 Cumberland Ave. Park Royal, NW10) This is a hard plastic which is resistant to distortion and has good machining properties. It is however unsuitable for steam sterilization. The head straps were made of woven nylon and their buckles were made of moulded nylon. These cause no artefact on biomedical images.

2. THE HEAD FIXATION DEVICE AND METHOD

The base plate

The described method of non-invasively and reproducibly fixing a sterotactic frame to the head employs a base plate onto which conventional sterotactic equipment is mounted. This obviates the need to design a completely new sterotactic instrument with stereoguide and a complete set of localisers or fiducials for the different imaging modalities. Any sterotactic instrument or reference system could potentially be mounted onto such a base plate. However because of personal familiarity with the Brown Roberts Wells (BRW) sterotatic system the baseplate was designed to accommodate fixation of this frame.
The dimensions of the BRW base ring therefore define the geometry and size of the baseplate design. Attachment of the BRW ring to the base plate is achieved by self centring conical screws located in existing screw holes spaced circumferentially around the BRW ring. When the BRW ring is positioned on the base plate the conical screws engage with six appropriately placed lugs on the base plate. When tightened they ensure precise and repeatable fixation. The base plate has laterally placed wings accommodating fixation holes for attachment to a series of brackets that hold the frame during imaging or sterotatic procedures. The holes are positioned in the mid transverse axis of the base plate to ensure maximum stability of the fixation. The design of the base plate additionally provides clearance for the three cam locks which project below the level of the BRW base ring.

The dental impression

The advantage of using the upper jaw as the prime site for locating the base plate is that the teeth provide the most rigid point of non invasive location on the skull, and being the hardest structures in the body are able to comfortably withstand pressures of up to 500 lbs per square inch. In contrast, all other possible sites of location on the head are covered with skin which is compressible and slides over the skull making accurate relocation unreliable, and rigid fixation potentially painful if not impossible. The numerous contours provided by the patients teeth ensure that a precise impression will fit the teeth in a uniquely determined position. In addition the U shape of the upper dentition combined with the dome shape of the hard palate prevents movement of the impression in all directions other than downwards (fig.19). When the impression is held firmly in position with an upward force, it provides the means for accurate and rigid fixation of the base plate to which it is attached.

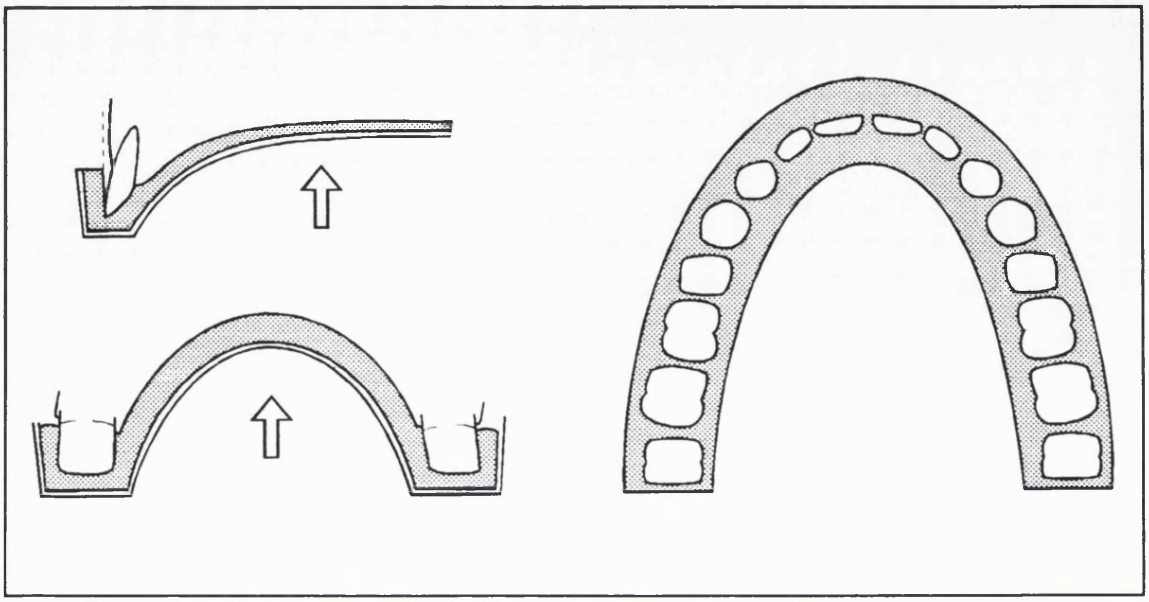


Figure 19 The stability of a dental impression held firmly on the upper arch.

In edentulous patients the hard palate is also capable of comfortably taking high loads when evenly distributed and of giving reliable relocation characteristics because of its combined U-shape and dome shape. The mucoperiosteum which covers the upper jaw and separates the impression from the bone is approximately 1mm in thickness. It is relatively incompressible and does not slide on the bone as it is firmly adherent to it.

The essential requirements of the dental impression are that it should intimately fit the many contours of the teeth with the maximum surface area of contact, but excluding the undercuts, whose clearance is necessary to allow its removal. It should be formed of a rigid material of minimum bulk and be simple and quick to make.

These requirements have largely been met by using P.E.M. as the impression material. Additional advantages of this material are that it forms a chemical union with the acrylic dental tray to form a combined structure that is extremely resistant to distortion. It can be worked by simple hand tools allowing modification if necessary. Such modifications to the impression may be required to provide further clearance of the undercuts if there is too tight a fit when it is repositioned. Excessive removal of the undercuts from the impression, which are predominantly on the buccal surface of the teeth, is of no consequence. This is because accurate and stable location of the impression on the teeth is met by its engagement with the occlusal and inner surfaces of the teeth alone. In fact with judicious use of the impression material an impression of only these aspects of the teeth may be made by applying a relatively thin layer of the material to the bottom and medial sides of the dental tray. A further reason for modifying the impression may be that a patient has undergone dental treatment such as fillings or crown work between

fittings of he frame. In these circumstances the drilling away of the impression in the affected areas is unlikely to alter its overall relationship to the teeth in view of the many hundreds of points of contact.

To form an impression of an edentulous patient the dental tray is loaded with a generous amount of the PEM impression material and the patient bites on the tray with the lower denture in position. To maximize the surface area of contact and increase the stability of the impression on the upper jaw it should include as much of the buccal surface of the maxilla as possible. The impression material can be allowed to set hard in the mouth as the problem of undercuts does not arise.

There are great variations in the dentition of individuals as there are in the size and shape of the upper jaw. Although three sizes of dental tray are provided which will normally accommodate the full range of adult jaw sizes there may be exceptions. In these circumstances, and with children, special sizes and shapes of tray may need to be custom made.

Occasion may arise where a patient with irregular teeth and an unequal bite fails to adequately locate into an existing tray of the appropriate size. An example of this would be where a tooth in the upper jaw has over-erupted into a gap in the lower arch. In such a case the existing tray being made of Perspex can easily be modified by drilling a hole in the appropriate place so that the long tooth will protrude through it. The remaining teeth should then meet the tray allowing an impression to be formed.

It is essential for the accuracy of frame repositioning and for its stable and rigid fixation that the dental impression is correctly located on the upper jaw. This is best achieved by the patient biting firmly on the impression so that any discrepancy on the loading of the teeth will be felt. Built up sections beneath the mid transverse axis of the dental tray in the region of the premolar teeth ensure that when the patient bites, the lower premolars will engage with this section and the applied force will be equally distributed on the upper dentition. By placing a small amount of the PEM impression material over the built up sections and taking impressions of the lower premolars while the patient bites on the tray it distributes the loading on these teeth. It also compensates for those patients with an uneven bite who's lower teeth would otherwise engage on one side only, and make the upper impression vulnerable to rocking.

Although individuals are very sensitive to tiny discrepancies in the loading of their teeth an independent means of checking the location through viewing ports in the side of the impression is felt to be essential. This is particularly so when checking location in an anaesthetized patient. If the occlusal surface of the teeth meet the impression at the central transverse axis where the viewing ports are positioned then all the other teeth must be in similar contact.

Localiser unit

The localiser unit provides the means of fixing the base plate to the head in a desired orientation for imaging and stereotactic procedures. It permanently records the relationship between the dental impression and the base plate for a given patient. It can be detached from the base plate and stored between repositionings.

A stereotactic frame is generally fixed with the head positioned centrally and without any degree of angulation in the coronal plane. To include the brain volume in the defined stereotactic space it should be positioned at or below the skull base. The degree of angulation in the sagittal plane, or pitch, varies depending on the clinical setting. In most instances however, a stereotactic frame is fixed to the head with a degree of pitch that corresponds with the conventional CT imaging plane. This is parallel with the radiological base line or canthomeatal line. The canthomeatal line joins the outer canthus of the eye to the middle of the external auditory meatus. This imaging plane allows images to be taken through the posterior cranial fossa without irradiating the orbits. Occasionally, for functional neurosurgery, the frame is fixed to the head parallel to the Frankfurt line {also called the anthropological base line, or Reids base line}. This line passes between the inferior orbital margin and the superior margin of the external auditory meatus. The angular relationship between the Frankfurt line and the cantheomeatal line is 12°, (m=f 11.8 +/- 1.6 SD): (Tokunga et al.1977).

When the base plate is being positioned around the head for the first time, the localiser unit is in its constituent parts.Its two positioning plates are fixed laterally and parallel to one another on the under surface of the base plate and the dental piece containing the dental impression is held firmly on the upper jaw. The lateral edges of the dental piece come into contact with the medial faces of the positioning plates during this procedure which constrains the head from moving laterally in the frame from its mid line position, but allows antero-posterior movement, vertical movement, and adjustment of pitch. By maintaining the frame horizontal to the head during positioning the lateral edges of the dental piece remain in contact with the positioning plates. Placement of the frame into a conventional position for stereotaxy can therefore be achieved with relative freedom of movement.

Once in position (ie parallel to the canthomeatal plane or parallel to the Frankfurt plane at the level of the skull base) the relationship between the patients upper teeth and the base plate will vary depending on their head size and cephalometric proportions. The likely range of head sizes and proportions that would be fitted into the frame therefore had to be taken into account when designing the geometry of the dental piece and the position and dimensions of the localiser plates. This is because rigid fixation of the dental impression to the base plate can not be assured unless the full extent of the lateral edges of the dental piece can be bonded to the medial faces of the localiser plates.

I took the likely head sizes that would be fitted into the frame to range between an adult head size + 2 Standard Deviations (2SD) and a 10 year old child's head size - 2SD. The adult head size + 2SD would exclude only 2.5% of the adult population who had head sizes larger than this. These patients would have heads of such a size that they would be unlikely to fit into the conventional BRW base ring. A 10 year old head size -2SD was selected because children younger than this would be unlikely to tolerate head fixation for multiple imaging and form only a tiny minority of patients who undergo stereotactic procedures.

Data on the cephalometric proportions of the mean adult head size (18yrs) + 2SD, and of a 10 year old child - 2SD were obtained from the Bolton Standards of Dentofacial Development and Growth (Broadbent et al. 1975).

Having established the cephalometric proportions of these skull sizes at the extremes of the range it was then possible to determine the relationship between the upper teeth and the base plate for each skull size when the base plate was fixed centrally on the head at the level of the skull base in the canthomeatal plane and in the Frankfurt plane.
The size of the localiser plates and geometry of the dental piece could then be determined to accommodate fixation of any head size within the established range (The method of establishing these parameters are shown in the Appendix I).

Although the geometry and dimensions of the localiser unit were designed to accommodate fixation of the largest and smallest defined head sizes, it would be possible to fix heads of a smaller size than 10yrs - 2SD. (It is of note that the cephalometric dimensions of a 10 year old - 2SD are approximately the same as the mean 5 year old's dimensions). For smaller children and infants, fixation could be accomplished by positioning the head more anteriorly in the frame or by forming a custom made supporting element. The latter would probably be necessary in any event, because the standard dental trays would be too large for an infant and so a custom made dental piece would be required.

When the base plate has been appropriately positioned around the head the points of contact between the lateral edges of the dental piece and the medial faces of the positioning plates are marked and then bonded together using "cold cure acrylic cement". This simple solution obviates the need to design a complex mechanical joint with the appropriate degrees of freedom and range of movement. In addition, by bonding the components together the relationship between the frame and a given patients head is permanently recorded. The "Localiser Unit" can be detached from the base plate by undoing four bolts. It is relatively small and can easily be stored until the frame needs to be reapplied to that patient. By bolting the Localiser Unit back onto the base plate the relationship between the head and the frame is immediately reestablished.

In contrast a calibrated mechanical joint with associated nuts and bolts or lockable slip joints would be prone to error when reassembled. An alternative arrangement would be a mechanical joint which could be permanently locked in a position that defines the relationship between the patients dental impression and the base plate and could then be detached from the base plate for storage. This however would be expensive to use on a single patient basis because the manufacturing costs of such a mechanism are likely to be high.

The head straps

The dental impression which is retained in the localiser unit is held firmly in position on the upper jaw by straps which pass over the head. To ensure even loading on the upper jaw the straps which pass coronally over the head have a line of pull which passes vertically through the mid transverse axis of the dental impression. Even tension is achieved in the coronal straps by the technician placing his two thumbs on the connector piece and pulling the straps up with equal force. Considerable force can be applied to these straps as the teeth will comfortably tolerate loading of up to 500 lbs per square inch. It is of course almost impossible for the technician to apply such force to the straps to achieve this degree of loading. The straps which pass sagitally over the head have a primary roll of positioning the connector piece in the region of the bregma so that the line of pull of the coronal straps is maintained.

To prevent bending and distortion of the frame when forces are applied to the straps, which would reduce the accuracy of relocation, certain design features were incorporated: The dimensional stability of the base plate is reinforced when it is fixed to the BRW base ring. The localiser unit, although made of acrylic is dimensionally stable under conditions of load, firstly because the positioning plates are retained in open boxes to prevent their lateral displacement and secondly the supporting element is in the form of a bridge. The anterior half of the dental tray is retained in the supporting element and its structure is further stiffened by the wedge of the occlusal surface and the height of its lateral walls. The rigidly with which the frame is fixed to the head is a function of the tension in the straps. However, because the dental impression is positioned at the anterior third of the frame upward forces exerted on the posterior portion of the frame will tend to pivot the impression on the molar teeth forcing it off the incisors. This lever action is countered by employing the head rest which engages with the lower near portion of the patients head.

The head rest

The head rest is in the form of a tray which contains a patient specific impression of the occiput. The tray has a lip inferiorly which holds the impression material beneath the occipital protuberance. The dome shape of the occiput ensures that a precise and firmly applied impression will tend to counteract forces in all directions other than anterior displacement of the head. This is prevented by firm engagement of the upper jaw in the dental impression and by the resultant moment of the force applied to the head by the combined

tensions in the coronal and sagittal straps. The material chosen for forming the occipital impression Vinylpolysiloxan (Panasil Putty) is easily handled and forms a highly detailed and dimensionally stable impression. When set, its hard rubbery consistency allows a small amount of give which will accommodate changes in the distribution of the hair between fittings so that an even pressure is applied over its surface area of contact with the scalp. When the frame is repositioned precise placement of the occipital impression is achieved by adjusting the verniated AP and vertical slides on the head rest bracket to their previously recorded "set up position".

CHAPTER 3

ACCURACY OF FRAME RELOCATION

Materials and Method.

Phantom studies.

Patient Studies.

Statistical methods.

Results.

a) Phantom studies.

b) Patient studies.

Discussion.

The method of assessment.

Phantom studies.

Patient studies

Sources of error in repositioning the frame.

What degree of accuracy is acceptable?

ACCURACY OF FRAME RELOCATION

Materials and method

PHANTOM STUDY

The reproducibility of repeated fixation was initially tested with a phantom skull. This was made to simulate a head by applying to the hard palate a silicone rubber coating to mimic the mucoperiosteum. A compressible scalp was simulated with a felt pad which was held in position with elastic bands allowing it to slide freely on the skull.

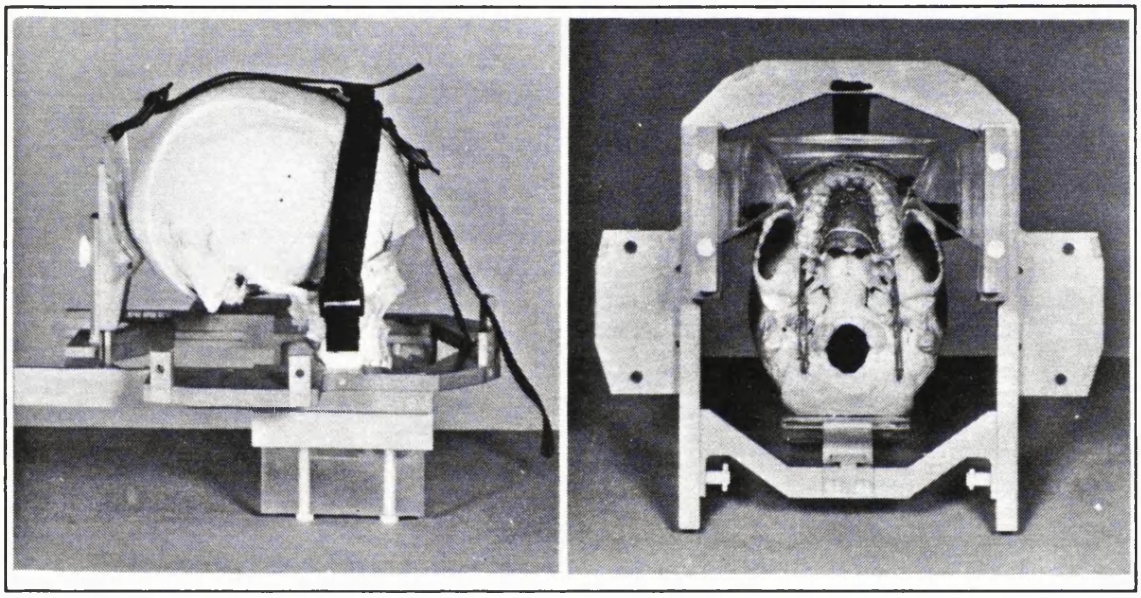


Figure 20 Phantom head in Relocatable Frame

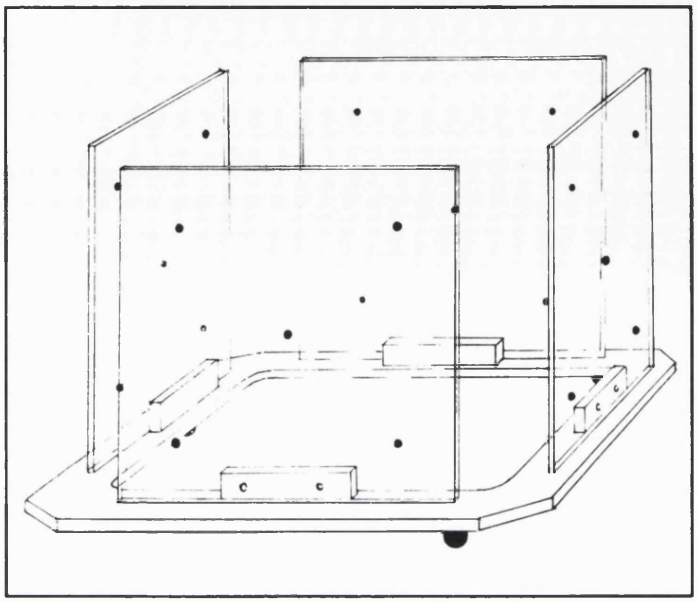
Four 1mm ball bearings mounted on Perspex rods were positioned in regions of interest, these were:

1. Right frontal (F)
2. Left parietal (P)
3. Left occipital (O)
4. Right thalamic (T)

A dental impression was made and the phantom was positioned in the frame. (fig. 20) The BRW stereotactic ring was secured to the base plate and on to this was mounted the SGV (Suetens-Gybels-Vandermeulen) angiographic localiser (Vandermeulen et al.1987). This consists of a rectangular base plate bearing on each of its sides a vertical Perspex plate. Each plate contains five metallic markers (fig 21).

Figure 21

The SGV Angiographic Localiser



With the frame fixed in the BRW floor stand and with fixed Xray sources and plates, AP and lateral radiographs were taken of the phantom each time it was repositioned. Three individuals alternately repositioned the phantom head in the frame. Different degrees of tension were applied to the straps and the direction of pull of the coronal straps was altered between positionings.

The first set of AP and lateral radiographs were developed as mask films and taken as a reference set. Fourteen subsequent AP and lateral radiographs taken after each location were developed as negatives. Pin holes were made through the centres of each 1mm reference ball on all films.

The reference set of mask films were secured to a light box and the sets of negative films sequentially superimposed on them so that the SGV markers subtracted. Displacement of the pinholes on the negative films from those on the mask films were measured to the nearest 0.1mm using a calibrated travelling microscope.The apparent AP displacement $(y)^m$ and the apparent vertical displacement $(z)^m$ of each reference point was measured on the superimposed lateral films. The apparent lateral displacement $(x)^m$ was measured on the superimposed AP films.

The actual displacement of each reference point in each cardinal axis (eg x,y or z) is calculated by the formula:-

$$\text{actual displacement of ref.point} = \frac{\text{measured displacement}}{\text{magnification factor at ref.point}}$$

The magnification factor at each reference point on the lateral radiograph is calculated by the formula:

$$\text{Magnification factor of ref.point on lateral radiograph} = \frac{\text{Lat. xray source to film distance}}{\text{Lat. xray source to ref. point}}$$

The lateral xray source to reference point distance was calculated by measuring the distance from the lateral xray source to the mid sagittal plane of the SGV/BRW system and then adding or subtracting the distance of each reference ball from the from the mid sagittal plane.(fig 22)

The reference point to the mid sagittal plane was measured for each reference ball using the BRW stereoguide to obtain the BRW coordinates of each reference ball.

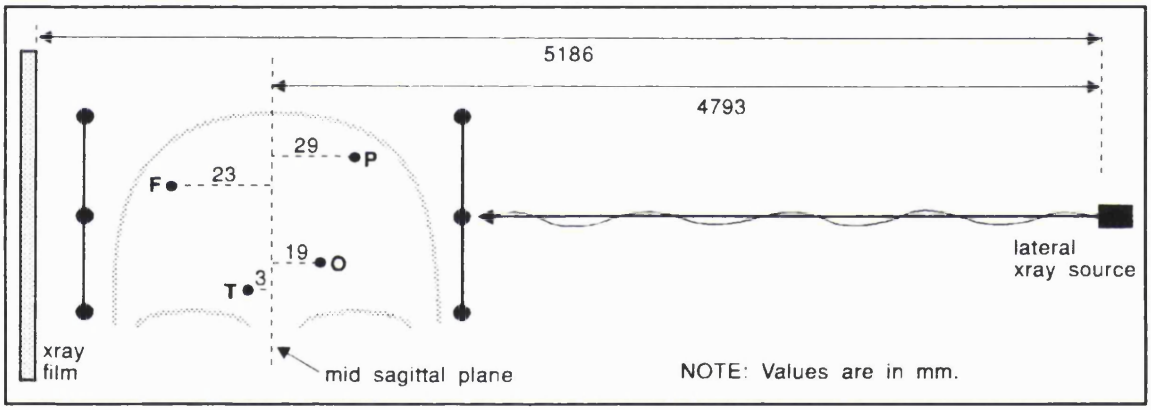


Figure 22 **Determination of magnification on lateral film (Phantom)**

The magnification factor at each reference point on the AP radiograph is calculated by the formula :

$$\text{Magnification of reference point on AP radiograph} = \frac{\text{AP xray source to film distance}}{\text{AP xray source to ref. point}}$$

The AP xray source to reference point distance was calculated by measuring the distance from the AP xray source to the mid coronal plane of the SGV/BRW system and then adding or subtracting the distance of each reference ball from the mid coronal plane.(fig. 23).

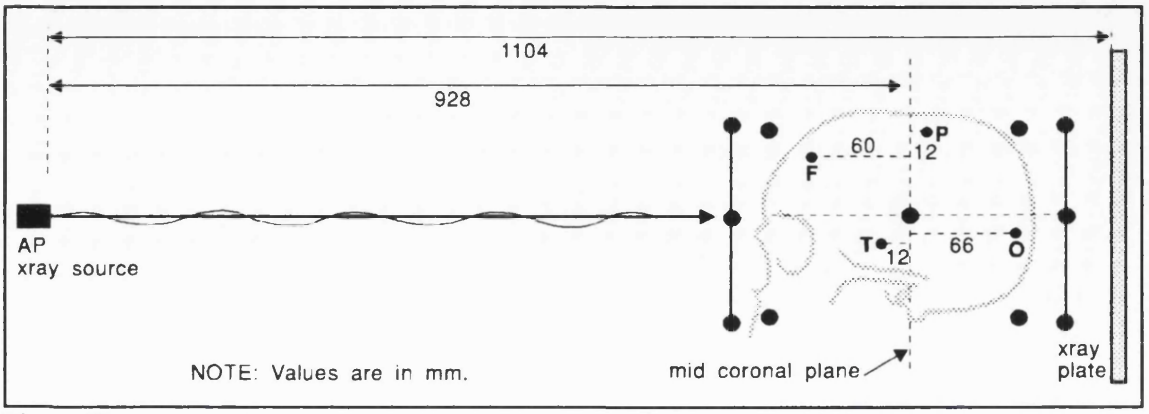


Figure 23 **Determination of magnification factors on AP film (Phantom)**

Having quantified the displacement of individual reference points from their position on the reference film for each relocation, the mean position of each point during the fixations was calculated. The displacement of each reference point from its mean position after each fixation was then determined in the x y and z axes. In addition, the relative displacement of a given reference point between any 2 repositionings was determined.

PATIENT STUDIES

The accuracy of frame relocation was assessed in two groups of patients. The first group were twelve patients undergoing stereotactic investigations and procedures at Maida Vale Hospital, each of whom had the frame fixed to their head by the author using the previously described method. The second group were 10 patients undergoing investigations and radiosurgery for arteriovenous malformations at St.Bartholomews Hospital. These patients were fixed in the Relocatable Frame by one of a number of clinicians or physicists using a different dental impression material (Vinyl polysiloxan putty).

The method of assessing the accuracy of relocation was essentially the same for both groups of patients. This was to take AP and lateral radiographs of the patient located in the frame with fixed xray sources and plates. Identical views were repeated at a later date when the frame was relocated. By superimposing the images the displacement of the head in each cardinal axis relative to the frame could be determined. The details of the method differed slightly at each centre due to differences in the hardware available at each site. These are outlined below.

Group 1 (Maida Vale Hospital)

The first group of twelve patients comprised nine males and three females with an age range of 32-65 years and a mean age of 48 years. One patient was edentulous. Nine patients underwent investigation and stereotactic biopsy for primary brain tumours and three underwent investigation and thalamotomy for Parkinsonian tremor.

Prior to each patients first CT scan the Relocatable Frame was fixed to the head and the BRW base ring fixed to it. The SGV angiographic localiser was mounted on the BRW base ring and the patient was fixed to the BRW floor stand which was bolted to the floor in the angiographic suite at Maida Vale Hospital. The floor stand has brackets which hold xray cassettes in a fixed position for lateral and AP radiographs. Ceiling mounted xray sources had a fixed relationship to the BRW floor stand for taking AP and lateral views. Lateral and AP radiographs were taken and developed as mask images. At a later date, and prior to a sterotactic procedure the patient was re xrayed using exactly the same setup. The AP and lateral radiographs were developed in the usual way.

Reference points were selected on the first lateral film for each patient. The first or "frontal point" was on the inner table of the skull at the Bregma (the meeting of the sagittal and coronal sutures).
The second, or occipital point, was on the inner table of the skull at the Lambda (the meeting of the sagittal and occipital sutures). A third point was selected midway between the frontal and occipital poles (the

thalamic point). These reference points were assumed to be in the mid-sagittal plane of the head. This plane was defined on the first set of AP films as being the mid-sagittal plane of the SGV system.

For each patient these three reference points were marked with pinholes through the first lateral film (Fig. 24). Their positions were then measured on these films with reference to the centre of the SGV localiser (this is the point where the mid-sagittal, mid-coronal and mid-transverse planes cross). The AP values measured from the mid-coronal plane were then corrected for the magnification factor on the lateral film at the mid-sagittal plane.

The reference points were then transposed to the mid-sagittal plane of the first AP film after multiplying the vertical distance of each reference point from the mid-transverse plane by the magnification factor it would have had on the AP film at its given distance from the X-ray source. These points were marked with pinholes through the first AP film.

The second set of AP and lateral films were now superimposed on the first set so that the skulls completely subtracted. Pinholes were now made through the second set of films so that they corresponded with those on the first set.

The two sets of films were realigned so that the reference markers on the SGV localiser completely subtracted (Fig 25). Using a calibrated travelling microscope the displacement of the pinholes in the AP (y) and vertical (z) axes were measured on the lateral films. The lateral (x) displacement of each pinhole was measured on the AP films. All measurements were made to the nearest tenth of a millimetre.
The displacement of each reference point relative to the frame between the two frame fixations is determined in the AP and vertical axes by the formula:

$$\text{actual displacement} = \frac{\text{measured displacement}}{\text{magnification factor at mid-sagittal plane}}$$

and in the lateral axis by the formula: * (see discussion)

$$\text{actual displacement} = \frac{\text{measured displacement}}{\text{magnification factor at mid-coronal plane}}$$

The x, y and z displacements of the intracranial reference points that occurred after relocating the frame on each of the 12 patients were determined.

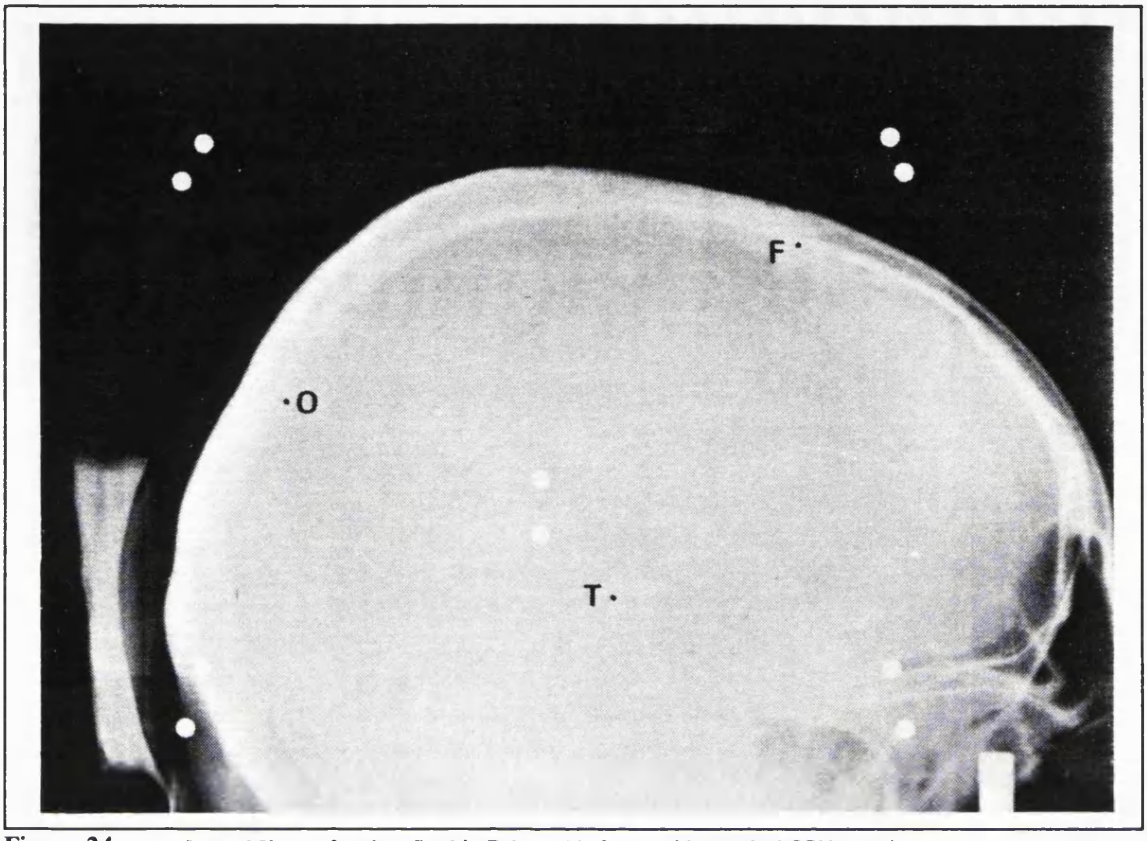


Figure 24 **Lateral X-ray of patient fixed in Relocatable frame with attached SGV localiser**
(pinhole reference points indicated - F = Frontal; O = Occipital; T = Thalamic.

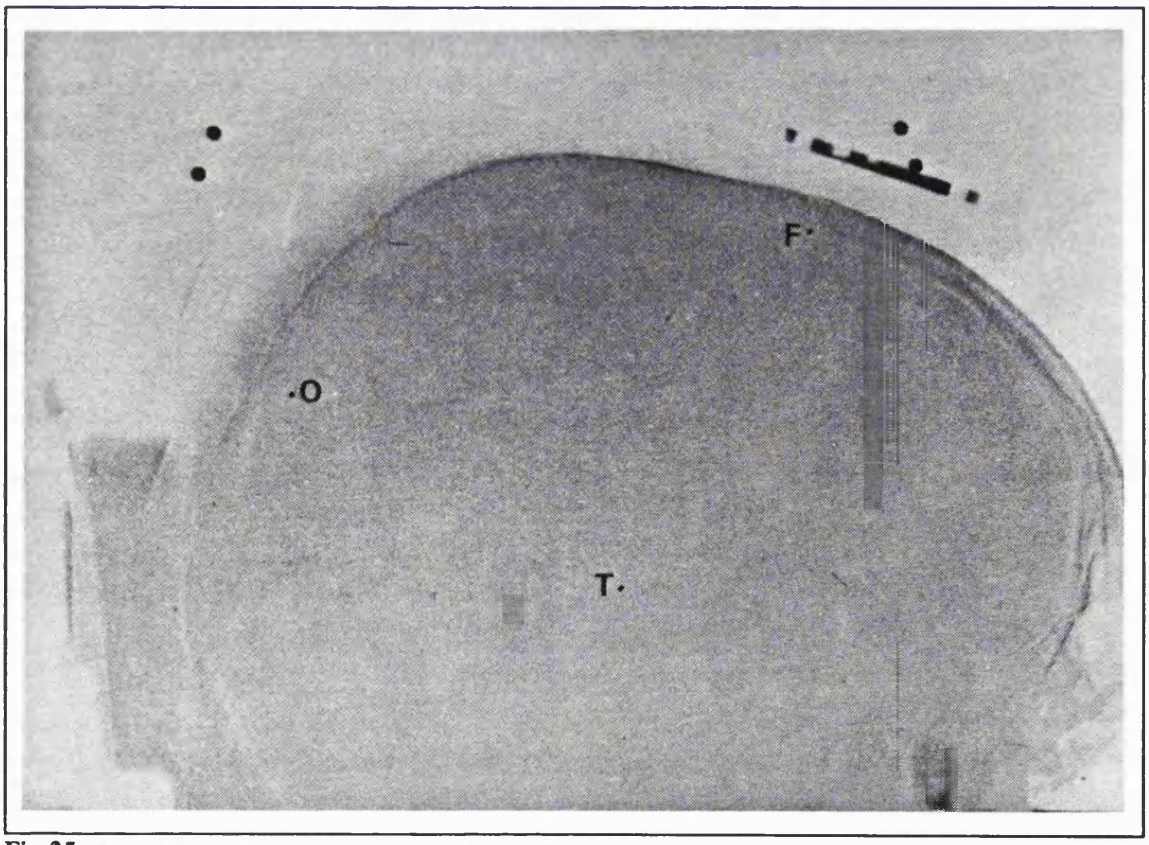


Fig 25 **Lateral X-Ray taken after second positioning of the frame superimposed on a mask film taken after the first positioning so that the SGV reference points subtract**

Group 2 (St.Bartholomews Hospital)

The second group of ten patients comprised two males and eight females with an age range of 8 - 44 years and a mean age of 35 years. There was no edentulous patient in this group. All the patients had arterio-venous malformations and had radiosurgery planning using contrast enhanced CT data obtained under stereotactic conditions using the BRW stereotactic system fixed to the Relocatable Frame.

Although each patient had cerebral angiography performed at their referring hospital these were not taken under stereotactic conditions and so could only be used indirectly to determine the treatment volume by comparison with the stereotactic CT images. One patient from this group did however have a stereotactic angiogram when an angiographic localiser became available and was integrated into the planning programme.

Following the initial fixation of the frame to the head the patient is positioned in a treatment simulator (Varian Ximatron-CX). The frame is attached to the couch by means of an intermediary bracket. A three sided Perspex box is then placed over the patients head and fixed to the frame. The box has the cardinal axes of the BRW coordinate system engraved on the Perspex plates.

The simulator couch is moved so that the centre of the coordinate system is at the centre of the simulator. Anteroposterior and lateral radiographs are then recorded. The position of the central axis of the beam is indicated on these radiographs by the position of the cross wires (fig.26). As these are aligned with the Perspex box the position of the crosswires gives an indirect indication of the position of the frame. Once the images are recorded the Perspex box and the relocatable frame are removed, refitted and repeat radiographs are taken exactly as described above.

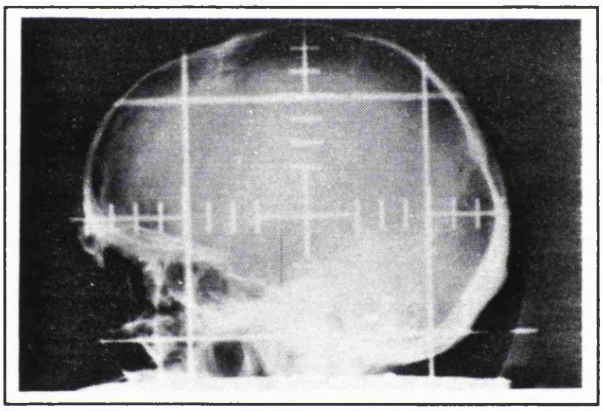


Figure 26 **Lateral radiograph of patient in simulator in the Relocatable frame**

The method of determining the accuracy of relocation from these paired images is as described for Group 1. The exception being that X-ray source and plates are at a fixed separation of 140cm for both the AP and lateral views. The distance between the X-ray source and the mid-coronal plane or mid-sagittal planes are the same, at 100cm. Prior to the planning CT scan and prior to radiosurgery treatment, each patient was again positioned in the simulator to ensure accurate relocation. Thus each patient had the frame positioned four times. The displacement of each intracranial reference point relative to the frame could therefore be quantified between any two repositionings from six combinations of paired images per patient.

STATISTICAL METHOD

In assessing the reproducibility of this method of head fixation the information that is useful to the clinician is; what the maximum likely displacement of a chosen reference point in the head might be, relative to the frame, between any two repositionings. In addition, it is useful to know what is the average displacement between any two repositionings and to have an indication of the spread of the displacements.

Because the prime site of location and fixation of the head in the frame is the upper jaw, one can assume that intracranial reference points furthest from the upper jaw will have the greatest displacement. The displacements of several reference points in the cranium were therefore analyzed. These were frontal, occipital and thalamic points. For the phantom studies an additional reference point was selected in the parietal region.

Although the 3-dimensional displacements of these reference points would give an overall impression of the repositioning accuracy they could be misleading. This is because a quoted 3-D displacement between two points in space has no direction. What concerns the clinician performing a biopsy or targeting a lesion, is what the likely error will be in each cardinal axis. For example, if a biopsy target is selected from an axial scan image that is 3mm from a major blood vessel, and the estimated maximum 3-D error after relocating the frame is 3mm, then the clinician would have the impression that he would run a reasonable risk of hitting the vessel. However, the maximum 3D displacement is infact the result of maximum displacements in each cardinal axis. So that the maximum likely AP displacement may be just 1.3mm, the lateral 1.2mm and the vertical 1mm. His chance of hitting the vessel is therefore insignificant.

Phantom Studies:

In the phantom studies the phantom can be considered as one individual selected at random on to which the frame was positioned fifteen times. The displacement of individual reference points in each cardinal axis from their positions on AP and lateral reference films were measured after repositioning the frame. From this data the displacements in each cardinal axis of individual reference points from their mean position were calculated. Histograms of these are shown in the results section (Fig. 27). Six times the standard deviation of the displacement of a reference point in a given axis will include the likely range of displacements in 99.7% of relocations. These likely maximum ranges are shown in Table 1.

To evaluate the spread of the displacements of an individual reference point in each axis between any two repositionings of the frame, cumulative frequency curves are most valuable. From these the range of displacement of a point can be evaluated for a given percentage of relocations (eg., in 75% of paired relocations the displacement in the z axis was no greater than xmm). The displacement at the 50th centile is the median displacement.

By way of example the cumulative frequency curves for the displacement of the phantoms frontal reference point in each cardinal axis are shown in Fig. 28. For each phantom reference point the maximum recorded displacement in each cardinal axis and the median and mean displacements are shown in Table 1.

The three dimensional displacement of each reference point between any two repositionings of the frame is calculated by the formula:

$$3D.displacement = \sqrt{(x-\bar{x})^2+(y-\bar{y})^2+(z-\bar{z})^2}$$

where $x - \bar{x}$ = lateral displacement of reference point
$y - \bar{y}$ = AP " "
$z - \bar{z}$ = Vertical " "

Cumulative frequency curves for the 3-dimensional displacement of each phantom reference point between any two repositionings are shown in Figure 29. The maximum recorded 3-D displacement and the median and mean displacements are shown in Table 2.

Group 1:

In this group of 12 patients, the displacement of frontal, occipital and thalamic reference points were measured in each cardinal axis after the frame was positioned twice on the head by the author. A rigid acrylic dental impression material was used in all cases. One patient was edentulous.

The sample size was too small to make predictions about the likely displacement of reference points in a large population incorporating the full range of head sizes and shapes, and so standard deviations of the displacements are not presented.

The maximum recorded displacement of each reference point in each cardinal axis and the mean and median displacements for the group are shown in Table 3.The cumulative frequency curves for the displacement of the frontal reference point in each axis are shown by way of example in Fig. 30.

Cumulative frequency curves for the 3-D displacement of the frontal, occipital and thalamic reference points are shown in Fig. 31. The maximum recorded 3-D displacement and the median and mean 3-D displacements are shown in Table 4.

Group 2:

The 10 patients in Group 2 each had the frame positioned four times by a variety of technicians, physicists or radiographers. A rubbery dental impression material was used. There were no edentulous patients in the group.

For every patient the displacement of each reference point was measured in each axis between paired repositionings. This gave a total of six combinations of paired relocations per patient.

The maximum recorded displacement of each reference point in each cardinal axis and the mean and median displacements for the Group 2 patients are shown in Table 5.

Cumulative frequency curves for the displacement of the frontal reference point in each axis are shown by way of example in Figure 32. Cumulative frequency curves for the 3-D displacement of each reference point are shown in Fig. 33.
The maximum recorded 3D displacement and the median and mean 3D displacements are shown in Table 6.

Results

a. PHANTOM STUDIES

Figure 27 Displacement of phantom reference points in each cardinal axis from their mean position (mm). (n= 15 frame positionings)

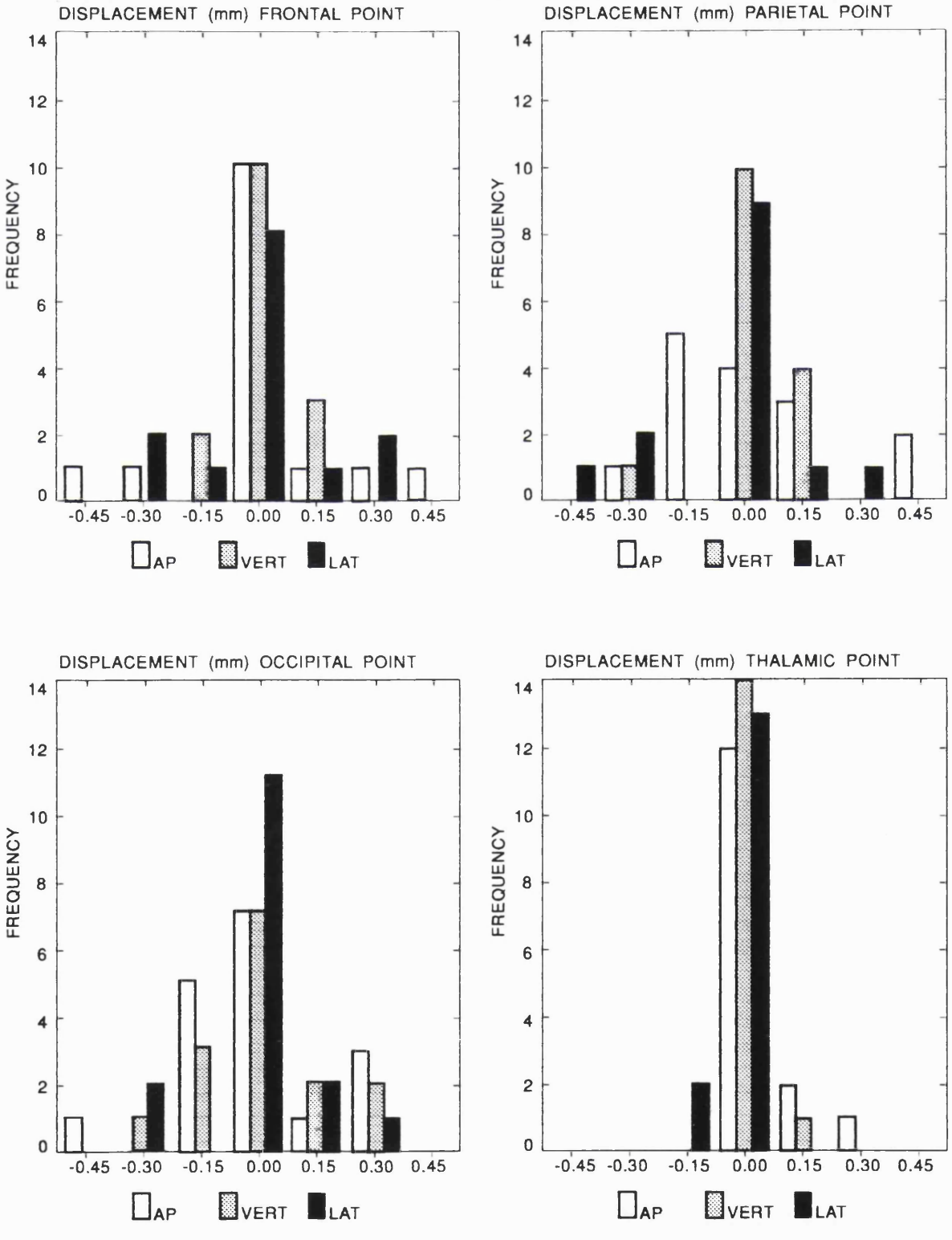
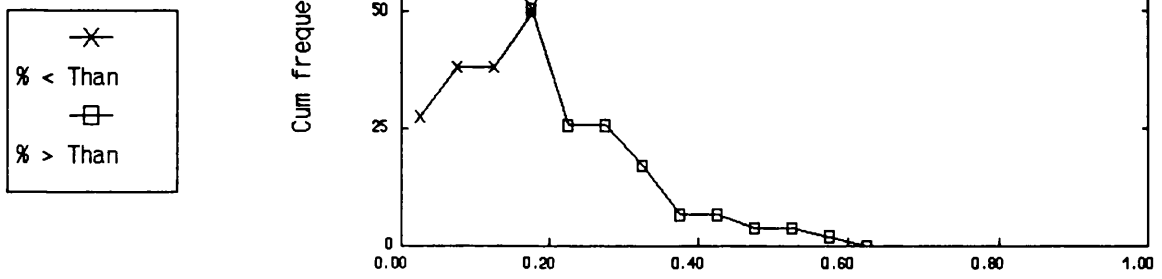


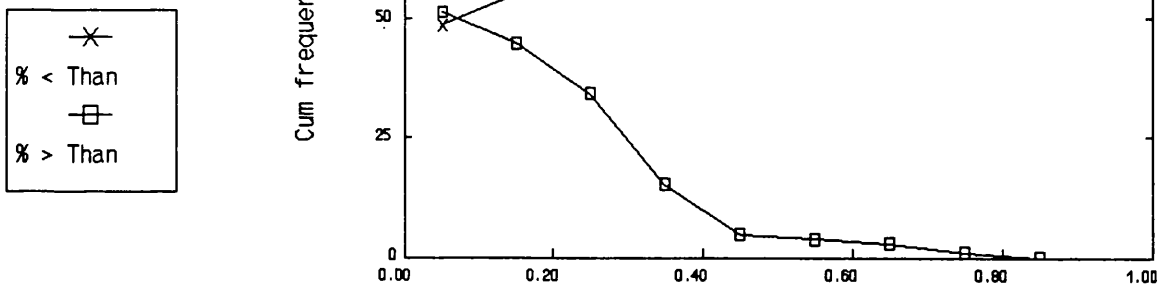
Figure 28. Displacement of phantom's frontal point in each cardinal axis between paired relocations (mm).

Cumulative frequency. (n=105 pairs from 15 frame positionings)

Lateral(x) displacement



AP(y) displacement



Vertical (Z) displacement

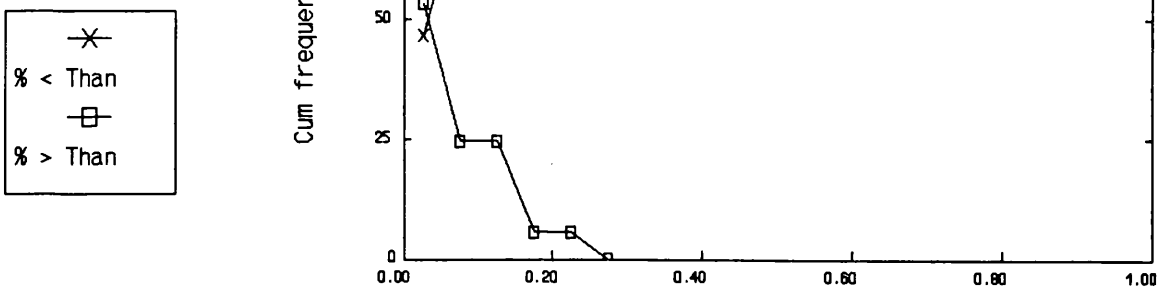
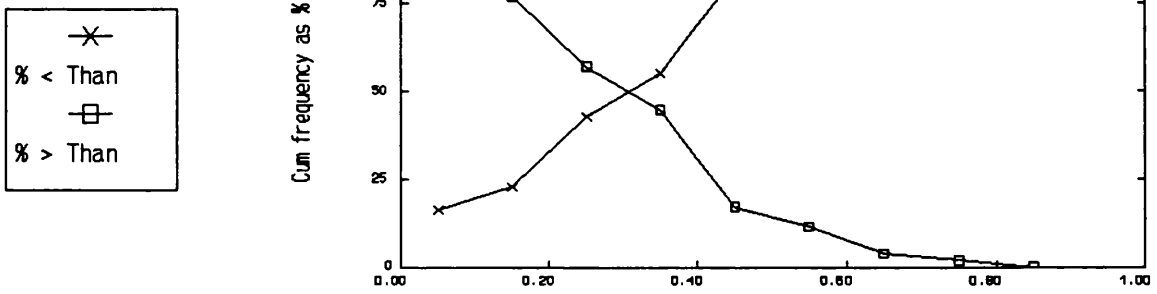
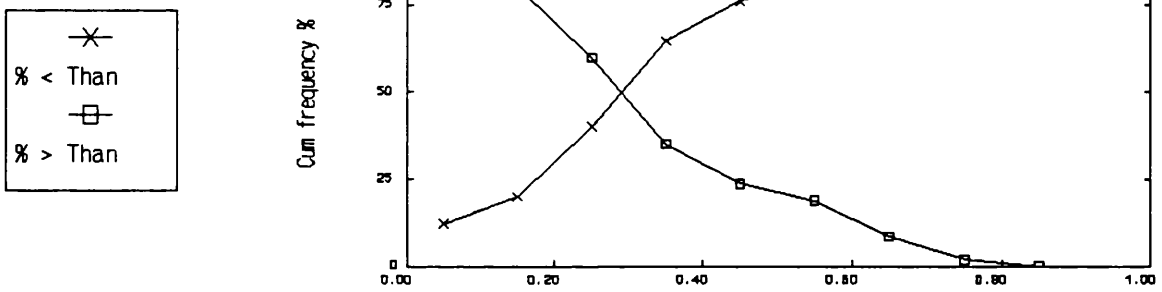


Figure 29. 3D displacement of Phantom's reference points between paired relocations (mm) : Cumulative frequency (n=105 pairs from 15 frame positionings)

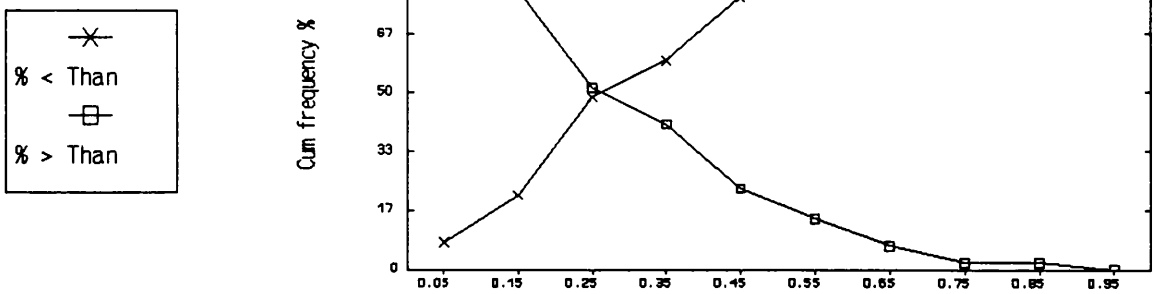
Frontal ref Point



Parietal ref point



Occipital ref point



Thalamic ref point

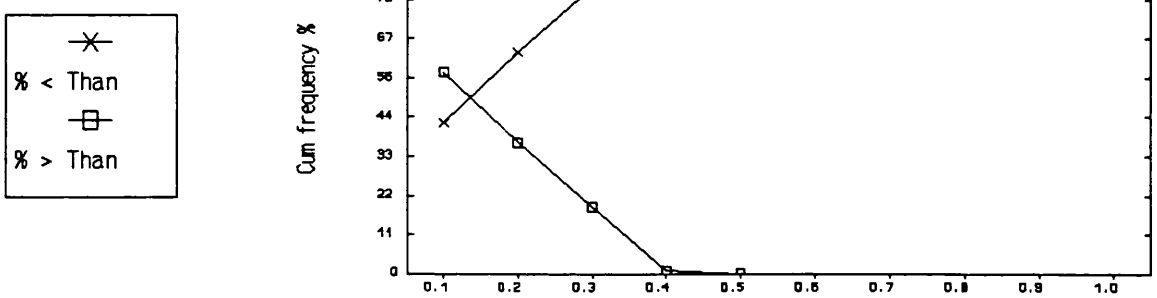


Table 1. Displacement of Phantom's reference points in each cardinal axis between any two repositionings of the frame (mm).
*(n=105 pairs from 15 frame positionings)

REF POINT	FRONTAL			PARIETAL			OCCIPITAL			THALAMIC		
Axis	x	y	z	x	y	z	x	y	z	x	y	z
Expected maximum range in 99.7% of relocations (6SD)	1.0	1.2	0.5	1.1	1.1	0.7	0.8	1.1	1.0	0.4	0.7	0.3
Maximum recorded * displacement	0.6	0.8	0.3	0.8	0.6	0.5	0.5	0.7	0.5	0.3	0.4	0.2
Mean displacement *	0.2	0.2	0.1	0.2	0.2	0.1	0.1	0.1	0.2	0.1	0.1	0.0
Median displacement *	0.2	0.2	0.1	0.2	0.2	0.1	0.1	0.1	0.2	0.0	0.1	0.0

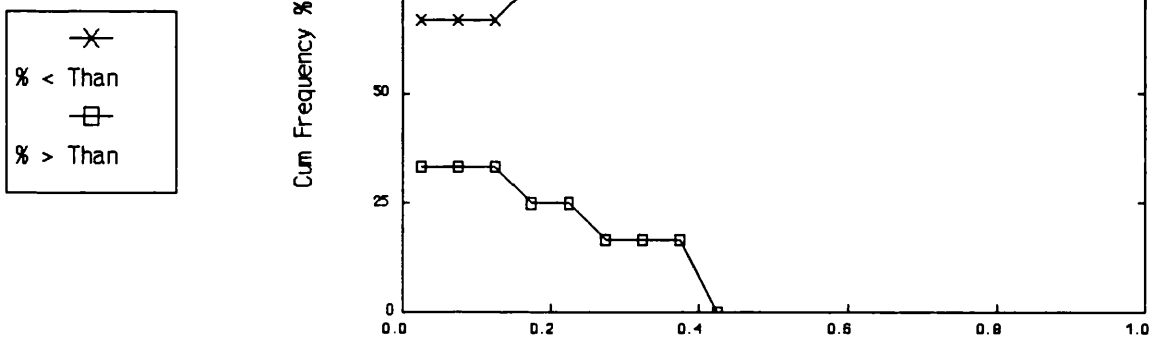
Table 2. 3D displacement of Phantom's reference points between any 2 repositionings of the frame (mm). (n= 105 pairs from 15 frame positionings)

REF POINT	FRONTAL	PARIETAL	OCCIPITAL	THALAMIC
Maximum recorded	0.9	0.8	1.0	0.4
Mean displacement	0.3	0.4	0.4	0.2
Median displacement	0.4	0.3	0.3	0.2

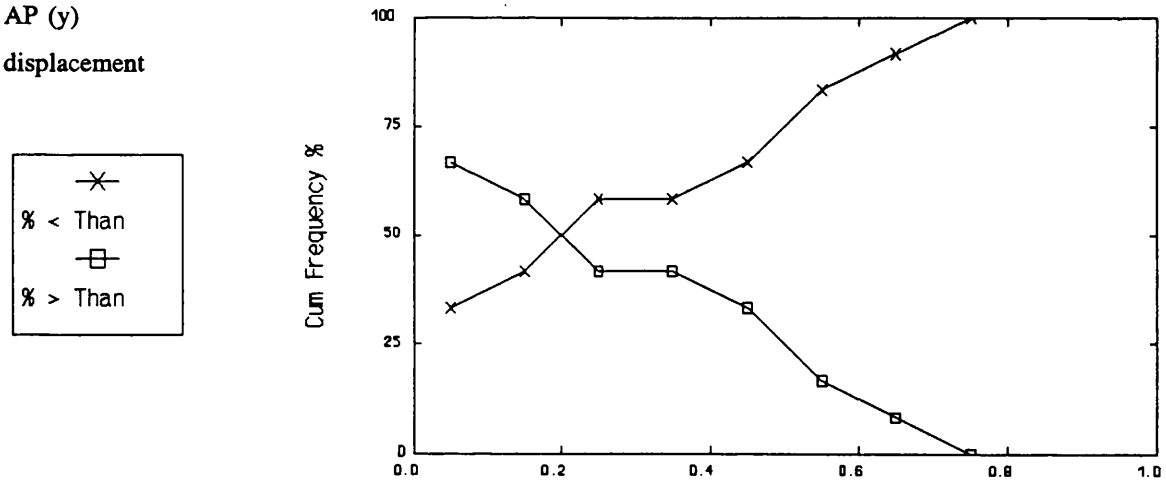
b) PATIENT STUDIES

Figure 30 **Group 1** - Displacement of frontal ref. point in each cardinal axis between 2 frame positionings on each of 12 patients (mm). [cumulative frequency]

Lateral (x) displacement



AP (y) displacement



Vertical (z) displacement

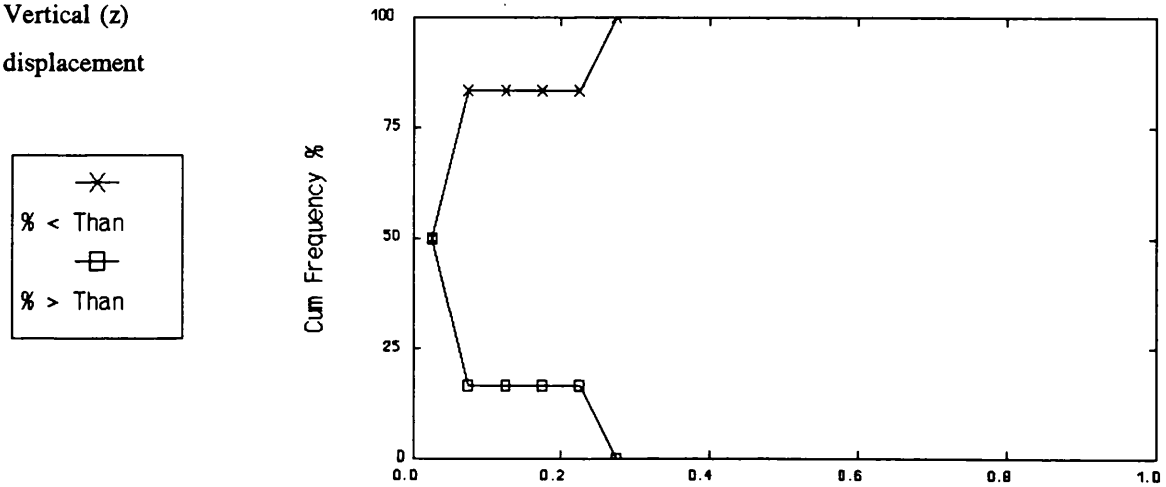
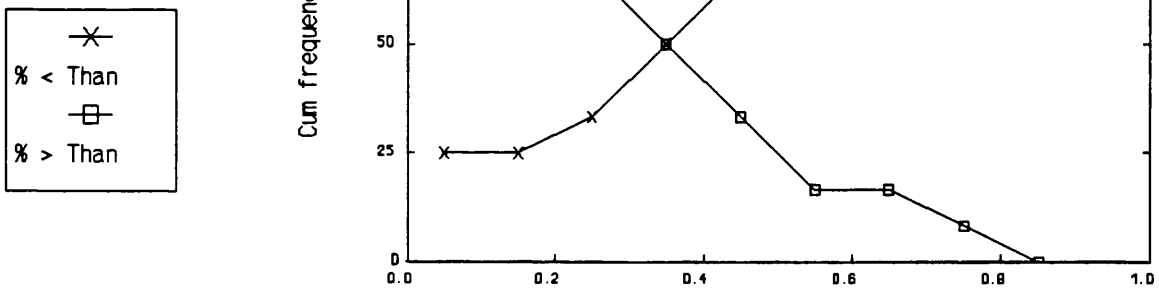
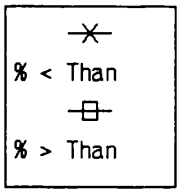


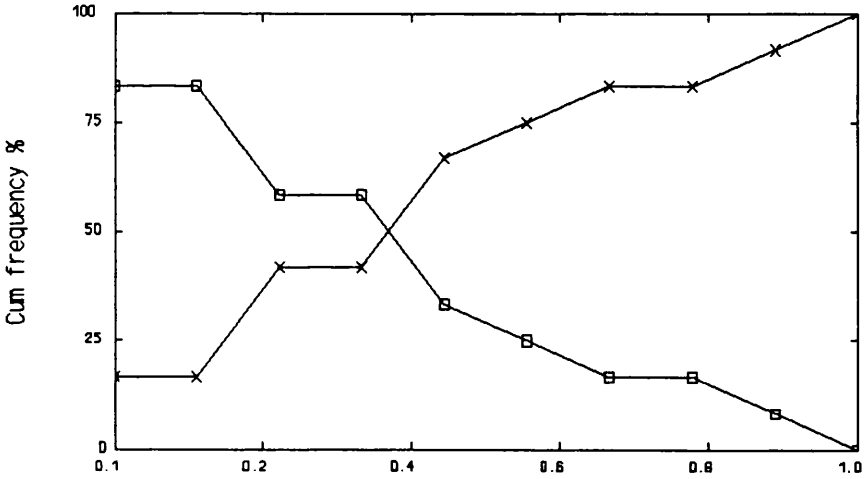
Figure 31. Group 1 : 3D displacement of reference points between 2 frame positionings on each of 12 patients (mm). [cumulative frequency].

Frontal ref. point

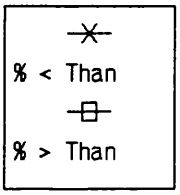


Occipital ref point





Thalamic ref point



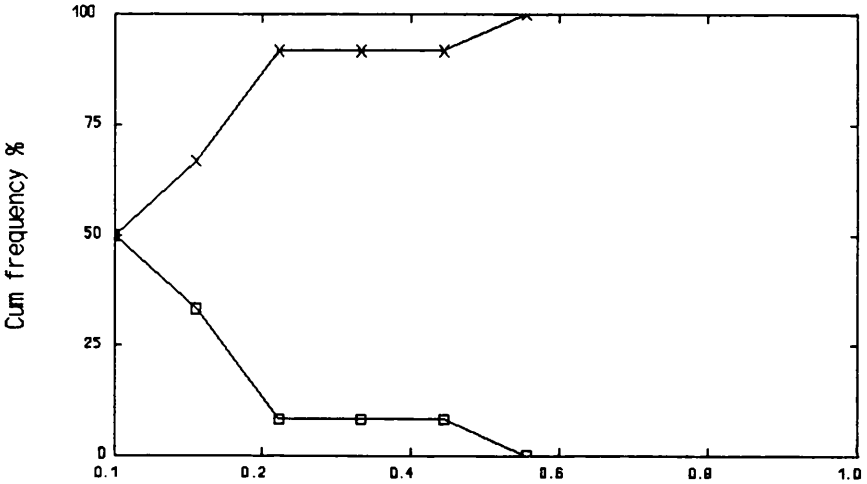


Table 3. **Group 1:** Displacement of reference points in each cardinal axis between any two frame positionings on each of 12 patients (mm).

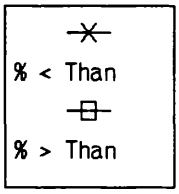
REF POINT	FRONTAL			OCCIPITAL			THALAMIC		
Axis	x	y	z	x	y	z	x	y	z
Maximum recorded displacement	0.4	0.7	0.3	0.3	0.7	0.6	0.1	0.5	0.2
Mean displacement	0.1	0.3	0.1	0.0	0.2	0.3	0.1	0.1	0.1
Median displacement	0.0	0.3	0.1	0.0	0.2	0.3	0.0	0.1	0.1

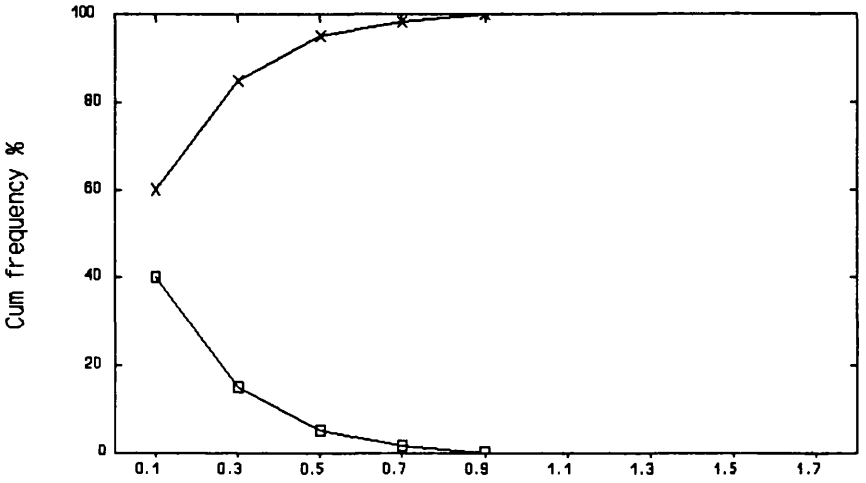
Table 4. **Group 1:** 3D displacement of reference points between 2 frame positionings on each of 12 patients (mm).

REF POINT	FRONTAL	OCCIPITAL	THALAMIC
Maximum recorded	0.9	0.9	0.5
Mean displacement	0.4	0.4	0.2
Median displacement	0.4	0.5	0.1

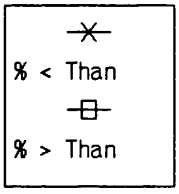
Figure 32 **Group 2 :** Displacement of frontal point in each cardinal axis between any two positionings of the frame on each of 10 patients (mm). [cumulative frequency].
(n=60 paired positionings - 4 on each of 10 patients)

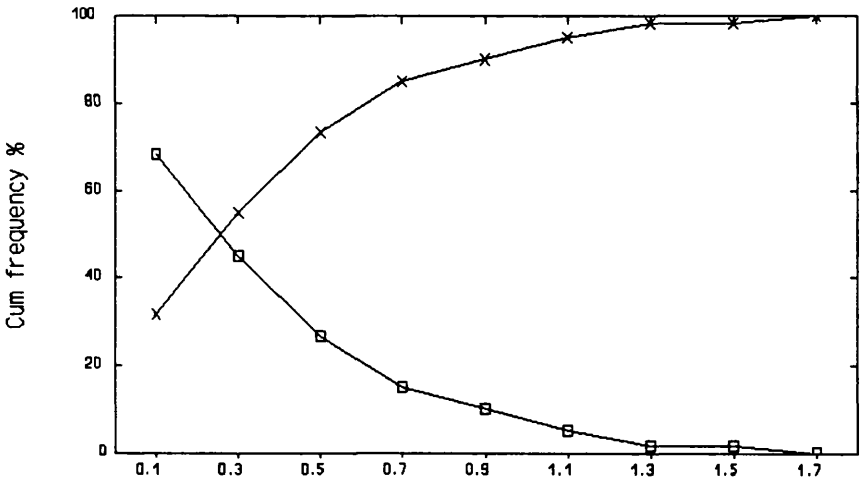
Lateral (x) displacement



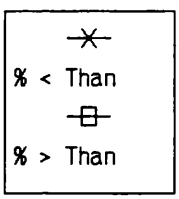


AP (y) displacement





Vertical (z) displacement



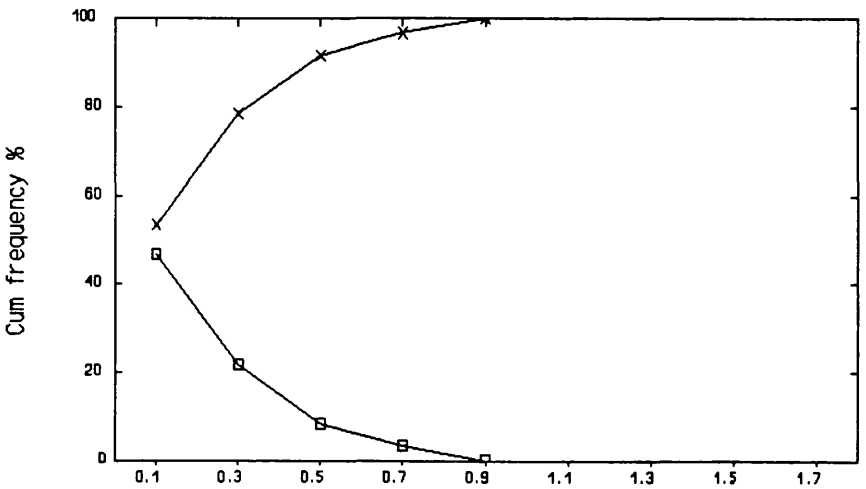
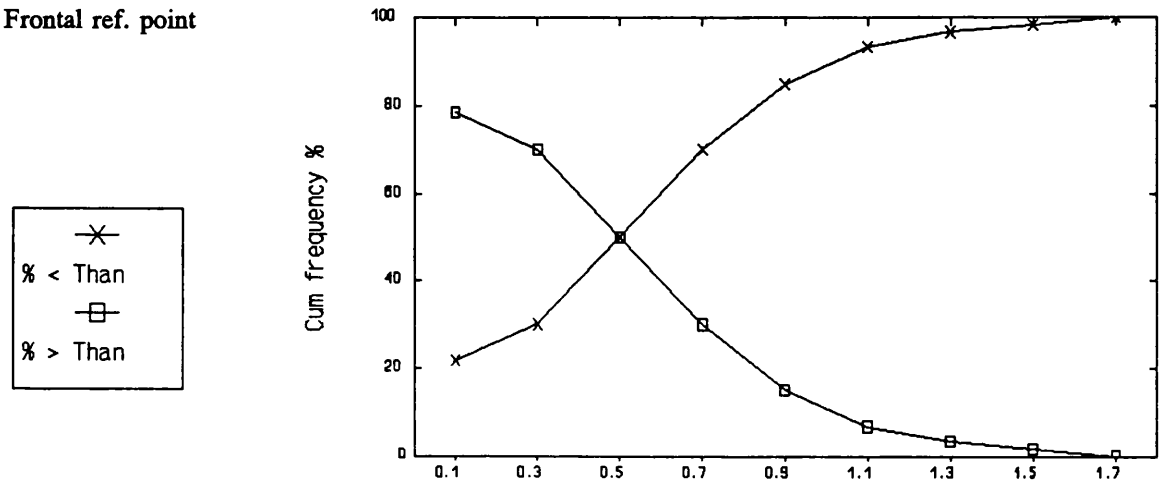
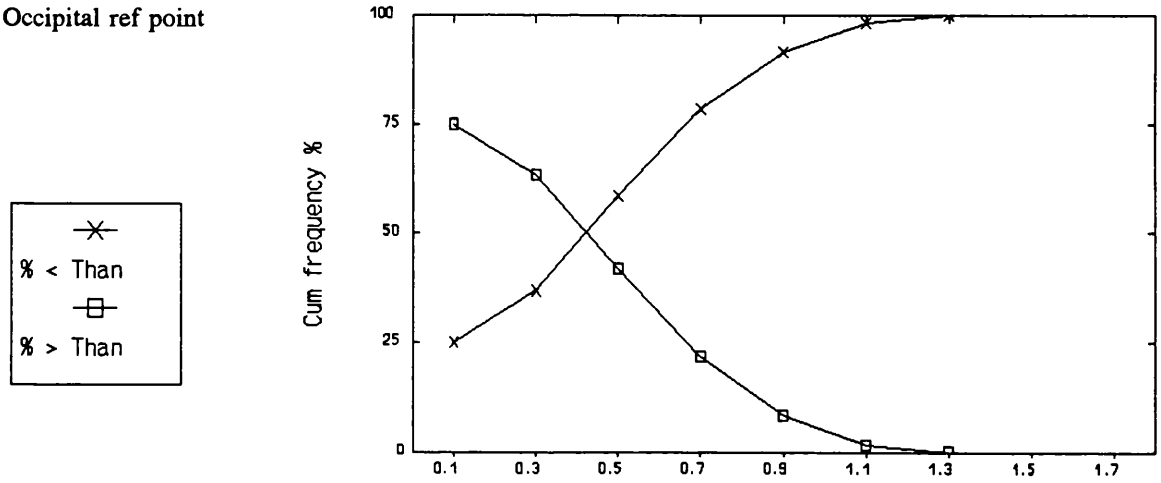


Figure 33 **Group 2 : 3D displacement of reference points between any 2 frame positionings on each of 10 patients (mm). [cumulative frequency].**
(n=60 paired positionings - 4 on each of 10 patients)

Frontal ref. point



Occipital ref point



Thalamic ref point

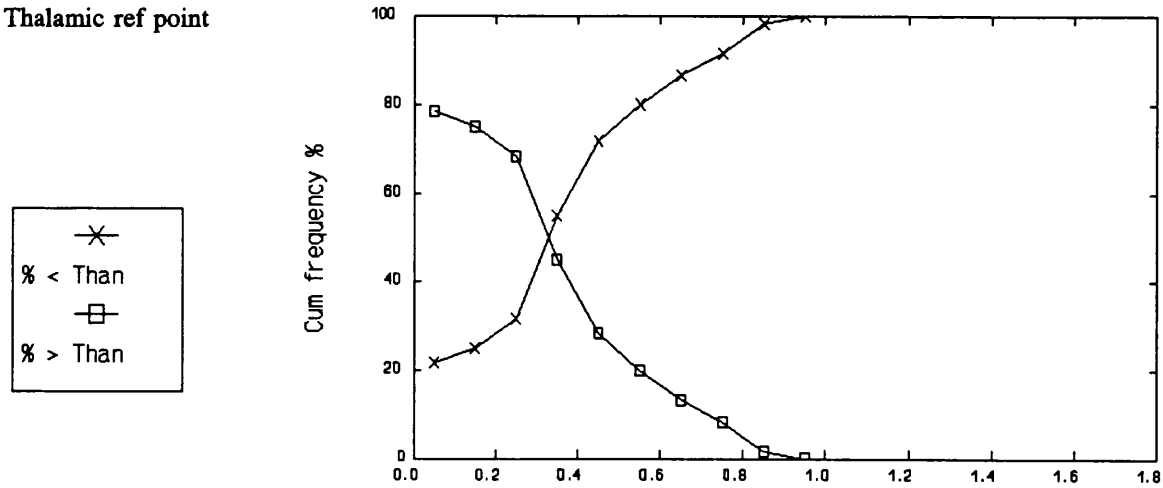


Table 5. **Group 2:** Displacement of reference points in each cardinal axis between any two positionings of the frame per patient (mm). (n=60 paired positionings - 4 on each of 10 patients)

REF POINT	FRONTAL			OCCIPITAL			THALAMIC		
Axis	x	y	z	x	y	z	x	y	z
Maximum recorded displacement	0.9	1.8	1.0	0.7	0.8	0.9	0.7	0.7	0.7
Mean displacement	0.2	0.4	0.2	0.2	0.2	0.3	0.1	0.2	0.2
Median displacement	0.1	0.4	0.1	0.1	0.2	0.4	0.0	0.2	0.2

Table 6. **Group 2:** 3D displacement of reference points between any 2 positionings of the frame per patient (mm). (n= 60 paired positionings - 4 positionings on each of 10 patients)

REF POINT	FRONTAL	OCCIPITAL	THALAMIC
Maximum recorded	1.8	1.3	0.9
Mean displacement	0.6	0.5	0.4
Median displacement	0.6	0.5	0.4

Discussion

THE METHOD OF ASSESSMENT

The reproducibility of frame fixation was assessed by measuring the displacement of points of interest in the head on AP and lateral radiographs with fixed x-ray sources and plates. Radiographs were used rather than CT or other imaging modalities because the spatial resolution of radiographs is extremely high (i.e., the grain size on the film). By contrast the spatial resolution of CT is relatively poor being dependant on the voxel size (eg .6 x .6 x 1.5mm). Although the SGV localiser was used to provide external reference points from which to measure frame repositioning error, the SGV software was not used because this averages out the co-ordinate positions to the nearest millimetre which was felt to be of insufficient accuracy.

One of the main difficulties with this radiographic technique if one does not have access to a dedicated teleradiographic set-up, is the requirement to exactly reproduce the x-ray source to frame to film relationship each time a patient is re-imaged. In particular, errors in the realignment of the central axis of the x-ray beam relative to the stereotactic frame between images can result in the apparent displacement of fixed reference points. Significant errors may therefore be introduced into comparative measurements made between the films.

Alignment of the central axis of the x-ray source for the phantom studies was of less consequence than for the patient studies, because after the initial set-up the frame remained fixed relative to the AP and lateral x-ray sources for all repositionings of the phantom head.

For the Group 1 patients at Maida Vale Hospital the ceiling mounted x-ray sources were at fixed distances from the BRW floor stand. The alignment of the central ray for each x-ray source was achieved when the light beam from each source struck the central reference markers on the opposing AP or lateral plates of the angiographic localiser. The alignment was checked on AP and lateral films and compared with previous radiographs prior to the patient being repositioned in the frame.

For the Group 2 patients, malalignment of the central beam may have played a more significant role in introducing error. Simulator couch movements were used to align the central beam of the treatment simulator x-ray source with the centre of the BRW co-ordinate system of the frame. This was achieved by the alignment of a laser light on the x-ray source to crosses engraved on three faces of a Perspex localiser box indicating the central cardinal axes of the co-ordinate system. The errors introduced by this method of alignment are difficult to assess but may be as much as 0.3mm.

Points of interest were marked in the phantom skull by positioning 1mm metallic ball bearings which could be identified on the AP and lateral films. These were in the frontal, parietal, occipital and thalamic regions. In the patient studies, reference points in the mid-sagittal plane were defined by pinholes in the

lateral reference film at the Bregma (frontal point), the Lambda (occipital point) and at the midpoint between the frontal and occipital poles (thalamic point). The pinhole reference points were then transposed to the mid-sagittal plane on the AP film taking into account the relevant magnification factors. The advantage of using pinholes to identify points in the skull rather than visible bony landmarks alone, is that it is extremely difficult to reliably identify the same bony points on AP and lateral radiographs. In addition, if one is attempting to measure sub-millimetre displacement of bony points on a series of films, then one could not rely on an individual to repeatedly identify the same point on a series of radiographs with an accuracy better than 1 to 2 millimetres.

In contrast, by using the 'pinhole' method described, points identified on a reference film can be transposed to subsequent films of the same patient with an accuracy in the order of 0.1 millimetres. When a radiograph and a reference mask film are superimposed then any minute degree of mis-matching at any of the many thousands of potential reference points on the skull will be seen as an interference pattern of black and white lines on a grey background. When the films are perfectly matched the images will completely subtract. The pinhole reference points made in the reference mask film can now be made through the matched film with great precision.

When the superimposed films are realigned so that the SGV reference markers completely subtract, then the displacement of each pinhole from its counterpart in the reference film is measured to the nearest 0.1mm. It did not seem reasonable to measure displacements with greater precision than 0.1mm (the width of a human hair), because this was assumed to be the approximate accuracy with which one could match superimposed films.

One shortcoming of using the pinhole method of transposing reference points from one film to another is apparent when reference points at different depths along the mid-sagittal plane are transposed from one AP film to another. If these were actual points in the brain visible on an AP radiograph and lateral displacement of the head occurred between the first and second AP film, then the differential displacement of the frontal reference point would appear to be greater than that of the occipital point. This is because the magnification factor at the position of the frontal reference point is greater than at the occipital as it is furthest away from the film. Using the 'pinhole' method described, the mid-sagittal points are transposed from the reference AP film to the test film by superimposing the skulls. The films are then realigned so that the SGV markers subtract. This obviously makes all the points on the mid-sagittal plane together irrespective of their different magnification factors.

To determine the actual lateral displacement of each point, the assumption is made that in matching the skulls on superimposed AP films, the 'best fit' is made at the mid-coronal plane. If there is lateral displacement of the head between frame fittings, then the measured lateral displacement of each point along

the mid-sagittal plane can be corrected to its actual displacement by dividing its value by the magnification factor at the mid-coronal plane.

PHANTOM STUDIES

When the phantom was positioned fifteen times in the relocatable frame the maximum recorded displacement of any point in the head between repositionings was no greater than 0.8mm in any axis. The maximum expected range of displacement of any point in the head between relocations in 99.7% of cases was no greater than 1.2mm in any axis.

The maximum recorded 3-dimensional displacement of any point in the head between repositionings was 1mm. This displacement occurred at the occipital reference point. The maximum displacement of the frontal and parietal points between repositionings were 0.9mm and 0.8mm respectively; and that of the thalamic reference point was 0.4mm.

Because the frame is located and fixed via the upper jaw, one would expect that the greatest displacement of the head would occur at a point furthest from the dental fixation. This has been demonstrated by the maximum displacement occurring at the occipital reference point.

PATIENT STUDIES

The accuracy of repositioning the frame in the first group of twelve patients was very similar to the accuracy of repositioning the frame on the phantom head. The maximum recorded displacement of any point in the head between repositionings was no greater than 0.8mm in any one axis. The maximum recorded 3D displacement of any point in the head between repositionings of the frontal and occipital reference points were 0.8,, and 0.9mm respectively. That of the thalamic reference point was 0.5mm. The patient with the maximum displacement of the occipital and thalamic reference points had full dentition. The patient with the maximum displacement of the frontal reference point was edentulous.

The majority of targets selected for stereotactic procedures are deeply situated. The potential displacement of the thalamic reference point is therefore of most relevance to the clinician. The thalamus has the least recorded displacement relative to the frame, because it is closest to the primary site of fixation on the upper jaw.

The Group 2 patients from St Bartholomew's Hospital had greater errors in repositioning the frame than in the phantom and Group 1 studies. The maximum recorded 3D displacement between repositionings of the frontal and occipital points were 1.8mm and 1.3mm respectively. That of the thalamic point was

0.9mm. The most significant difference between these groups was the use of the dental impression material (vinyl polysiloxane putty) at St Bartholomew's Hospital.

It is of note that the St Bartholomew's group were using the Relocatable Frame for stereotactic radiosurgery of arteriovenous malformations where precision of dose delivery is essential. Where detectable errors in relocation occurred between the application for acquiring the planning CT and the application for treatment (as established from superimposed simulator films), the error was corrected by finely adjusting the position of the LINAC couch. By this means the planned target was brought exactly to the isocentre of the LINAC.

The accuracy of repositioning the frame has been independently assessed by Mr. A. Sofat at the National Hospital, Queens Square. The method he employed, was to apply the frame together with the BRW stereoguide such that a guided probe pointed to a spot on the scalp. This was marked using a fibre tip pen. The frame was removed and reapplied. The proximity of the probe to the point previously marked was noted.

Patient	Application 1	Application 2	Application 3
3	<0.5mm	<1.0mm	<0.5mm
4	<0.5mm	<0.5mm	
5	<0.5mm	<0.5mm	<1.0mm
9*	<1.0mm	<1.5mm	<1.5mm
14+	<0.5mm	<0.5mm	

* Edentulous patient.
\+ Partially dentulate patient.

(Reproduced with permission of A. Sofat unpublished work).

There are obvious limitations in the method of using a ruler to measure sub-millimetre displacements of a pen mark on a movable scalp relative to a metal pointer. The results however, would indicate that the accuracy of repositioning the frame in this group of patients was similar to the Group 1 patients previously presented. All the patients in this group had dental impressions made from acrylic, which were pressure formed over a plaster model of the patients teeth. This forms a rigid impression similar to the PEM impression previously described.
Dr J D Graham at the Royal Marsden Hospital independently assessed the accuracy of relocating the frame in four patients using the rubbery dental impression material vinyl polysiloxane. (Graham 1991).

The mean AP displacement between relocations was 1.0mm (range 0.7 - 1.2mm), and the overall mean lateral displacement was 1.0mm (range 0.4 - 1.6mm). These larger errors which result from the rubber impression material are comparable to those of the Group 2 patients from St. Bartholomew's Hospital who used the same material.

SOURCES OF ERROR IN REPOSITIONING THE FRAME:

It is evident from patient studies that the reference points furthest from the point of fixation on the upper jaw have the greatest repositioning error. Although the dental impression is the prime site of head localisation, stability of fixation is dependent upon the head straps and head rest. Each of these elements may therefore contribute to errors in relocation to a variable degree.

Variation in tension applied to the head straps by different individuals is likely to contribute to errors in repeated fixations of the frame. Insufficiently tightened straps will allow the head to move relative to the impression and when unevenly tightened may act to displace the head from the impression. When the coronal straps are correctly positioned and tightened they produce a force that acts along a vector passing through the centre of the dental tray. Depending on the friction between the scalp and the coronal straps the tension in the sagittal straps, which immobilise the coronal straps over the vertex, will vary. In these circumstances the resultant vector of the combined forces may pass behind the molar teeth tending to rotate the head backwards. Although the head rest should prevent posterior rotation of the head it is possible that the displacements recorded could occur as a result of variable compression of the scalp, or due to the scalp sliding over the occiput. Variation in hair thickness between the scalp and the occipital mould between repositionings of the frame may also play a part in introducing error.

Head repositioning errors that could be attributed to displacements occurring at the point of dental fixation may result from a patient being edentulous, from movement of the teeth in their sockets, movement of the teeth in the dental impression, or movement of the dental impression relative to the frame.

i. Edentulous patients

In edentulous patients movement of the impression on the upper jaw will result from differential compression of the mucosa covering the alveolar margin and hard palate. One would obviously expect greater errors of frame relocation in this group of patients than in those with dentition. It is therefore interesting to note that in group 1 patients the one patient who was edentulous had a repositioning error that was greater than the average for those with dentition and had the highest 3D error for the frontal reference point but it was a patient with full dentition in whom the greatest errors were recorded at the occipital and thalamic points. None of these displacements exceeded 1mm. In Mr Sofats repositioning data one patient was edentulous and had the greatest inaccuracy in frame relocation, but this was less than 1.5mm.

ii. Movement of the teeth in their sockets

The amount that a tooth will move in its socket is dependent upon the magnitude and direction of the applied force and the properties of the periodontal ligament.

The periodontal ligament attaches the tooth to the adjacent alveolar bone and occupies a space approximately 0.5mm in width around all parts of the root. It is composed of a network of collagenous fibres which run at an angle, and attach further apically on the teeth than on the adjacent alveolar bone.

Other constituents of the periodontal ligament include mesenchymal cells and tissue fluids. The tissue fluids act as a shock absorber.

When the teeth are forced onto the fixed surface of the dental impression, the direction of the force is generally perpendicular to the occlusal plane which tends to intrude the teeth into their sockets. The threshold for tooth movement is very small and tooth movement increases in relation to the applied force up to the point where the periodontal ligament is almost fully compressed (i.e., compressed to about half its resting thickness = 0.25mm). Because an intruded tooth concentrates the applied force on the periodontal ligament over a small area at the apex of the root, this point is reached with fairly small applied forces.

For an incisor tooth the force required to fully intrude it is approximately 15g. For a molar tooth this force is greater and in the region of 25g. This is because the applied force is distributed over a larger surface area of periodontal ligament (Proffit 1986)

Therefore when the dental impression is applied to the upper teeth with an applied force per tooth greater than 15-25g there should be negligible movement of the teeth in their sockets. Such forces are easily achieved by tightening the head straps, and forces of much greater magnitude than these are quite comfortably tolerated. For example during mastication of soft food the teeth normally take loads ranging from 1-2 Kg , but will take loads of as much as 50 Kg per tooth when biting more resistant objects.

iii. Movement of the teeth in the impression.

Instability of the dental impression on the teeth will result from:-

a. A loose fitting impression

This may occur as a result of shrinkage of the impression material during setting. All impression materials will shrink to some extent during setting, the acrylic materials for example will shrink by 1-3% during polymerisation.

Excessive removal of impression material from the buccal surface in order to provide clearance of the undercuts of the teeth may also allow the teeth to rock on the impression.

b. A distorted impression

Impressions taken using materials such as PEM which require removal from the mouth prior to the final set are vulnerable to distortion during this act.

To achieve an accurate impression with such materials is therefore very technique dependant and requires some expertise. If the material has not reached its elastic state prior to removal from the mouth it may flow and distort prior to its final set. The most significant error occurs if the dental tray is not withdrawn cleanly from the teeth. Any tipping of the tray during withdrawal will distort the occlusal surface of the impression and result in subsequent instability on the teeth.

If the impression is made of a soft and flexible material such as vinyl polysiloxane then it will be

continually prone to distortion. The fixation of the frame relative to the head will therefore be inherently less stable. Despite this vinyl polysiloxane has been used as an impression material in the Group 2 patients at St. Bartholomews Hospital.

The accuracy of relocation in this group appears to be surprisingly good, although obviously worse than in the Group 1 patients. One explanation for this may be that in forming the impression the patient bites through the soft material to the hard dental tray beneath. This may then provide two or three points of rigid fixation for subsequent relocation.

c. A partially obstructed impression.

The teeth may be prevented from coming into full contact with the impression by the presence of a foreign body in the dental tray. Alternatively the fit on the teeth may be too tight in one area of the impression again preventing proper seating of the teeth.

iv. Movement of the dental impression relative to the frame.

Despite optimising the design of the perspex dental piece and tray to minimise distortion under load it is quite possible to bend the dental piece manually with moderate force, particularly when applied to the posterior part of the tray.

WHAT DEGREE OF ACCURACY IS ACCEPTABLE ?

The accuracy with which a target can be defined within the brain using radiographic imaging is, in the first instance, dependent upon the size of the smallest voxel in which it can be identified. Most stereotactic procedures are performed using CT data whose smallest voxel size is a cube of dimensions 0.6 x 0.6 x 1.5 mm (slice thickness).
The greatest 3D displacement a target can have within a voxel of this size is 1.7 mm. So that if one excludes all errors in a stereotactic localisation system and stereoguide, the greatest accuracy with which a target can be defined using CT is within 1.7 mm. MRI and PET images have voxels of larger size than CT thereby further decreasing the accuracy of localisation.

The accuracy with which CT generated coordinates can be transposed to stereotactic systems has been referred to in Chapter 1. For most stereotactic systems the expected error is between one and two millimetres. A further factor to take into consideration when evaluating the magnitude of errors in defining brain targets stereotactically is the movement of the brain in the skull. The brain is a pulsatile organ whose volume will change depending on physiological variables such as venous return and carbon dioxide saturation. When a patient moves from the prone to the supine position the cerebral hemispheres may move by several millimetres particularly in the elderly who have more atrophic brains.

When invasive stereotactic procedures are performed such as biopsy or electrode placement, the inadvertent drainage of CSF and the passage of a probe through the brain will displace a previously defined target. I have personally observed the displacement of a firm tumour by as much as 5mm during a biopsy procedure which was monitored using dynamic ultrasound imaging.
Bearing these factors in mind, the precision with which a probe can be stereotactically guided to a brain target defined on high resolution CT must have an uncertainty of at least 3-4mm. The additional uncertainty introduced by the use of the Relocatable frame that is in the region of $\pm$ 0.5 mm for deep targets or $\pm$ 1 mm for cortical targets is I believe acceptable in view of the magnitude of error intrinsic to the stereotactic method.

CHAPTER 4

GEOMETRIC CORRELATION OF BRAIN IMAGES (using the Relocatable Frame)

Materials and Method

Results

Discussion

GEOMETRIC CORRELATION OF BRAIN IMAGES (using the relocatable frame)

Combinations of brain images from CT, MRI, PET and angiography have been geometrically correlated for the planning of stereotactic procedures in 10 patients with primary brain tumours. In addition, a number of these patients had follow-up imaging in stereotactic space to quantify the effects of post-operative radio-therapy. Multi-modality image correlation was achieved by the method of reproducible head positioning and fixation in each imager using the Relocatable Stereotactic Frame.

Materials and Method

Patients:

The patients selected for this study (6 males and 4 females: age range 35 - 65 years), had a clinical history strongly suggestive of a primary brain tumour and had positive CT scans. The various combinations of stereotactic investigations and procedures performed on each patient are shown in Table 7. Three had post-radiotherapy follow-up imaging under stereotactic conditions between 2 and 7 months later to quantify changes in the lesions.

Table 7 Stereotactic investigations and procedures

PATIENT No	Sex	Age	Pathology	INVESTIGATIONS CT	PET	MRI	Angio	PROCEDURE	FOLLOW UP Ix(months)
1	F	35	AA	1	2			Biopsy	
2	F	56	GBM	1	1			Biopsy	
3	M	59	GBM	1	1			Biopsy	
4	F	63	GBM	1	1			Biopsy	
5	M	65	GBM	1	1			Biopsy	
6	M	41	1°Lymphoma	1+1*	1+1*			Biopsy	4
7	F	39	GBM	1+1*	1+1*	1		Biopsy+craniot	7
8	M	60	GBM	1	1	1		Biopsy	
9	M	38	AA	2			1	Biopsy	
10	M	35	1°Lymphoma	1+1*				DXT	2

AA = Anaplastic Astrocytoma
GBM= Glioblastoma Multiforme

* Follow up stereotactic investigation

Scanners :

CT

Contrast enhanced CT examinations were performed with a GE8800 or a GE9800 scanner after the intravenous injection of 1ml of iohexol (Omnipaque 300 mgI/ml. Nycomed) per Kg. body weight. Images were acquired from the GE8800 scanner (at the National Hospital, Maida Vale), using a 35cm field of view and a 320x320 reconstruction matrix with a resultant pixel size of 1.1mm^2. The minimum slice thickness was 1.5mm with 1.5mm slice separations. Using the GE9800 scanner (situated at the Nat.Hosp. Queen Square) images were acquired from a 34.5cm field of view with a 512x512 reconstruction matrix and a pixel size of 0.67mm. The minimum slice thickness was 1.5mm with slice separations of 1.5mm.

PET

PET imaging was performed with an ECAT 931-08/12 scanner (Spinks et al. 1988) situated at Hammersmith Hospital. 15 contiguous planes of data were recorded simultaneously over a trans axial length of 10.8cm. Images were reconstructed using a 0.5 Hanning filter resulting in a spatial resolution of 8.4x8.3x6.6mm FWHM at the centre of the field of view. Prior to each study a transmission scan of 15 minutes was performed using an external ring source of Germanium ^{68}. This was used for subsequent attenuation correction of the emission scans.

The halogenated pyrimidine ^{18}F-Fluorodeoxyuridine (^{18}FUDR) was used as the PET tracer. This has been shown in animal studies to be incorporated into the nuclear fraction of proliferating cells (Abe Y, 1983) and was used in the study to assess its value in measuring tumour proliferation and the extent of tumour spread in vivo.(Authorization for the use of this radionuclide was given by the Administration of Radioactive Substances Advisory Committee. Permission to carry out this study was obtained from the Ethics Committee of Queens Square and Hammersmith Hospital. All patients gave informed consent). 100-150mBeq of^{18}FUDR (specific activity > 95 %) were infused over three minutes into a peripheral venous line. Arterial samples were withdrawn from a radial artery canula at frequent intervals and counted in a well counter to determine the arterial activity. Patients were scanned over a period of 2-3 hours.

MRI

MRI images were obtained with a 0.15 Tesla Picker prototype imager (at the RPMS Hammersmith Hospital). Single slice contiguous inversion recovery 1500/500/44 and spin echo 1500/80 sections of 8mm thickness were imaged. The field of view was 30cm and the pixel size 1.2mm^2.

Image acquisition under stereotactic conditions:

Prior to the acquisition of CT, MRI or PET images the Relocatable Frame is bolted to each imager couch by means of specially constructed interface brackets. Each interface bracket is U-shaped and comprises a couch fixation plate with vertically extending posts (see figs. 34, 35). A series of couch fixation plates have been constructed to attach to the conventional head rest fixation points on each scanner. Screws on the plates can be adjusted to alter their degree of pitch, yaw or tilt relative to the end of the scanner couch. Couch fixation plates for the CT scanners and PET scanner are constructed from aluminium and for the MRI scanner from the composite material Tufnol. The vertical posts are common to all the interface brackets and engaged with the couch fixation plates in transverse T-slides to allow lateral adjustment of the frame position in the imager. Vertical adjustment of the frame position is accomplished by fixing it to blocks which engage in lockable T-slides on the posts. The posts and blocks are constructed from Tufnol and the clamping screws from acetal.

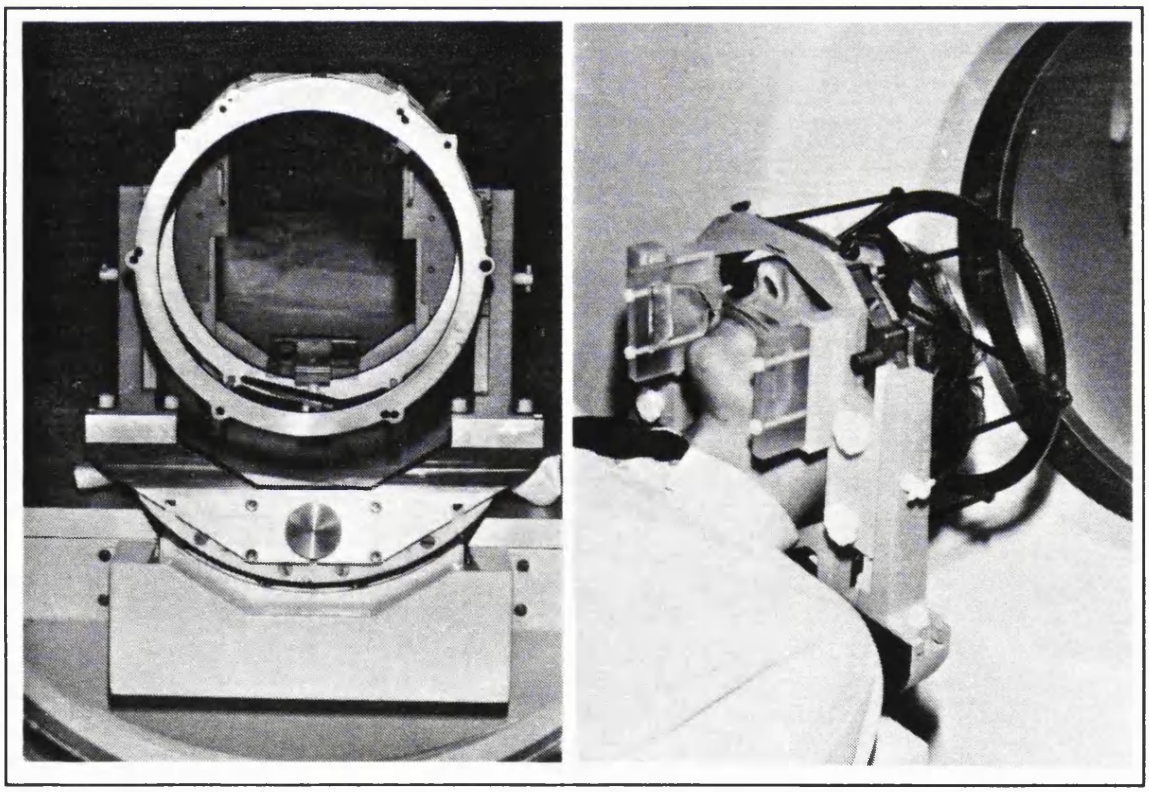


Figure 34 Relocatable frame with BRW system fixed to CT Scanner couch via Interface bracket

Figure 35 Patient fixed in CT scanner

Following fixation of the Relocatable Frame to the imager couch the BRW base ring with an attached imaging compatible fiducial system is then secured to its base plate. Using a combination of mechanical couch movements and fine adjustments on the interface bracket the position of the frame is adjusted so that the BRW base ring is isocentric with and parallel to the imaging plane. This is ensured when calibrated crossed lasers fixed to the scanner gantry in the imaging plane coincide with AP and lateral reference marks

on the BRW base ring. Images are then taken through the top and the bottom of the fiducial system to make certain that its isocentricity and parallelism is maintained through the image volume. Loss of congruity in the position of vertical fiducials can be measured on the display screen using a cursor centred on each fiducial section. Any error can then be corrected by adjustments to the interface bracket.

When these calibrations have been accomplished the Relocatable Frame is removed from its attachment to the interface bracket and non invasively fixed to the patients head. The patient is then positioned on the couch and the relocatable frame with attached BRW base ring and localiser, resecured to the interface bracket. (see fig.35) Cross laser alignment is then rechecked prior to image acquisition.

It is of note that patients undergoing dynamic PET imaging requiring multiple scans over 2-3 hours can be removed from the scanner and the Relocatable Frame for breaks between imaging sequences and then precisely repositioned by repeated fixation.

The stereotactic localiser used for imaging with CT and PET was the conventional BRW fiducial system comprising 9 carbon fibre rods arranged circumferentially as 3 N shapes. The rods were clearly visible as a series of radially positioned points on axial CT and transmission PET images. It was not visible on emission PET images but because transmission images were acquired prior to each set of emission images with the patient fixed in the same position, the stereotactic space defined on the transmission images could be transposed to the emission images.

For MRI imaging a localiser of identical geometry to the BRW fiducial system was constructed from hollow acrylic tubes which were filled with insert tubes containing 5% copper sulphate solution. (This localiser could made compatible with CT by filling the insert tubes with radiographic contrast solution or compatible with transmission and emission PET imaging using a solution of radionuclide). The diameter of the standard BRW fiducial system (30cm) was larger than the diameter of the standard MRI head receiver coil (29cm). A special two-turn saddle receiver coil was therefore made around a 30cm diameter acrylic cylinder that fitted snugly around, and was secured to the fiducial system. This was tuned to optimise the image resolution.

Generally all images were taken from the same base line axial slice position with the minimum slice thickness and slice separations for each imager throughout the head volume. However, to minimise radiation exposure to patients having high resolution CT head scans, narrow slice thicknesses and separations were confined to the volume of interest (ie the volume containing the tumour or for functional procedures, the volume containing the third ventricle and the thalamus). The remainder of the image volume was then completed with larger slice separations eg 5mm or 1cm depending on the requirements of the data.

In one patient in this series (case 9) stereotactic angiography was correlated with CT data to plan an avascular trajectory for biopsy of a deeply situated lesion. The stereotactic angiogram was obtained by fixing the patients head in the Relocatable Stereotactic Frame with attached BRW base ring and the SGV Angiographic Localiser. The patient was positioned on a couch in the angiographic suite and the Relocatable Frame fixed to the BRW floor stand by a specially constructed interface bracket. Using fixed X-ray sources and radiographic plates, AP and lateral radiographs were taken during the injection of contrast (Omnipaque. Nycomed) into the right and left carotid arteries.

The CT derived stereotactic coordinates of the biopsy target within the tumour were transposed to the AP and lateral angiographic films with reference to radio-opaque markers on the angiographic localiser. This was achieved by overlaying a millimetre grid on the angiographic films and establishing coordinates for 8 reference points visible on each AP and lateral film. These X-ray coordinates were entered into a portable microcomputer which then calculated the mathematical transformations between BRW coordinates and the X-ray coordinates using the SGV software program. When the biopsy target coordinates are entered the computer then prints out the corresponding X-ray coordinates. The target can then be located on the films using the millimetre grid overlay. A biopsy trajectory that would avoid vessels was then planned from the AP and lateral angiograms and the coordinates of an entry point into the skull were then transformed from the X-ray coordinates to the BRW coordinates. The target and entry point coordinates were then used to calculate the arc settings and probe depth on the BRW stereoguide.

Image correlation

Image data was transferred from each imager to a Sun 3/260 computer (Sun Microsystems Inc. Mountain View Calif.) by magnetic tape. The software used for image correlation and analysis was Analyze Version 2 (Biodynamics Research Group. Mayo Clinic, Rochester Minn.)

A 3D computer matrix was constructed of voxel sizes identical to the first high resolution CT volume. Its total dimensions just incorporated the stereotactic space defined by the BRW stereotactic system such that each voxel position could be identified in terms of BRW coordinates. The base line slice from the first CT volume was positioned precisely in the matrix so that the x,y and z coordinates matched. The vertical position of the base line slice was known as it was the datum used in the set up procedure prior to image acquisition. The centre of the image corresponded with the zero coordinates for x and y. These positions were confirmed by measuring the relationship between the vertical and oblique fiducials seen in section on the axial slice which allowed calculation of the x,y and z coordinates of the central pixel on the image using a pre programmed portable computer (Epson HX-20). When the base line slice was positioned the subsequent axial slices in the CT volume were placed into the computer matrix. Correct alignment of both volumes were confirmed by calculating the x, y and z position of the central pixel in the top axial CT slice.

Any misalignment could be corrected by rotating or translating the CT volume appropriately.

Image volumes to be correlated with the first CT volume (eg MRI, PET or additional CT images) were scaled to match the voxel size of the primary image volume and then placed into the 3D computer matrix as previously described. The accuracy of multimodality image correlation was checked by selecting corresponding axial slices from the top and bottom of each image volume and measuring the coordinate positions of the vertical and oblique fiducials to ensure that they were identical. Paired image slices could also be superimposed or subtracted from one another to ensure accurate matching of the fiducial positions.

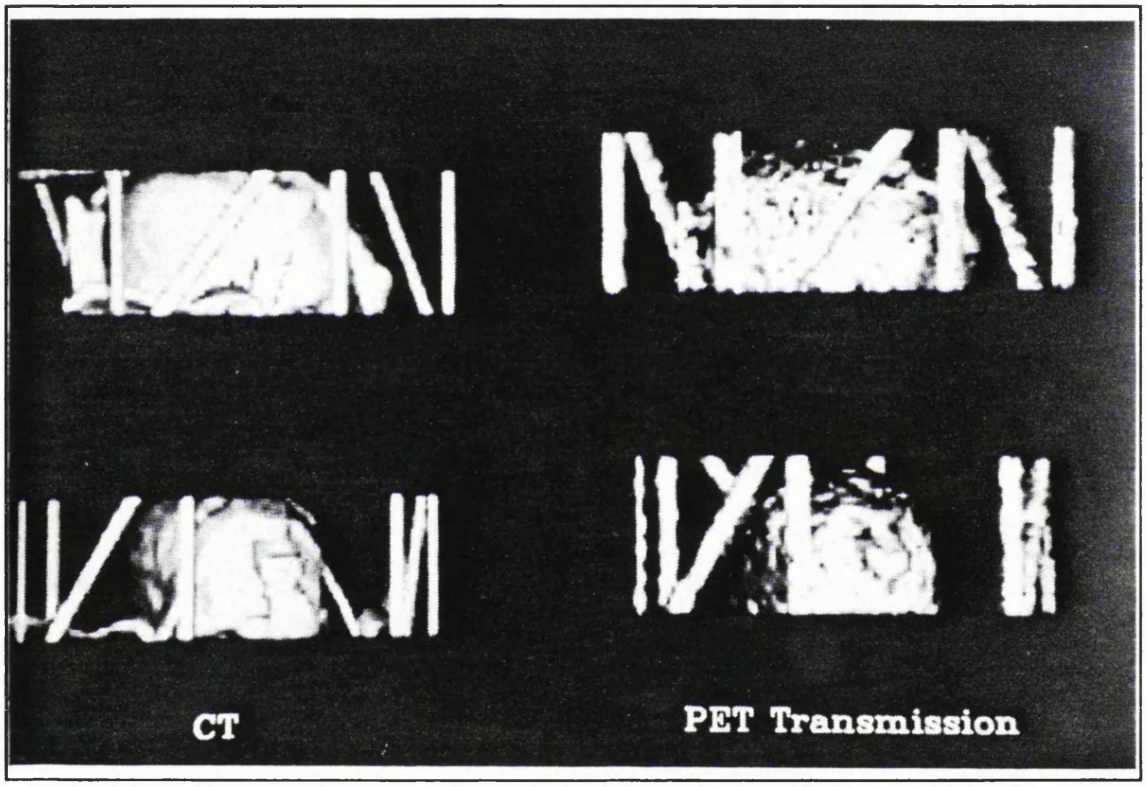


Figure 36 Geometrically correlated CT and Transmission PET volumes of patient in Relocatable Frame.

A computer graphics reconstruction of the fiducials in the 3D computer matrix was used as a fiducial check of image correlation. The fiducials were represented by lines in space which corresponded with the central axes of each rod. Each imaging volume was resliced in a series of 3 vertical planes that passed through the central axes of each set of N shaped fiducials. By superimposing the graphic display of the fiducials over the reconstructed image taken through the same plane, any variation in rotation, translation or scaling could be measured and corrected for each image volume. It is of note that any computer manipulations performed on transmission PET images to achieve precise geometric correlation with other images were also performed on the PET emission data so that these were geometrically correlated by virtue of the fact that they were acquired with an identical set up to the transmission images. Geometrically correlated CT and transmission PET volumes are shown in fig.36.

Planning stereotactic procedures

For planning stereotactic biopsy using geometrically correlated images, regions of interest within the lesion were selected from the combined images. Trajectories were planned to avoid critical areas aided by the use of 3 dimensional surface rendered views of the tumour volume (as defined on CT, MR or PET images) suspended in stereotactic space in cut away CT surface projections of the skull. These give the surgeon an immediate appreciation of the 3D shape and size of the lesion and its relationships. The coordinates of the chosen entry point and target could be read directly from the images. Along the axis of this defined trajectory the images were reconstructed parallel to the sagittal and to the coronal planes for display. From these reconstructed views the apparent tumour boundaries seen on each imaging modality were outlined. The apparent tumour boundaries defined from different imaging modalities could then be compared by superimposition of the outlines.

In this series, serial stereotactic biopsies were performed through brain tumours using a Nashold side-cutting biopsy cannula that took cylinders of tissue 1cm in length and 2mm in diameter. The depth of each biopsy sample was adjusted peroperatively using a microdrive. The positions of the serial biopsies were planned and displayed by subdividing the trajectory path on the images into a series of 1cm long and 2mm wide rectangles which were numbered. The biopsy trajectory was transposed to the BRW stereotactic frame for serial biopsy by entering the coordinates of the entry point and the deepest target point into the portable pre-programmed computer that is supplied with the BRW system. This calculates the appropriate arc angle settings and probe depth on the stereoguide.

Correlated CT and PET data was used in one patient (case 7) to plan a stereotactically guided tumour resection via craniotomy. This was achieved by placing the PET defined tumour volume into a spatially matched CT volume depicting the skull. The BRW coordinates defining the height, width and length of the tumour volume were established from the image volume and the location and dimensions of a rectangular craniotomy bone flap overlying the lesion planned from this information. Surgery was simulated by erasing the portion of the skull that would be removed during craniotomy on the image volume. Using a 3D surface rendered projection of the combined PET and CT volumes the tumour could be viewed through the simulated craniotomy flap to ensure adequate access. At surgery the stereoguide was set to the coordinates of each corner of the craniotomy flap in turn and these points were marked on the scalp. When the craniotomy bone flap had been reflected and the dura opened the stereoguide was set to a target at the deepest part of the PET defined tumour volume on a trajectory that passed through the centre of the lesion. This was used peroperatively to guide surgical resection.

Results:

The results of image correlation are illustrated with selected case studies:

Case 1

A 37 year old woman presented with a 3 month history of left leg weakness, left arm paraesthesia and headaches. A diagnostic CT scan demonstrated a deep callosal space occupying lesion, the extent of which was poorly defined despite contrast enhancement. CT and PET images were acquired under stereotactic conditions in the relocatable frame. PET imaging using ^{18}FUDR as a tracer clearly delineated an extensive lesion infiltrating into both hemispheres. The extent of the (^{18}FUDR) PET defined lesion did not appear to be due to simple diffusion across the damaged blood brain barrier because a PET study with Rubidium^{81} demonstrated a less extensive lesion (fig. 37).

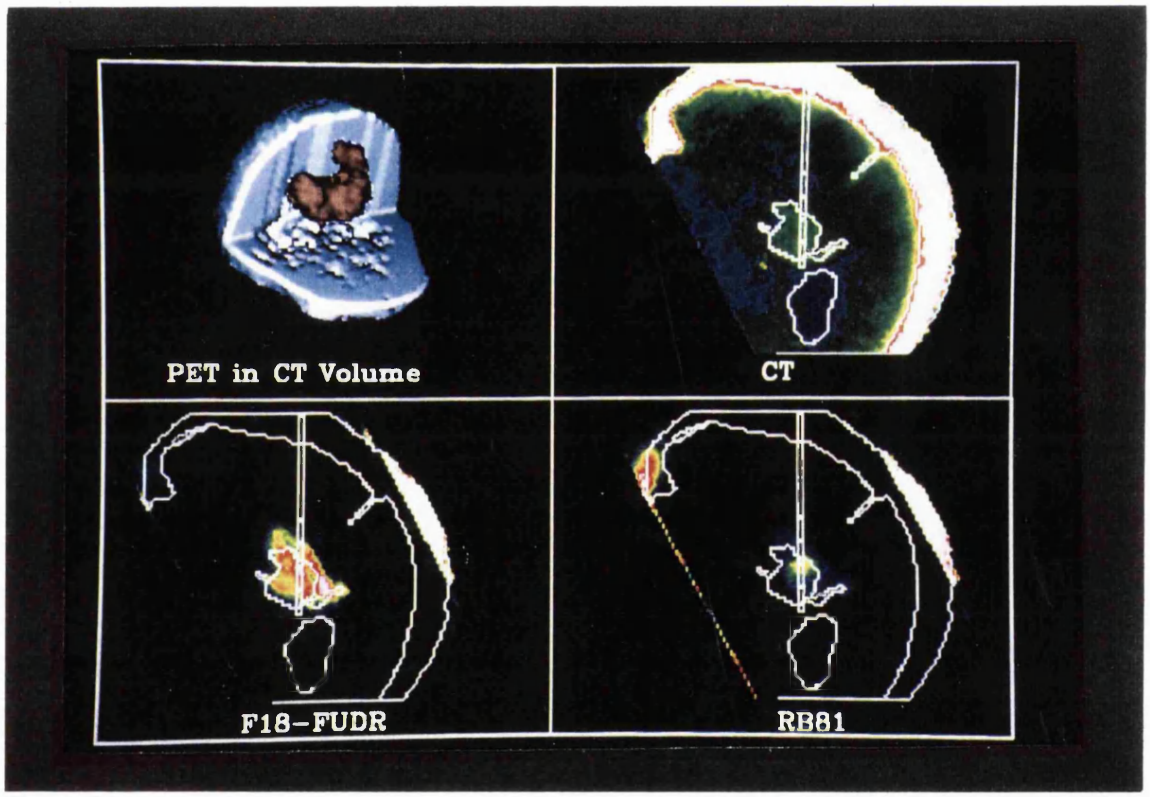


Figure 37 **Case 1: Correlated contrast CT, (F18-FUDR)PET and (Rb81)PET. Images reconstructed along biopsy trajectory. (CT boundry overlaid on PET images)**

The histology obtained from serial stereotactic biopsy was consistent with an anaplastic astrocytoma (grade III) and its histological boundary showed a good correlation with the (^{18}FUDR) PET defined boundary (fig. 38)

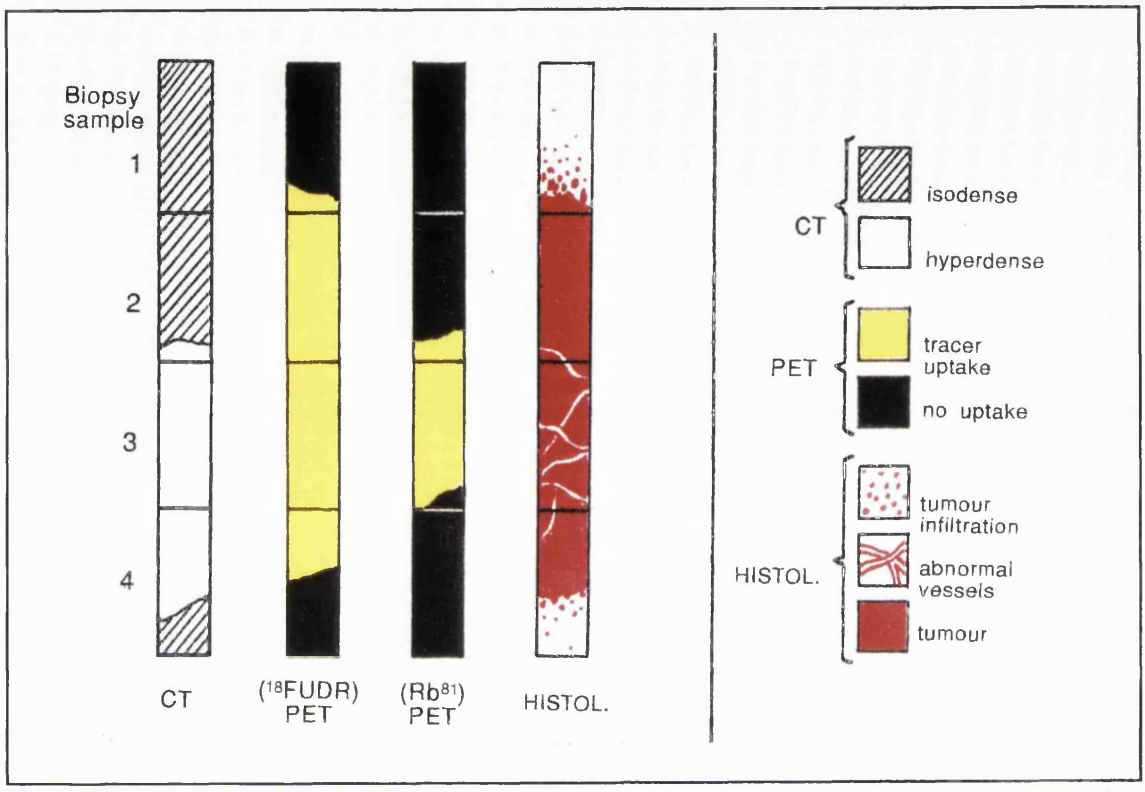


Figure 38 **Case 1. Comparison of contrast enhanced CT, (F18-FUDR)PET and (Rb81)PET with histology obtained from serial stereotactic biopsy.**

Case 3:

A 57 year old man presented with a 6 week history of headaches, left sensory inattention and a left homonymous hemianopia. A diagnostic CT head scan demonstrated a right occipito-parietal ring enhancing lesion. Serial stereotactic biopsy was planned from combined CT and (^{18}FUDR) PET imaging. The extent of the lesion defined by each modality differed with CT demonstrating ring enhancement just outside the PET defined boundary and hypodensity in areas within the lesion in which there was a high uptake of ^{18}FUDR on the PET image. (fig.39).

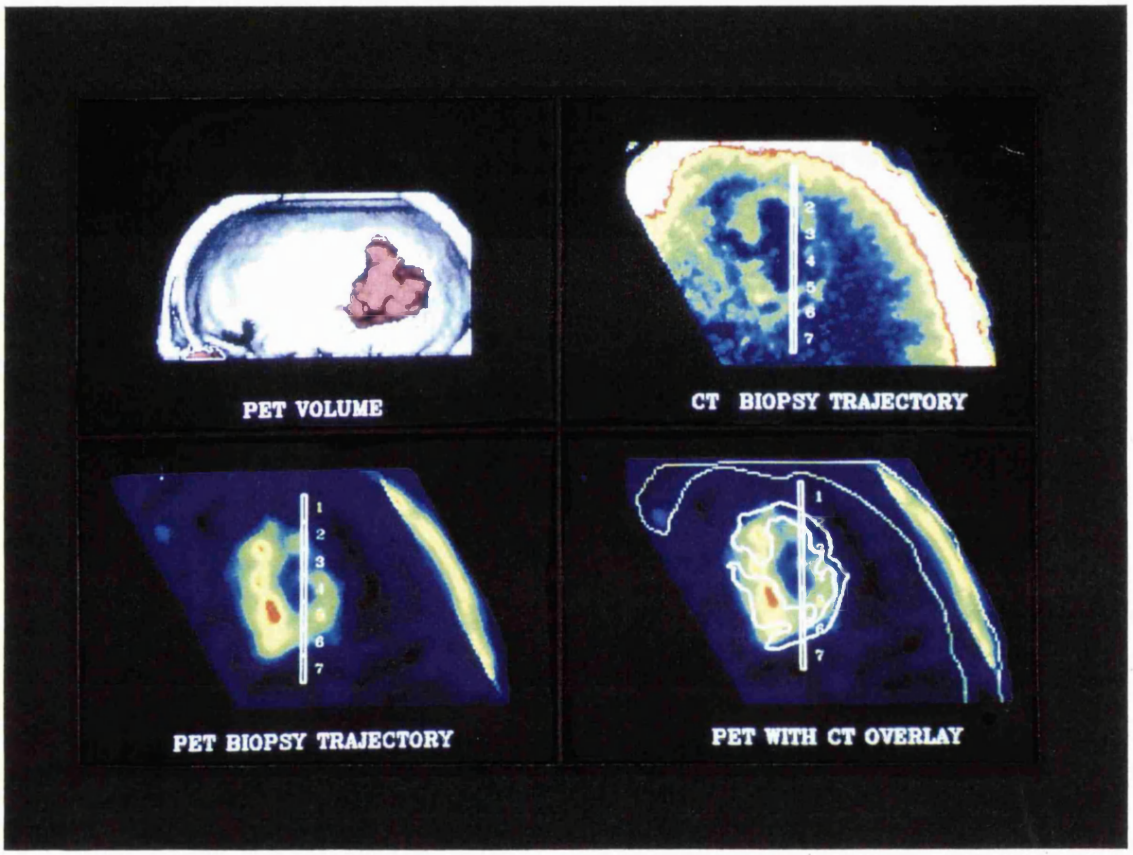


Figure 39 **Case 3: Correlated contrast enhanced CT and (F18-FUDR)PET. Images reconstructed along biopsy trajectory.**

The histology obtained from the proximal part of sample 2 (fig. 40) which correlated with the area of ring enhancement on CT showed gliotic tissue with some tumour infiltration and abnormal vessels. It did not demonstrate areas of solid tumour in sample 2 (distal portion) or sample 3 which were hypodense and indistinguishable from areas of necrosis (eg sample 4). By contrast the (^{18}FUDR)PET images showed increased uptake of tracer in areas where solid tumour was demonstrated histologically.

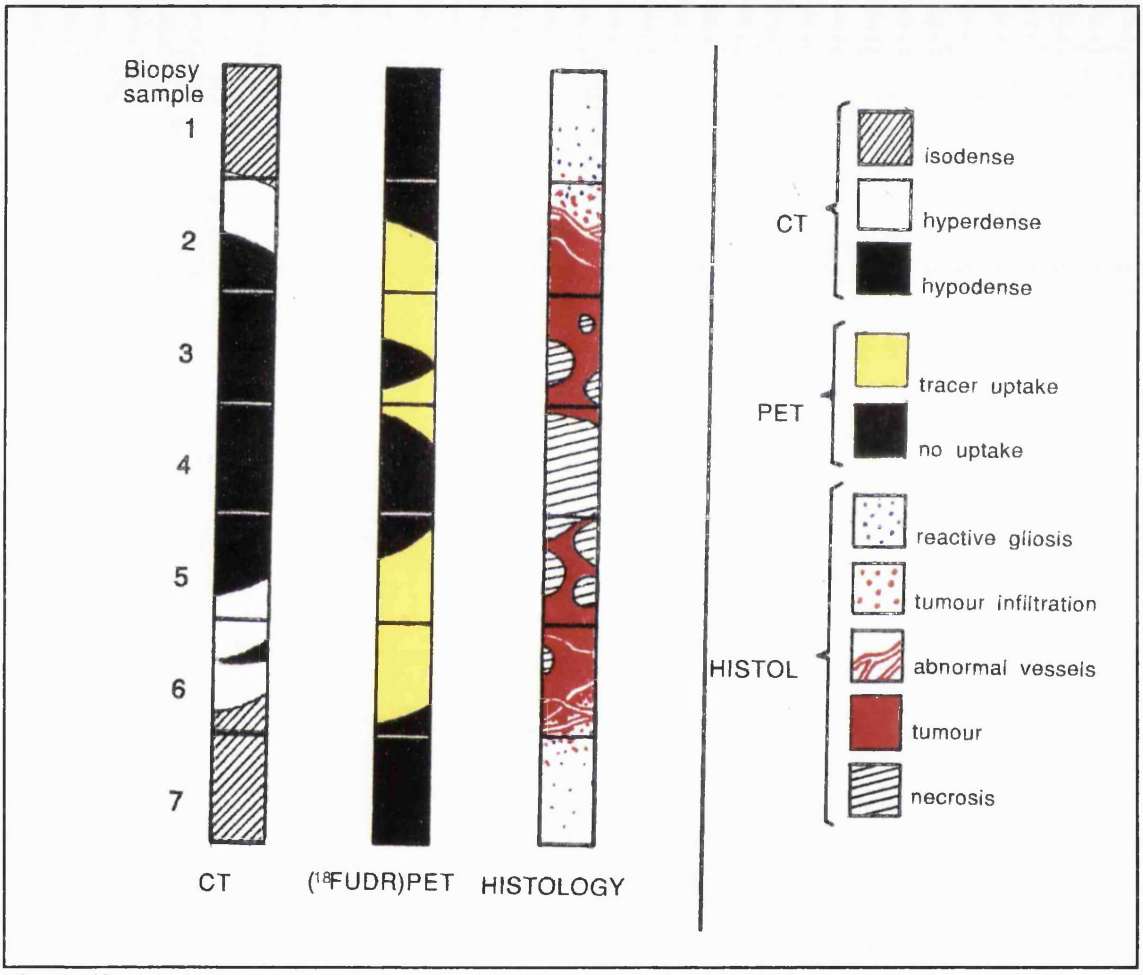


Figure 40 **Case 3: Comparison of contrast enhanced CT and (F18-FUDR)PET with histology obtained from stereotactic biopsy.**

Case 7:

A 39 year old woman presented with a three week history of sensory epilepsy involving the left arm and face. Examination revealed pyramidal weakness in the left arm. A CT scan demonstrated a right parietal ring enhancing lesion. She underwent a stereotactic biopsy and a craniotomy with guided excision of the lesion using integrated CT and (^{18}FUDR)PET data. The tumour proved to be a glioblastoma multiformé. The image simulated craniotomy is illustrated in fig.41.

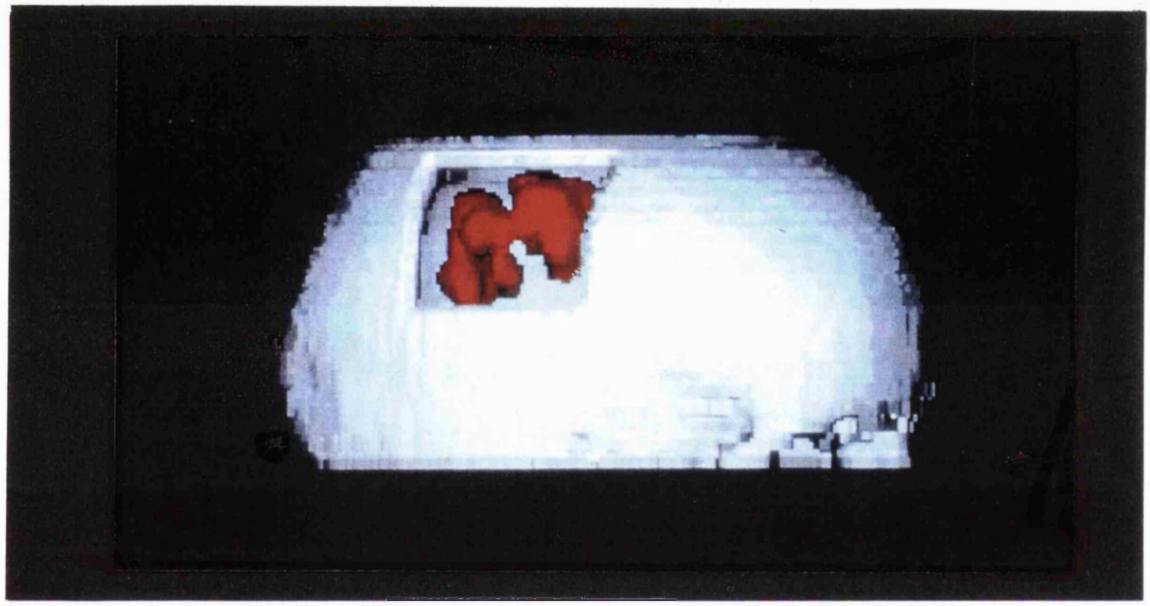


Figure 41 **Case 7: Image simulated craniotomy from correlated CT & (F18-FUDR)PET data.**

She made a good post operative recovery with improvement in left arm weakness and was treated with radiotherapy. At follow up 7 months later she had developed a recurrence of left hand weakness. Follow up CT PET and MRI imaging was performed under stereotactic conditions. (fig. 42)

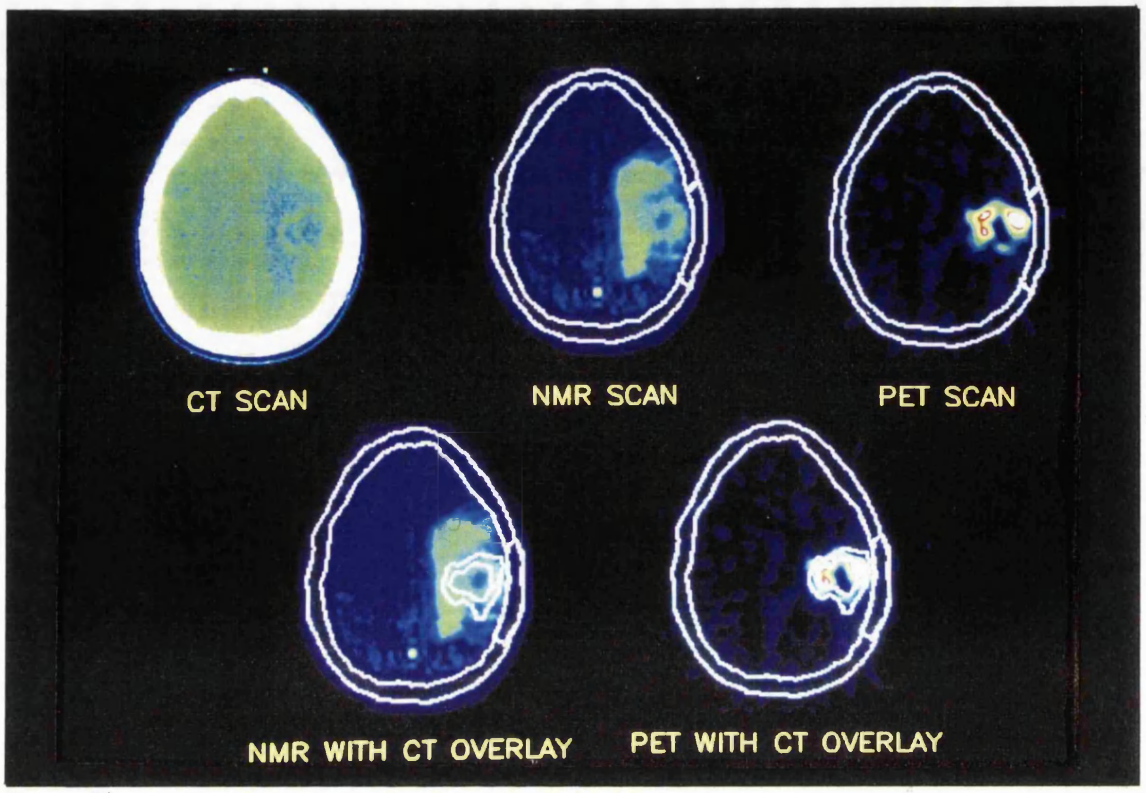


Figure 42 **Case 7: Correlated CT, MRI and (F18-FUDR)PET demonstrating recurrence of tumour post craniotomy and radiotherapy**

These showed recurrence of the tumour, the extent of which appeared to be most clearly depicted on the PET images. The use of the Rrelocatable Frame also allowed the precise geometric correlation of this data with the CT and PET images taken 7 months previously (fig. 43). Such correlations facilitate the objective measurement of changes in tumour volume.

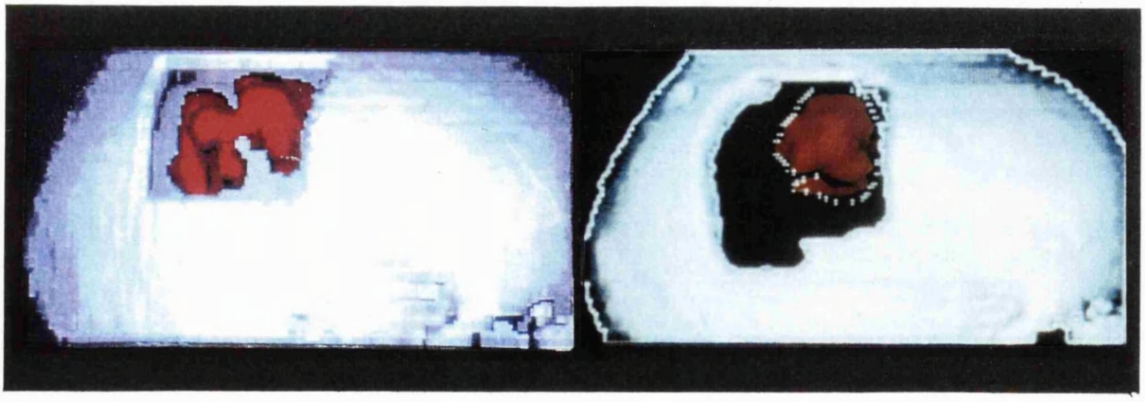


Figure 43 Case 7: a. Pre treatment PET volume in planning CT volume for craniotomy b. Post craniotomy & radiotherapy. Showing recurrent Tumour (as PET volume) in skull with actual craniotomy bone flap erazed

Case 9:

A 38 year old man presented to the casualty department after striking his right eye on an open car door. He also complained of recent poor memory. Examination revealed a right homonymous hemianopia.

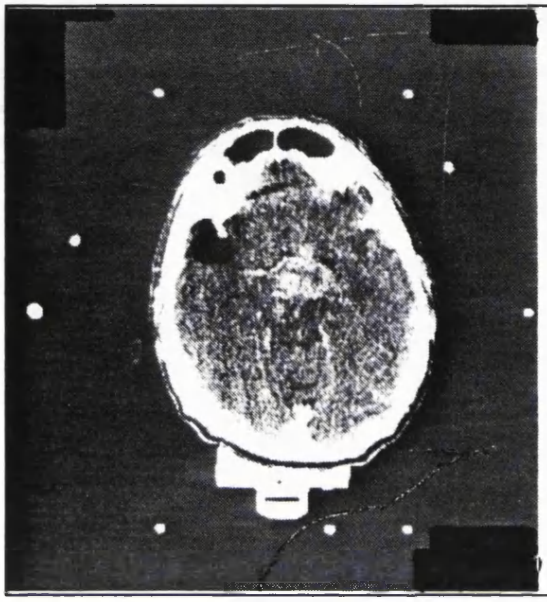


Figure 44 Case 9: CT scan showing biopsy target

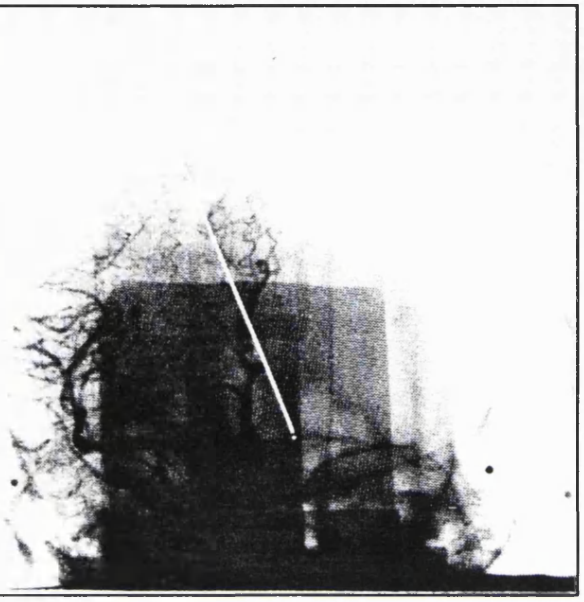


Figure 45 Case 9: Stereotactic Angiogram (AP) showing planned trajectory

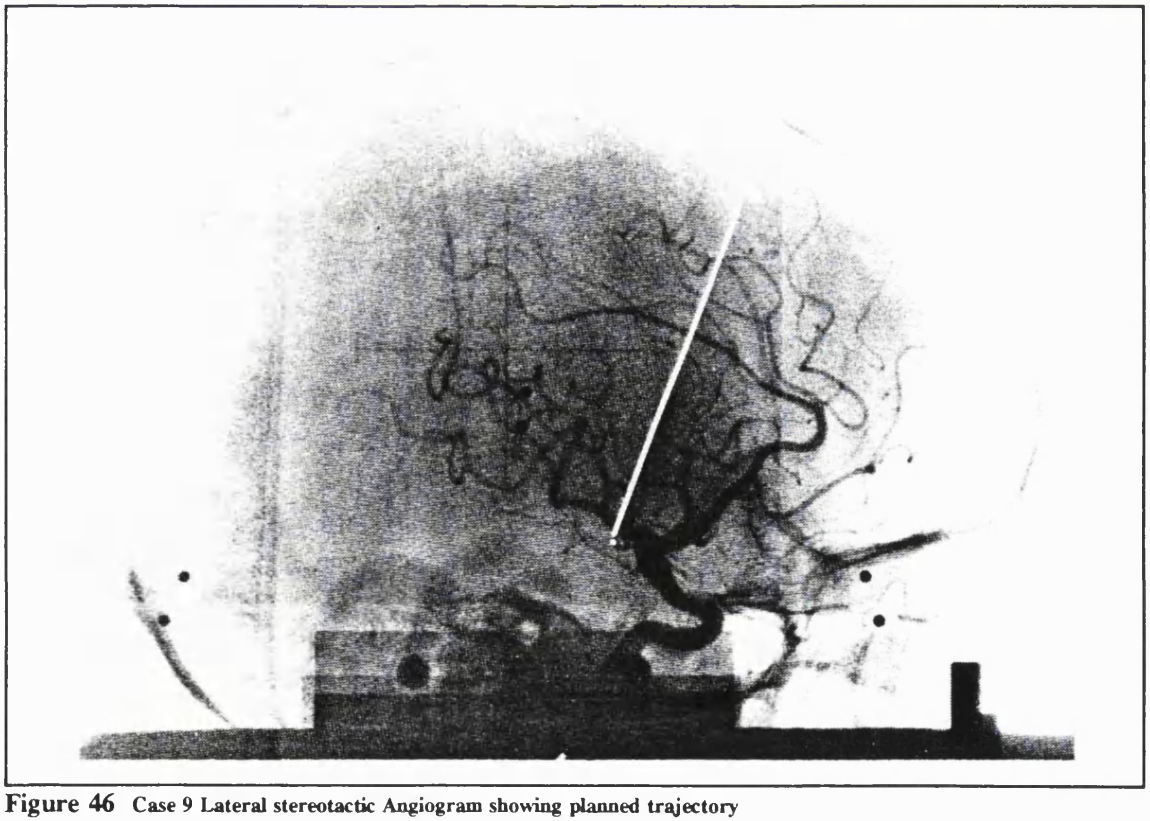


Figure 46 Case 9 Lateral stereotactic Angiogram showing planned trajectory

A diagnostic CT head scan demonstrated an enhancing mid-brain lesion that extended to the suprasella region. Due to the close proximity of major cerebral vessels stereotactic biopsy was planned from the combined information from CT and angiography performed under stereotactic conditions. The biopsy target was selected from the contrast enhanced CT images (fig. 44) and an avascular trajectory from the stereotactic angiograms figs 45 and 46.

The biposy was performed without complication and proved to be an anaplastic astrocytoma.

Case 10:

A 35 year old man presented with Jacksonian epilepsy involving the left arm and leg. On examination he had pyramidal weakness in the left arm. A CT head scan revealed enhancing lesions in the corpus callosum, right frontal and posterior right frontal regions. Open excision biopsy was performed on the right frontal lesion which proved to be a primary cerebral lymphoma. He was referred for stereotactic radiotherapy and had stereotactic CT performed in the relocatable frame for planning. Due to the extent and multiplicity of the lesions stereotactic radiotherapy was felt to be inappropriate and he had a course of conventional radiotherapy. He was re imaged under the same stereotactic conditions 2 months later to monitor the effects of therapy. The matched images are shown in fig: 47.

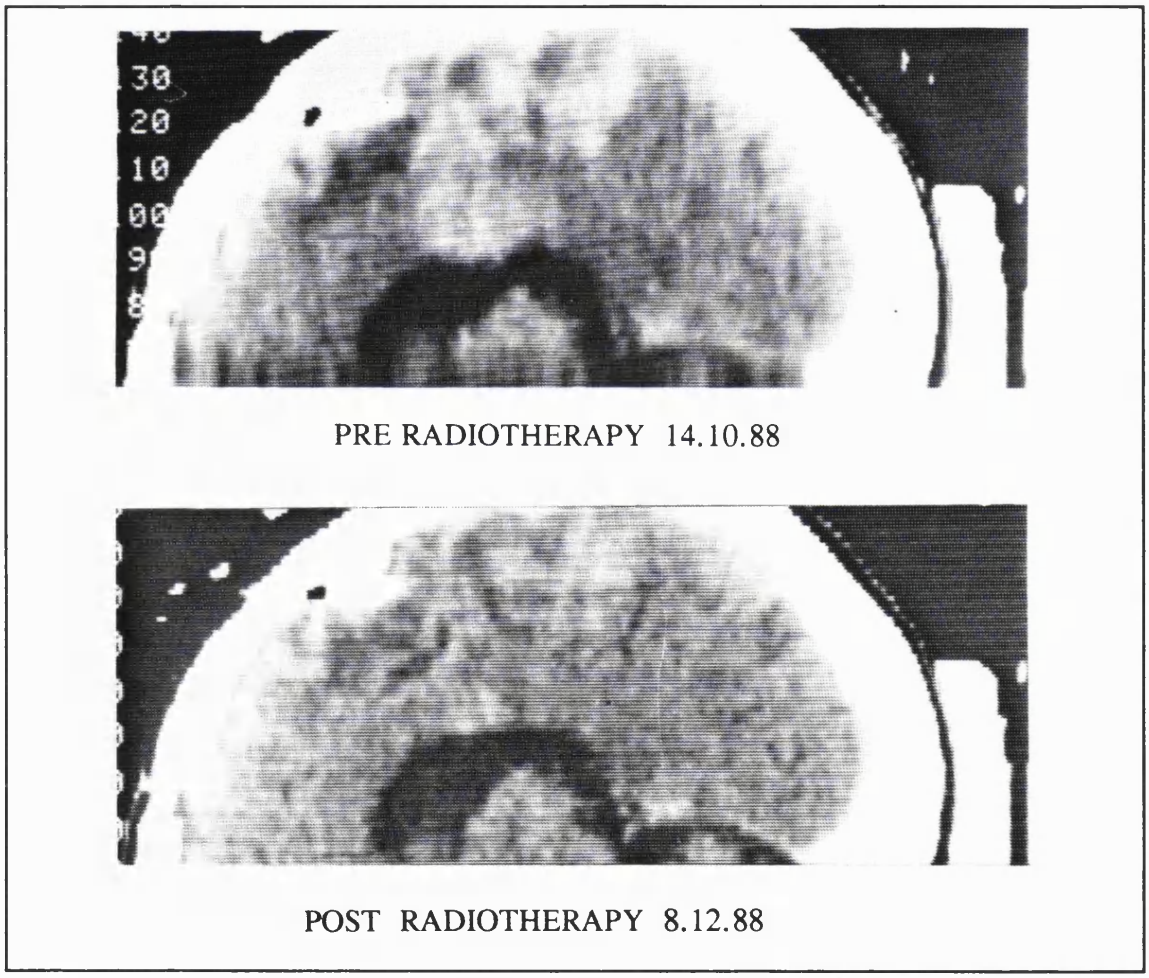


Figure 47 Case 10: Correlated CT images (para-sagittal reconstructions) demonstrating the response of a primary lymphoma to radiotherapy.

Discussion:

The geometric correlation of CT, MR and PET images have been achieved by the method of reproducible head positioning and fixation in each imager using the Relocatable Stereotactic Frame. The facility to non invasively relocate the frame allows images from different modalities to be acquired under the same stereotactic conditions at any time, and if indicated (eg for follow up studies) many months apart. The method has been tested and applied in a number of clinical settings.

The prime advantage of using this method rather than the computer correlation of randomly positioned brain images is that, unlike the latter method, spatial matching of image volumes can be achieved with a displacement error less than the voxel sizes of the matched images. In addition it avoids the necessity of rotating and translating image volumes to achieve a match which results in image degradation due to partial volume averaging.

The use of the BRW fiducial system provides an independent means of checking the accuracy of repositioning the frame in each scanner and allows any error to be measured and corrected by computer manipulation of the respective image volume. In this study such manipulations were rarely necessary due to the careful set up procedures employed. Each axial image displays nine fiducial points and so for image volumes containing between 15 and 30 contiguous slices the total number of reference points for correlation ranged between 135 and 270. For images with a poor spatial resolution such as PET which have significant partial volume effects, vertical reconstructions of the images in the plane of each set of N shaped fiducials provided a simple and effective means of assessing and correcting any mismatching of volumes. By virtue of the method any measurable error in matching fiducial positions on the images are corrected and so any mismatching of brain images is the result of inaccuracies in relocating the head in the frame. These errors have been quantified and account for less than 1mm displacement in any cardinal axis for any point in the head.

Problems encountered with the method were the need for multiplicity of brackets to fix the frame to the scanner couches and the time taken to check the correct alignment of gantry mounted lasers and of the frame relative to the imaging plane. Initial test runs on the GE8800 CT scanner indicated that there was loss of isocentricity and parallelism of the frame in the imaging plane during table advancement. This was corrected by replacing the worn bearings on the couch. In addition an error was detected in the scanners reconstruction algorithm resulting in a rotation of the image by 1°. This was corrected by reprogramming the scanners computer.

MR image distortions due to inhomogenities in the main magnetic field and to non linearity of orthogonal

field gradients were not quantified or corrected in this study and may have introduced error in image correlation. A method of correcting MR image distortions as described by Schad et al (1987)[1] will be necessary in future studies to achieve optimal geometric correlation with other images.

Image correlation with PET data posed no particular problems other than the poor spatial resolution of the images. Although MR spectroscopy and SPECT imaging were not performed in this study their acquisition under the same stereotactic conditions and integration with other imaging modalities would appear to be straight forward.

The indirect correlation of cerebral angiograms with CT images has been demonstrated in one case in this study. Such correlations are most applicable to planning radiosurgery treatment of arteriovenous malformations. For this purpose the Relocatable Frame is presently being employed using a similar method to the one described (Dr P.N. Plowman, Radiotherapy Dept. St.Bartholomews Hospital, London, personal communication). A true 3 dimensional computer correlation of cerebral angiograms with other imaging modalities will only become possible when digital subtraction angiograms can be acquired as a 3 dimensional volume. This is technically feasible using a rapidly rotating gantry carrying an X-ray tube and image intensifier as described by Ottomo and Nakanishi (1986). Never the less with advances in MR imaging 3 dimensional MR angiography may replace DSA in the foreseeable future.

The described method of multimodality image correlation has been shown to be both practical and accurate when applied in clinical practice. In a number of these case studies the geometric correlation of functional PET images with anatomical images from CT and MRI has proved useful in elucidating the extent of brain tumour spread and in defining areas within heterogenous tumours that are likely to yield diagnostic tumour tissue from biopsy. Six patients in this group have been included in a comparative study of PET using ^{18}FUDR, CT scanning, histology and KI67 antibody to assess the value of (^{18}F/FUDR) PET imaging in quantifying tumour proliferation and extent of spread in vivo (see Appendix II).

The geometric correlation of images taken many months apart has also been demonstrated in this study. The accuracy of correlation is greater than that achievable by any other available method. This has important application in the quantitative measurement of pathological change and the response to various treatments.

CHAPTER 5

INTEGRATION OF BRAIN IMAGES WITH STEREOTACTIC PROCEDURES (using the Relocatable Frame)

1. Stereotactic Biopsy
2. Stereotactic Craniotomy
3. Functional Stereotaxy
4. Interstitial Radiation Therapy
5. Stereotactic Radiosurgery / Radiotherapy

INTEGRATION OF BRAIN IMAGES WITH STEREOTACTIC PROCEDURES:(using the Relocatable Frame)

The Relocatable Stereotactic Frame not only facilitates precise geometric correlation of multiple brain images but allows the clinician to direct instruments or focused irradiation to brain targets selected from any one or combination of images. The facility to non-invasively relocate the frame and there by reestablish the same 3D co-ordinate system within the head will in addition enable stereotactic procedures to be repeated over an extended period. These advantages have application in all aspects of stereotactic neurosurgery, and are outlined below:

1. STEREOTACTIC BIOPSY

A combination of stereotactic CT and MRI or PET information is often necessary to accurately define deep seated brain lesions. Combining this information with stereotactic angiography will help the clinician to plan a trajectory which will avoid blood vessels. By using the Relocatable Frame, all these investigations may be performed at convenient times, and from this integrated 3D data the targets and trajectories planned. Stereotactic biopsy can the be performed on a routine list within a few days. When the trajectories are already established the biopsy procedure can be performed within twenty minutes under local or general anaesthesia. To date over twenty patients have had stereotactic biopsies performed at the National Hospital, Queen Square using the Relocatable Frame. (Sofat, et al. 1992)[2].

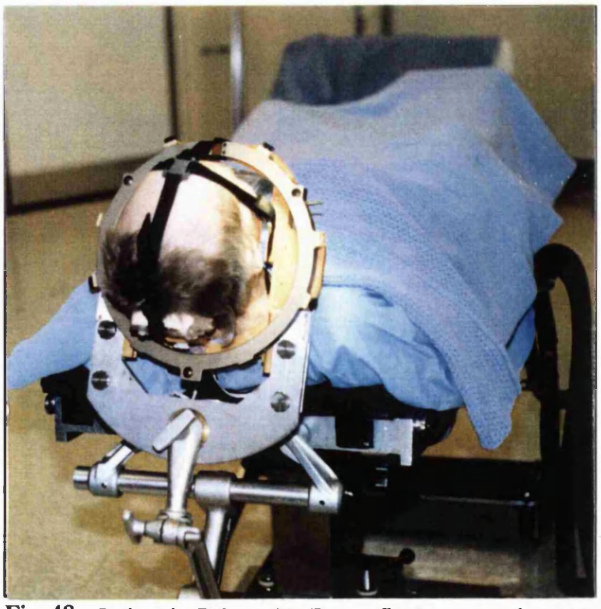


Fig 48 **Patient in Relocatable Frame fixed to operating table via interface bracket to the Mayfield head holder**

To provide head fixation to the operating table during the biopsy procedure an interface bracket was made to fix the frame to a conventional Mayfield head holder.

The Relocatable Frame is fitted in the anaesthetic room in the conscious patient as previously described. Prior to tightening the head straps they are positioned so that they are clear of the entry point site where the burr hole is to be made. Several patients have been anaethetised for the biopsy

procedure. They are intubated orally or nasally prior to the surgeon fitting the frame to the head. To ensure access to the upper jaw in those patients who have been orally intubated, the ET tube should be fixed with adhesive tape to the lower jaw.

Once the patient has been positioned on the operating table the frame is fixed to the Mayfield head holder via the interface bracket (fig 48).

The head is prepared and draped in a conventional manner and stereoguide (BRW or CRW) fixed to the frame with the target coordinates pre set (fig 49).

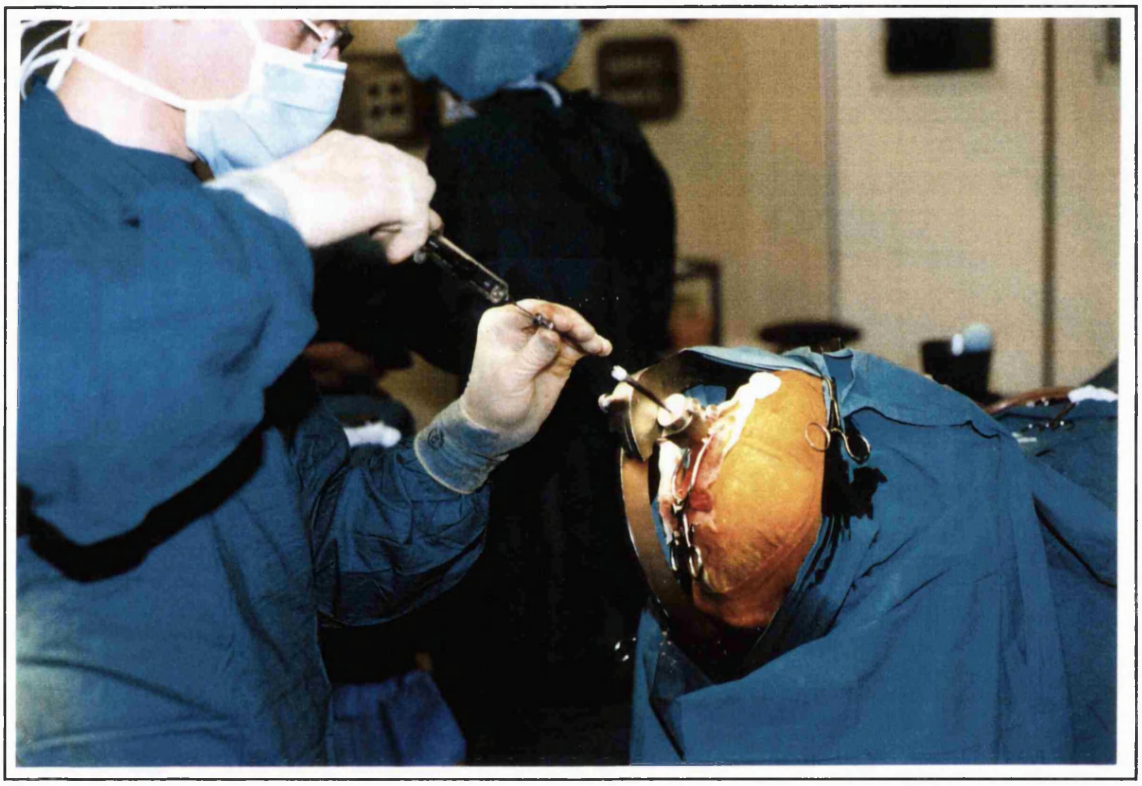


Figure 49 Stereotactic biopsy being performed in the Relocatable Frame using the BRW stereoguide.

After infiltrating the scalp at the entry point with local anaesthetic a small incision is made down to the bone and a self retaining scalp retractor is inserted. A burr hole is then made. My personal preference has been to use a motor driven ¼" drill with a depth stop that is guided by the stereoguide. This creates a small burr hole that gives sufficient visualisation of the dura and (when opened) of the cortical surface to allow vessels to be coagulated with bipolar diathermy. The side cutting biopsy cannula (Nashold biopsy cannula) is then inserted down its guide to a premeasured depth to reach the target. Four quadrant biopsies are generally taken at each target site by rotating the biopsy cannula. Each biopsy sample is a cylinder 1cm in length and 1.5mm in diameter.

Following the procedure the cannula is withdrawn and the scalp is closed in layers with interrupted sutures. The stereoguide and frame are then removed from the head.

The rigid fixation of the head in the relocatable frame prevents movement of the head relative to the stereoguide during the biopsy procedure. The greatest stresses on the head occurring during the making of a burr hole. The use of a motorised ¼" drill guided by the stereoguide creates a burr hole without the need to apply undue force on the head or on the frame.

In my personal series of nine cases in which multiple serial stereotactic biopsies were performed in the frame seven were performed under local anaesthesia and two under general anaesthesia. There were no complications and a histological diagnosis was made in each case.

One short coming of this method of fixation is that the occipital headrest obstructs a direct approach to biopsying occipital pole and posterior fossa lesions. Brain stem lesions are generally approached from a trans-frontal trajectory for which the frame offers no obstruction (Thomas et al.1988). Occipital pole and cerebellar lesions can never the less be directly biopsied using image data acquired in the relocatable frame. In these instances the relocatable frame is fitted to the head at the time of surgery as previously described and the conventional BRW head posts are fixed to the base ring. The four posts are driven radially inwards so that they come into firm contact with the scalp at each quadrant of the head. The threaded fixation pins are then inserted into opposing posts and tightened simultaneously with torque drives. When pin fixation to the outer table of the skull has been accomplished the head straps, head rest and dental impression can be detached from the frame which remains fixed to the head in the same relationship. Full access to the occipital pole and posterior fossa having been obtained, biopsy can the proceed in a conventional manner.

It is of note that in a recent series of 292 CT directed biopsies that were routinely performed (Thomas and Nouby 1989) in only one case (0.3%) was a biopsy performed of a cerebellar lesion. There were 10 occipital lesions biopsied (3.4%) but a number of these may well have been accessible by a more lateral approach which would not have necessitated removal of the head rest.

2. STEREOTACTIC CRANIOTOMY

The method of planning a stereotactic craniotomy from multiple images has previously been described. For these procedures freedom from obstruction in the operative field and complete rigidity of frame fixation is necessary. This is achieved by fixing the relocatable frame to the skull with pins after it has been repositioned for surgery and then removing the straps, head rest and dental impression.

A limited craniotomy flap can then be raised using the stereotactically planned data and the lesion resected freehand. A stereotactic probe can be used peroperatively to guide the surgeon to the resection margin. Alternatively guided extirpation can be performed through a cylindrical retractor whose trajectory and advancement is adjusted by the surgeon interacting with information from an operating room graphics monitor displaying reformatted tumour outlines in stereotactic space.

The particular advantage that the relocatable frame has for stereotactic craniotomy is that it facilitates multimodality image acquisition (including PET) and complex treatment planning from the combined data without the time constraints that are imposed by the use of conventional methods of fixation. Conventional methods demand a single application of the frame which remains invasively fixed to the head during image acquisition, treatment planning and surgery.

3. FUNCTIONAL STEREOTAXY

Despite advances in the pharmacological treatment of functional disorders, stereotactic lesioning or stimulation can be of great benefit as an adjunct to control refractory symptoms or as a treatment in itself in those patients who are resistant to medication.

Indications for functional stereotactic interventions in movement disorders include Parkinsonian tremor, essential tremor, cerebellar tremor, the post traumatic movement disorders, tortion dystonia torticollis spastica and hemidystonia. Patients with intractable pain, particularly head and neck pain from cancer may show considerable benefit from stereotactic mesencephalotomy or pontine tractotomy. In chronic 'benign' intractable pain syndrome such as thalamic syndrome, the phantom limb and other denervation pain syndromes the stereotactic implantation of stimulating electrodes in the peri-aqueductal grey matter can achieve satisfactory control of symptoms. Other indications for functional stereotactic intervention are in the placement of chronic depth recording electrodes to elucidate the site of an epileptic focus, or to create lesions in patients with otherwise intractable epilepsy that interrupt the conduction pathways.

Otherwise intractable psychiatric disorders, particularly severe obsessive - compulsive neuroses and phobias may be influenced effectively by stereotactic lesioning in the anterior cingulum or in the anterior part of the internal capsule. The ethics of performing such psychosurgical procedures however remains contentious.

The relocatable frame would have application in all these areas of functional neurosurgery, but to date its use has been limited to thalamotomy for the control of Parkinsonian tremor that is resistant to medication. Four cases have been treated of which 3 were in a personal series. In these 3 patients the diencephalic target selected in each case was the nucleus ventralis intermedius (Vim).

Prior to image acquisition the relocatable frame was secured to the head in a horizontal plane which was approximately parallel to the intercommisural line.

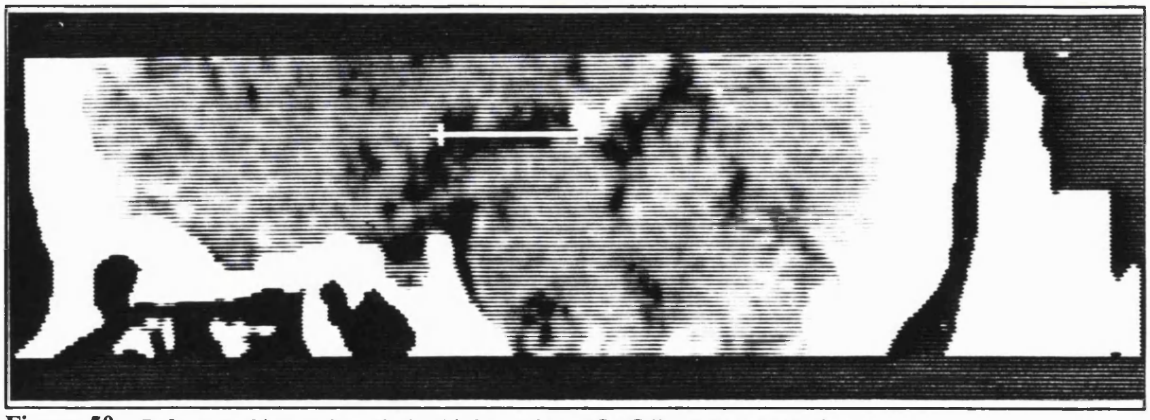


Figure 50 Reformatted image through the third ventricle. AC-PC line drawn on the image

The BRW localiser was then attached to the frame and CT images were acquired in a GE8800 scanner with the frame fixed to the scanner couch via an interface bracket so that it was parallel to and isocentric with the imaging plane. Fifteen axial slices were taken starting just above the level of the posterior clinoid

process.

1.5mm thick slices were taken with 1.5mm slice separations on a medium body format at a magnification factor of 1.4. These slices were then reformatted to provide a mid sagittal reconstruction of the 3rd ventricle.

The anterior and posterior commissures are identified and using computer graphics the AC-PC line is drawn and measured (fig.49).

The coordinates for the nucleus VIM are about 2/10 of the AC-PC distance in front of PC and 2mm above the AC-PC line with a lateral coordinate of approximately half the AC-PC distance. The target is marked with a cursor on the appropriate axial slice and its BRW coordinates recorded.

In each case Thalamotomy was performed in the Relocatable Frame within 48 hours of target identification. Following refixation of the frame the patient is positioned on the operating table with the frame fixed to the Mayfield head holder by an interface bracket.

The scalp is prepared and draped and the stereoguide, which has been pre set to the target coordinates is secured to the frame. After infiltrating the scalp with local anaesthetic a frontal burr hole is made just anterior to the coronal suture 2cm from the mid line on the appropriate side. An electrode is passed through the burr hole to the thalamic target, guided by the stereotactic instrument.

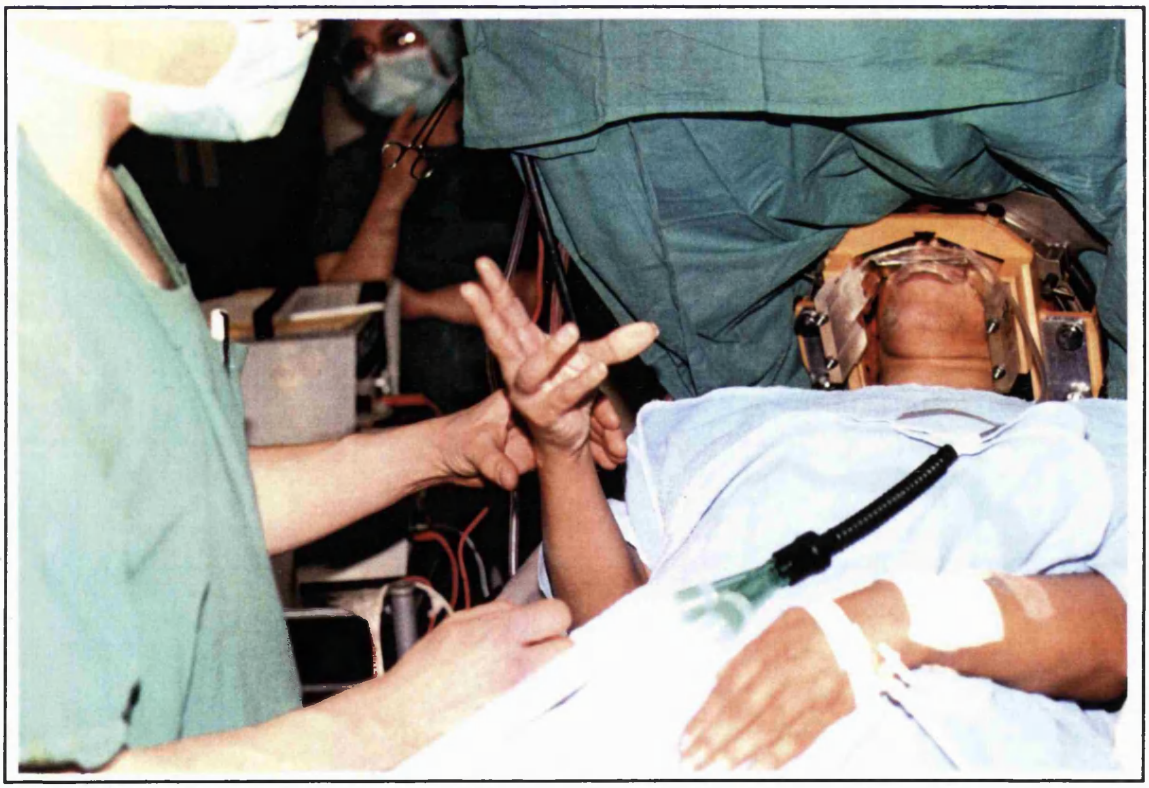


Figure 50 Assessment of motor response in a patient undergoing thalamic stimulation studies prior to the creation of a lesion to control Parkinsonian tremour

Stimulation studies are then performed in an attempt to block the tremour (100Hz) and exclude capsular motor involvement (2Hz). During these stimulation studies motor and sensory responses are assessed and

the patient asked to perform a number of motor tasks (fig 51). According to the response the position of the electrode can be adjusted prior to creating a temperature controlled radiofrequency lesion.

Post thalamotomy the three patients in my series had good control of upper limb tremour without neurological deficit.

The position and extent of the radiofrequency lesion was quantified the following day by reimaging the patient in the relocatable frame using an identical set up in the CT scanner. Usually four axial slices through the target were sufficient. In each case the lesion was exactly positioned at the predetermined target coordinates. See (fig. 52)

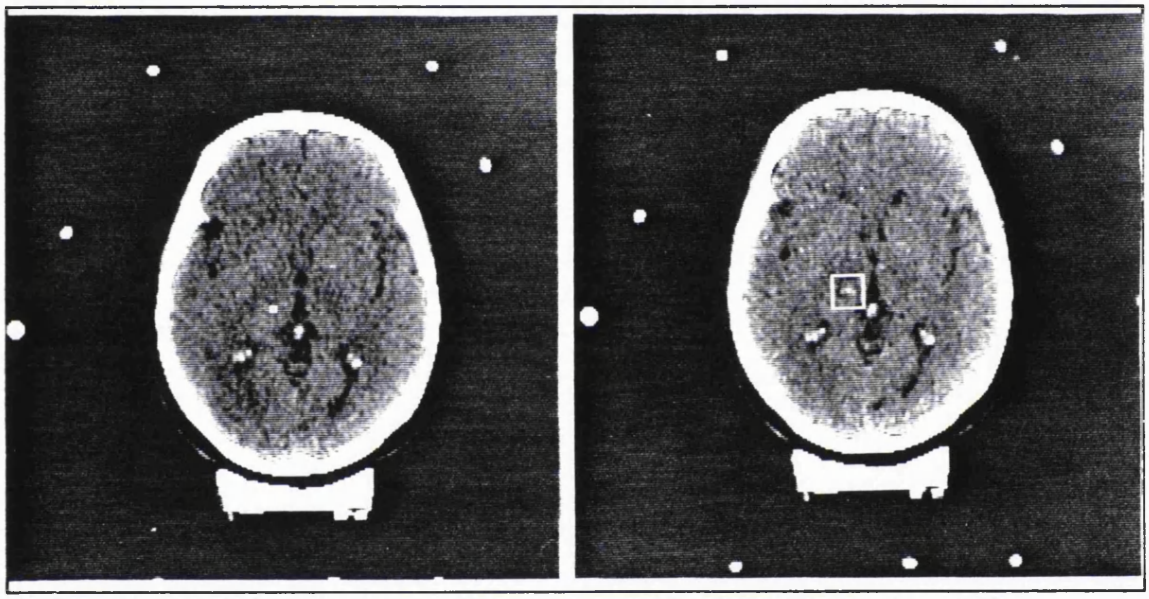


Fig.52 Planning CT indicating thalamic target in VIM. **Post thalamotomy scan shows position of thalamic lesion**

These images were obtained, not only to confirm the correct placement of the lesion but as a reference should the patients symptoms recur.

If an inadequate lesion is made recurrent tremor is often evident within a few days of thalamotomy as local oedema settles. In these circumstances a radiofrequency lesion could be extended or a second lesion made at different coordinates by repositioning the frame and carrying out the procedure using existing coordinates.

Conventionally CT guided thalamotomy has been performed in a single stage or in three stages. In single stage procedure a stereotactic frame is invasively fixed to the head under local anaesthesia. The patient is imaged and the coordinates of the target are established with reference to the frame. The patient is then transferred to the operating room and the guided thalamotomy performed after appropriate stimulation studies. The whole procedure can take a number of hours which monopolises the surgeons time and therefore theatre time and subjects the patient to a prolonged period of discomfort in the frame. If the lesion is subsequently found to have inadequately controlled the tremor then to repeat or extend the lesion requires

reapplication of the frame, reimaging and replanning prior to repeating it.
In the first stage of a three staged thalamotomy the stereotactic frame is invasively fixed to the skull under general anaesthesia prior to image acquisition and planning. The patient is transferred to the operating theatre and an entry point burr hole made. A Bennet ball is then fixed over the burr hole using screws driven into the outer table of the skull. The Bennet ball has multiple guide holes that pass in parallel through it. The ball is orientated so that a central guide hole is in the axis of the pre-planned trajectory. It is locked in position with locking plates. The scalp is then closed over this assembly and the stereotactic frame is removed. The second stage is performed a few days later under local anaesthesia. Here the wound is reopened and an electrode passed to a measured depth to the target and the lesion made after stimulation studies. The third stage is the removal of the Bennet ball which is performed one week later under general anaesthesia allowing time to repeat or extend the lesion if necessary.

The described technique of thalamotomy using the relocatable frame has a number of advantages over these conventional methods. Image acquisition and planning can be performed without anaesthesia and at a time prior to surgery that is convenient for the clinician. Valuable theatre time is therefore not monopolised. The procedure can be performed on a routine operating list and would not normally take more than 45 minutes. Finally the position and size of the lesion can be quantified post operatively and a lesion repeated if necessary by simply relocating the frame and redirecting the electrode to the same coordinates.

A further and perhaps more significant advantage of using the relocatable frame in the management of functional disorders is that it facilitates the acquisition of functional information from PET,SPECT or MRS in stereotactic space. Correlation of this data with structural information derived from stereotactic CT or MRI images may allow new and more specific functional targets to be accurately defined for lesioning, stimulation or tissue implantation. With the use of such methods the indications for stereotactic intervention may well increase, particularly for the treatment of intractable epilepsy and psychiatric disease.

4. INTERSTITIAL RADIATION THERAPY

Radiation therapy has remained the most effective modality for treating malignant brain tumours after surgery. Conventional radio-therapy seeks to exploit the greater sensitivity to radiation of tumour tissue compared to normal tissue. For gliomas this difference is small and the maximum amount of radiation that can be delivered is limited by the tolerance of the adjacent normal brain tissue. For these tumours localisation of delivery of radiation is the most important factor responsible for the differential effect of radiation on tumour and normal tissue. The technique of localising irradiation by stereotactically inserting radioactive sources directly into the tumour is long established (Boyesen et al. 1955).

Interstitial radio-therapy / brachytherapy has generally been applied to the treatment of unresectable tumours of less than 5cm in diameter. A number of different techniques have been used as well as a variety of radioactive sources and radiation doses. The results are varied with reported 18 month survival rates being as low as 10% to as high as 30% (Chin and Bertoni 1991).

Critical to the success of the technique is optimisation of the implanted dose to adequately cover the whole tumour volume. This in turn is dependent upon the accurate delineation of the extent of tumour spread from radio-diagnostic images. PET imaging using the tracer C^{11} -methionine has been shown to be the most accurate imaging method of defining tumour boundaries (Moskin 1989). PET can therefore be extremely useful in evaluating patients eligibility for brachytherapy and for dosimetry planning. To place this functional information into its anatomical context and within stereotactic space requires that PET images are acquired under stereotactic conditions and correlated with stereotactic CT or MRI images. The Relocatable Stereotactic Frame is ideally suited to this purpose and offers the advantage that it allows the clinician to perform complex treatment planning and three dimensional dosimetry calculations without time constraints.

Within a few days of treatment planning interstitial catheters can be inserted with stereotactic guidance after relocating the frame. This procedure can be carried out quickly and efficiently on a routine operating list as the coordinates and trajectory paths of each catheter are predetermined. The position of each catheter can be confirmed post insertion by reimaging the patient in the frame. The catheters may then be after loaded with radiation sources.

A further advantage of using the relocatable frame for this application is that it allows objective monitoring of the patients response to treatment by reimaging in the same stereotactic space. PET imaging using the tracer ^{18}F-fluorodeoxyglucose will distinguish recurrent tumour from radionecrosis (DiChiro et al. 1987). This important distinction may significantly alter the treatment plan for a patient. Correlation of this information with CT or MRI will allow selective biopsy of suspicious areas or facilitate stereotactically guided decompression of a radionecrotic mass or reinsertion of radio-isotopes into areas of recurrence.

The Relocatable Stereotactic Frame has been used for I^{125} brachytherapy for the treatment of recurrent malignant gliomas. The technique and early results are reported by Sofat et al.(1991 and 1992[2]).

5. STEREOTACTIC RADIOSURGERY / RADIOTHERAPY

Stereotactic radiosurgery is the delivery of a high dose of ionising radiation to a preselected and stereotactically localised intracranial volume in a single session. By delivering highly collimated beams of radiation from multiple angles to a defined intracranial target a sharply circumscribed lesion can be made with minimal irradiation of the surrounding tissue due to the extremely steep dose gradients achieved. The method was introduced by Lars Leksell in 1951 and is currently used for the destruction of a variety of intracranial targets.

The target is localised by imaging the patient in a stereotactic frame. From these images treatment is planned to optimise the dose to the target volume while minimising the dose to the surrounding normal tissue and avoiding critical structures. Treatment is then performed by fixing the target at the focal point of appropriately collimated beams of radiation using the stereotactic frame as a head holder.

TECHNIQUES

Current methods employ a variety of radiation sources and techniques of delivery:

The 'Gamma Knife' developed by Leksell (1983), delivers gamma-irradiation (photons) from multiple concentric cobalt 60 sources focused to a central point. The target diameter is defined by a secondary collimator which is a metal helmet drilled with the appropriately sized holes.For treatment, the stereotactic frame is secured within the helmet and the patient with the attached assembly is moved into the machine which contains the cobalt sources.

An alternative means of localised irradiation uses the property of Bragg peak of heavy particles in the form of cyclotron generated protons or heavy charged particles such as Helium ions (Larson 1958, Kjellberg 1962). These cause dense ionisation over a short distance and depth in tissue determined by the nature of the particles and the energy of the beam. Because their source is static it is necessary to rotate the patient within the stereotactic instrument and to use adjustable absorbers to bring the Bragg Peak to the target.

Modern linear accelerators (LINAC) which deliver high energy X-ray beams (photons) can be readily adapted for stereotactic radiosurgery (Colombo et al. 1985). The stereotactically defined target is marked on AP and lateral plates on the faces of a localiser box that is secured to the stereotactic frame. The frame is then fixed to the treatment couch by an interface bracket and the couch positioned so that the target is coincident with the isocentre of the LINAC. This occurs when calibrated cross lasers that identify the isocentre are aligned with the marked target position.

Using circular secondary collimators attached to the head of the machine a dose distribution equivalent to that produced by the gamma knife can be achieved at the target with an arrangement of multiple non-coplanar arcs using a combination of gantry and couch movements.

The main advantages of using the LINAC for radiosurgery is its general availability, flexibility and low cost. The technique can be integrated into the general radiotherapy workload of the machine with combined set up and treatment times taking approximately 40 minutes. By contrast Gamma units and heavy particle

accelerators are dedicated machines requiring considerable capital outlay and running costs. With the LINAC and heavy particle accelerators there is no limitation in field size, and beam shaping can be carried out for the treatment of irregular volumes. The Gamma Knife is limited to spherical or oval treatment volumes of <2.5cm in diameter making it relatively inflexible. Never the less the gamma unit has the advantage of having relatively few moving parts making treatment planning and delivery simpler and more precise than other methods (± 0.25mm compared with ± 1mm). It is doubtful whether this additional degree of accuracy of delivery results in any significant clinical difference because the greatest inaccuracy for all techniques remains the localisation of the target from the diagnostic images.
Radiosurgery using any of the described techniques requires a vigorous programme of quality assurance. This particularly applies to treatment with a linear accelerator because of the larger number of moving parts.

CLINICAL APPLICATIONS

Radiosurgery has applied to the treatment of arterio-venous malformations (AVMs) and brain tumours including high and low grade gliomas, metastases, meningiomas, acoustic neuromas and others.

ARTERIO-VENOUS MALFORMATIONS:

In the treatment of surgically un resectable and small AVMs (<3cm diameter) large single doses of focal irradiation (18-25Gy) have proved to be effective. Occlusion of blood vessels is a late effect of radiation damage to normal tissues and usually occurs within 2 years. The response to treatment appears to be dose and size dependent. The 2 year obliteration rate of AVMs less than 3cm in diameter using the Gamma Knife (Steiner et al. 1984), the LINAC (Colombo et al. 1989), and Helium ions (Steinberg et al. 1990) have been comparable and range from 80-95%. For LINAC and Gamma Knife treatment the rebleed rates within 2 years are in the order of 6-8% and the complication rates 3-6%, But for Helium ion treatment they are 12% and 20% respectively.

Problems arise with larger lesions >3cm which are often irregular in shape and where normal tissue may lie within the treatment volume. These can be treated with the LINAC or with heavy charged particles but the treatment parameters have yet to be fully established. They are usually treated with a reduced dose to reduce the risk of damaging normal brain tissue, although this results in a lower obliteration rate.

The Relocatable Frame has been used at St.Bartholomews Hospital for LINAC radiosurgery to AVMS <5cm in diameter (Thomson 1990) (fig. 53). Over one hundred patients have now been treated. The advantage of using the relocatable frame is that stereotactic CT and angiography can be performed some time prior to treatment. This enables the clinician and physicist to plan the treatment regimen and perform 3D dosimetry calculations from the images without time constraint. The regimen can then be simulated and

checked prior to the patient being fixed to the LINAC couch via the Relocatable Frame and receiving the treatment dose in a single fraction.

The Relocatable Frame may have particular application to the treatment of larger AVMs. These could theoretically be treated by selective targeting of individual feeding vessels on separate occasions. Alternatively relocation would allow fractionation so that a larger total dose could be delivered to the AVM that would damage the more radio-sensitive endothelial cells while sparing damage to the normal brain.

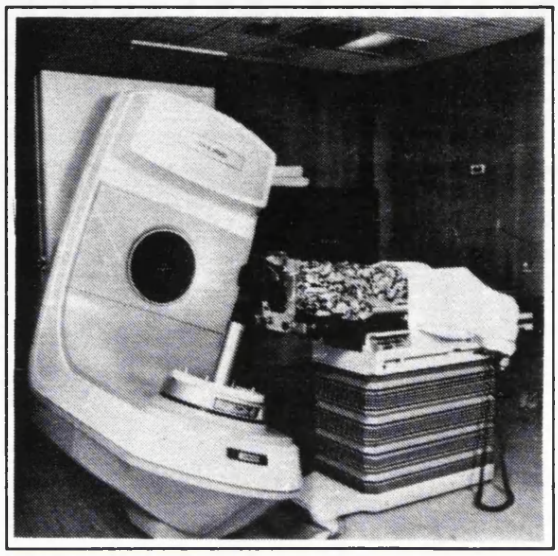


Fig 53 Radiosurgery using a LINAC. Patient fixed to treatment couch by the Relocatable Frame

BRAIN TUMOURS:

Stereotactic radiosurgery like interstitial radiotherapy can deliver a higher and more lethal dose of radiation to a tumour volume while minimising exposure to surrounding brain tissue. Unlike interstitial radiotherapy the radiosurgical technique is non invasive and without the inherent risks of haemorrhage and infection.

Gliomas

The diagnosis of a high glioma carries a poor prognosis. Even with surgery, radiotherapy and chemotherapy patients have a median survival of only 40-60 weeks (Shapiro 1986). When the tumour recurs after conventional treatment, localised irradiation of the area offers the best chance of prolonging survival. Loeffler and Alexander III (1991) have demonstrated that radiosurgery using a LINAC is as effective as interstitial radio-therapy in achieving this. They have also shown that by treating high grade gliomas with a radio-surgery boost at the time of the initial radiotherapy, patients survival is prolonged (71% survival at 10 months).

The role of radiosurgery in the management of low grade gliomas is unclear. The overall 5 and 10 year survival of patients with low grade gliomas is 40-50% and 10-20% respectively. Ostertag (1989) has reported an improved 5 year survival rate to 65% by treating patients with grade II astrocytomas with interstitial radiotherapy. As yet there are no long term follow up studies of patients treated with radio-surgery.

Metastases

Patients with cerebral metastases constitute 60-70% of brain tumour patients and have a median survival

of 3-4 months. Despite effective surgery and palliation with whole brain irradiation a third of patients recur with disease in the brain. Radical local treatment with radio-surgery offers a non-invasive alternative to surgery. Loeffler et al. (1990) treated eighteen patients with recurrent brain metastases with radio-surgery (9-25Gy in a single fraction). Excellent control of the disease was achieved within the irradiated field and the treatment was well tolerated. Two patients later had recurrence in the margin of the field. Similar results have been reported by Coffey et al. (1991) who treated 24 patients with solitary metastase following conventional whole brain irradiation. The survival of patients in both series was poor, but better than with conventional treatment alone (median survival ranged from 5-10 months). The disease recurred either elsewhere in the brain or systemically.

Meningiomas

Stereotactic radio-surgery has been introduced as an alternative adjuvant treatment in patients with incompletely excised meningiomas.

It has also been applied as an alternative to surgery for meningiomas <5cm diameter that are surgically inaccessible and in patients who are medically unfit for surgery. In a heterogeneous group of 50 patients that fulfilled one or other of these criteria a 2 year control rate of 96% has been reported after stereotactic radio-surgery using the gamma knife (Kondziolka et al. 1991). The effectiveness of the treatment is difficult to evaluate from these results due to the heterogeneity of the patients and the indolent nature of the disease.

Acoustic neuromas

D.G.Leksell(1987) has reported the results of treating 91 unilateral acoustic neuromas with Gamma Knife radio-surgery at the Karolinska Institute. These were small or medium sized lesions (the actual dimensions were unspecified). On CT 49% became smaller, 42% were unchanged in size and 5% progressed at an unspecified time after treatment. There were no deaths, facial nerve function was preserved in all cases and 25% of patients retained hearing at the pre treatment level. Even in the best hands these results are difficult to reproduce surgically.

By comparison Symon et al (1989) have reviewed 147 cases treated surgically in the past decade. There was a 1.4% perioperative mortality, 58% of patients had acceptable facial nerve function post operatively and the cochlear nerve was preserved in 13.5% (some retained hearing). Associated surgical complications included 18.4% with CSF leaks and 4.1% with other complications including post operative haematomas, hydrocephalus or injury of the lower cranial nerves.

Other tumours

Pituitary adenomas treated with surgery and conventional radiotherapy have a 10 year control rate of 90-95%. Radio-surgery may theoretically reduce the risk of radiation induced 2°tumours (which occur in 1-3% at 10 years) but otherwise would have little additional therapeutic advantage. Similarly, although patients

with Cushings disease and acromegaly have been treated radio-surgically (Degerblad et al. 1986, Kliman et al. 1987) the results so far show no clear benefit over conventional therapy.

Pineal germinomas are very radiosensitive and can be cured with relatively low doses of conventional fractionated radio-therapy.

Craniopharyngiomas are less radio-sensitive, but with conventional surgery and radio-therapy a 10 year progression free survival of 70-80% can be achieved. If these measures fail then radio-surgery may have a place in their treatment.

Unresectable clivus chordomas and chondrosarcomas are radio-resistant. Radio-surgery with proton beam therapy has been shown to be superior to conventional treatment (Austin-Seymour et al. 1989).

Finally, although medulloblastomas are radiosensitive and frequently radio-curable, those that recur tend to do so at the primary site in the posterior fossa. A theoretical advantage would be gained by treating the primary site with a radio-surgical boost. Such a regime has yet to be evaluated.

The true efficiency of radiosurgical treatments for different pathologies can only be determined with randomised controlled trials. It is important to appreciate that no such trials have yet been conducted and that all series presented to date have been in highly selected groups of patients.

The Relocatable Frame is ideally suited as a head fixation device for fractionated stereotactic radiotherapy (Gill et al. 1991).

At the Royal Marsden Hospital patients with a variety of intercranial tumours have been treated with stereotactic radiotherapy using the frame since 1989. The specially constructed interface bracket for fixing the patient to the LINAC couch and a localiser box for stereotactic CT image acquisition and target alignment in the LINAC are shown in figs.54 and 55.

To date the Royal Marsden Group have performed dose escalation studies and a variety of fractionation schedules on patients with recurrent high grade gliomas ($<$5cm diameter) to establish the optimal treatment parameters. Early results on the first 20 patients treated with dose escalations of 5Gy per fraction show a median survival of 7 months with doses ranging from 20 to 45 Gy to previously irradiated tumours.

Patients with cerebral metastases have also been treated. Results on 19 patients (with 23 lesions) who were treated with a fractionated boost following whole brain irradiation show a median survival of 17 months. Control of the metastatic lesions at the irradiated site has been excellent with a median progression free survival at the irradiated site of 15 months (Brada M., 1992, a personal communication). Presently a number of patients with metastases are being treated with stereotactic radiotherapy without whole brain irradiation, which may be as effective and has the advantage that patients may retain their hair.

The Relocatable Frame is also being used for fractionated stereotactic radiotherapy at the Brigham Hospital, Boston, Mass. This group, led by J. Loeffler, are treating high grade gliomas with a fractionated boost following conventional radiotherapy as well as treating tumour recurrence. In addition they are treating

patients with solitary metastases. Using this method up to 10 patients are treated per day, The results of therapy have yet to be evaluated.

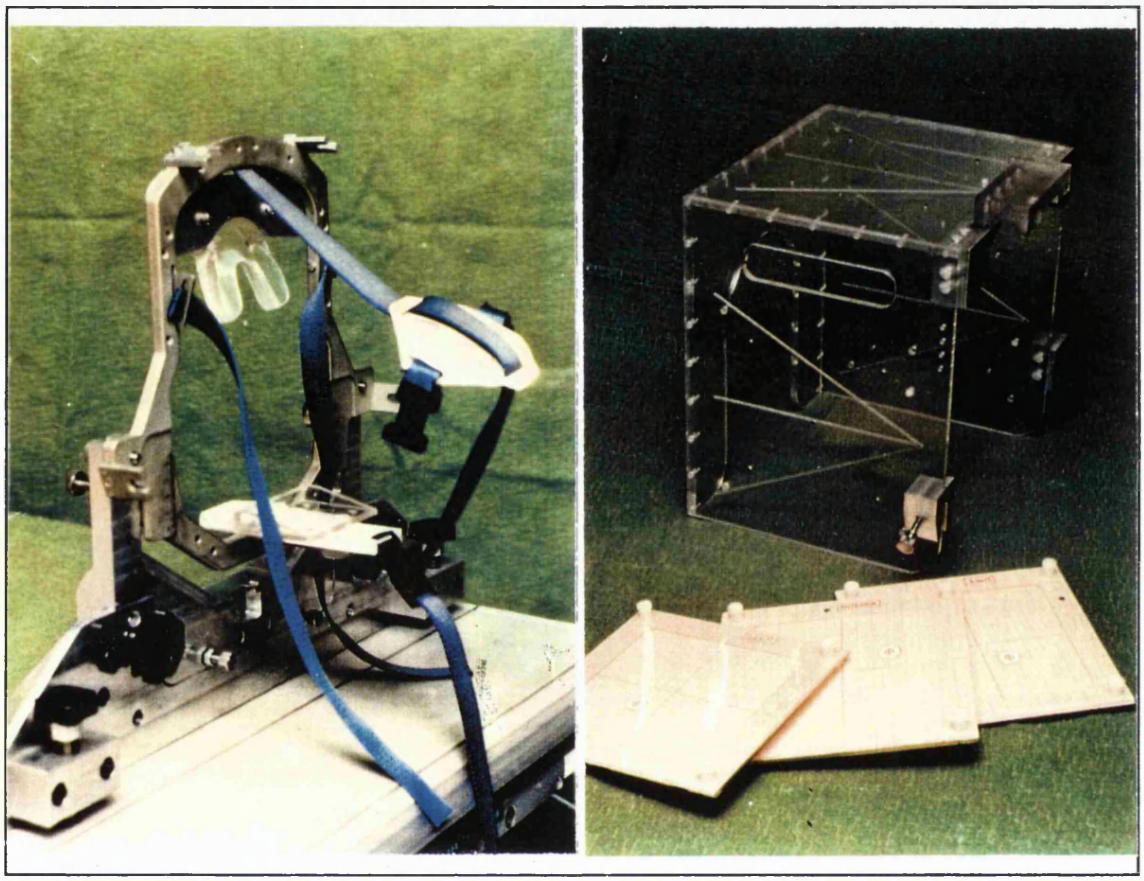


Figure 54 Interface bracket for fixing Relocatable Frame to LINAC couch (Adjustment screws on bracket will correct for loss of verticality of the frame due to couch sag)

Figure 55 Localiser box - 3 sets of fiducials facilitate CT localisation of target. The target is marked on 3 sets of plates which are attached to the box for laser alignment with the LINAC's isocentre prior to treatment.

CHAPTER 6

ASSESSMENT OF THE FIXATION METHOD IN CLINICAL PRACTICE

Method

Results

Discussion

ASSESSMENT OF THE FIXATION METHOD IN CLINICAL PRACTICE

Method

The method of patient fixation in clinical practice was assessed in a personal series of 13 patients who had the frame fixed to the head for multiple imaging and biopsy or thalamotomy. In addition other prototypes were used by three groups for stereotactic imaging and procedures including stereotactic biopsy, thalamotomy, brachytherapy, focused radiotherapy and radiosurgery. These groups were at the National Hospital for Neurology and Neurosurgery, Queens Square, London, supervised by Mr D.G. T.Thomas, at the Royal Marsden Hospital, London, supervised by Dr M.Brada, and at St,Bartholomews Hospital supervised by Dr P.N.Plowman. Individual aspects of the fixation method, and patient tolerance were assessed by each group who completed a questionnaire in January 1992 using patient data collected over three years.

The questionnaire follows overleaf:-

THE NON-INVASIVE RELOCATABLE STEREOTACTIC FRAME:
Assessment of fixation method in clinical practice

Clinician:_____ Centre:_____

PATIENTS

Number of adults treated: ....
Number of children treated (under 14 years) ....
Age range: ....
Mean age: ....
Sex - No of males ....
No of females ....

Status of dentition:
No with teeth ....
No edentulous ....

PATHOLOGY TREATED

AVM's: ....
1° brain tumours:
High grade gliomas ....
Low grade gliomas ....
Pineal tumours ....
Pituitary tumours ....
Acoustic neuromas ....
Meningiomas ....
Craniopharyngioma ....
Medulloblastoma ....
Lymphoma ....
Germinoma ....
2° brain tumours:
Solitary metastases ....
Multiple metastases ....
Parkinsonian Tremor ....
Epilepsy ....

IMAGING

Indicate the number of patients who have had a given combination of investigations in the frame

		+1 MRI	+1 ANGIO	+1 PET
1 CT				
2 CT				

Please list other combinations below:

TREATMENT:

How many patients had stereotactic biopsy in the frame? ....

How many patients had isotope placement in the frame? ....

How many patients had electrode placement in the frame

for Ix of epilepsy? ....

for thalamotomy? ....

For patients undergoing radiotherapy/radiosurgery in the frame. How many had:-

1 treatment ....

2 treatments ....

3 treatments ....

4 treatments ....

5 treatments ....

6 treatments ....

7 treatments ....

8 treatments ....

9 treatments ....

10 treatments ....

more (please state) ....

EXCLUSIONS

How many patients were excluded from the series due to:

1 Inability to fit into the frame? ....

2 Inability to tolerate the frame

2° to pronounced gag reflex? ....

2° to claustrophobia? ....

2° to pain in the teeth ....

MATERIALS AND METHOD

The dental impression

Which dental impression material was used and

in how many patients?

- Acrylic sheet pressure formed over dental model ....
- Polyethylmethacrylate PEM ....
- Panasil putty ....
- Dental composition material ....
- Light cured Acrylic (LCA) ....

Which dental impression material did you find most satisfactory ....

How many patients had the following problems with impression ?

- Abrasion to gums ....
- Unable to remove impression due to setting on teeth ....
- Rocking of impression on the teeth ....
- Damage to crowns ....
- Chipping of enamel ....
- Breaking of tooth ....
- Other please specify ....

How was accuracy of fit detemined (tick)

Patients judgement of stability ....

Technicians judgement of stability ....

Ports to view occlusal surface ....

Other please specify ....

Positioning the frame

In how many patients was the frame fixed:

- parallel to canthomeatal plane ....
- parallel to Frankfort plane ....
- parallel to another plane ....

Fixing the frame

How many patients had the frame relocated under GA ....

What was the longest period between fittings eg. follow up ....

How did you determine the accuracy of relocation

1 Rely on correct location of dental tray ....

2 Take AP and Lat. xrays and superimpose ....

3 Measure displacement of skin mark with stereoguide ....

In how many patients was adjustment of impression necessary between fittings ....

In how many patients has it been necessary to adjust the position of the head rest during treatment or follow up due to:

- change in hair thickness? ....

- steriod / radiotherapy induced swelling of scalp ....

PATIENT TOLERANCE

How many patients found wearing the frame:

Comfortable ....

a little uncomfortable ....

very uncomfortable ....

painful ....

Generally, how long after fixing the frame did patients complain of discomfort ....

Of those patient who found wearing the frame very uncomfortable or painful, was the prime site of discomfort in:

one or two teeth ....

all teeth ....

the gums ....

the occiput ....

the top of the head ....

What is the longest time patient has continuously worn the frame ....

On how many occaisions did you remove the frame during imaging because of:-

discomfort ....

Claustrophobia ....

Vomiting ....

Epileptic fit ....

The patients in my personal series completed a questionaire to asses their tollerance of the fixation method. This was completed after each patient had finnished their first CT scan in the frame. The period of fixation with the frame fixed in the scanner was aproximately 45 minutes. The questionaire was as follows.

PATIENT QUESTIONNAIRE

Name:

Did wearing the frame make

	NO	A BIT	A LOT
1. you feel claustraphobic			
2. you feel sick			
3. your mouth sore			
4. your teeth hurt			
5. the back of the head hurt			
6. the top of your head hurt			

Did you find wearing the frame

comfortable..... ☐

a little uncomfortable... ☐

very uncomfortable..... ☐

Painful..... ☐

Results

ASSESSMENT OF THE FIXATION METHOD IN CLINICAL PRACTICE

ASSESSMENT CENTRE:

MV = Maida Vale Hospital

QS = Queen Square Hospital

SB = St.Bartholomews Hospital

RM = Royal Marsden Hospital

PATIENTS

	MV	QS	SB	RM	TOTAL
Number of adults treated:	13	32	86	60	191
Number of children treated (under 14 years)	0	0	14	3	17
Age range:	35-65	22-65	2-75	11-62	2-75
Mean age:	48	42	30	35	39
Sex - No of males	7	19	58	39	123
No of females	6	13	42	24	85
Status of dentition:					
No with teeth	12	29	97	57	195
No edentulous	1	3	3	6	13
PATHOLOGY TREATED					
Number of AVM's:	0	0	74	10	84
1° brain tumours:					
High grade gliomas	8	27	1	21	57
Low grade gliomas	0	0	15	4	19
Pineal tumours	0	0	1	1	1
Pituitary tumours	0	0	2	2	4
Acoustic neuromas	0	0	1	1	2
Meningiomas	0	0	2	0	2
Craniopharyngioma	0	2	0	0	2
Medulloblastoma	0	0	2	3	5
Lymphoma	2	0	0	0	2
Germinoma	0	2	0	0	2
2° brain tumours:					
Solitary metastases	0	0	0	20	20
Multiple metastases	0	0	0	2	2
Parkinsonian Tremor	3	1	0	0	4
Epilepsy	0	2	0	0	2

IMAGING

Total number of Radiodiagnostic procedures performed on patients in the frame.

	MV	Q.S.	S.B.	R.M	TOTAL
CT	22	30	100	80	232
MRI	2	1	0	0	3
PET	11	0	0	0	11
ANGIO	1	0	35	10	46

Combinations of radiodiagnostic procedures per patient.

	MV	Q.S	S.B	R.M	TOTAL
1CT	0	29	65	30	125
2CT	5	0	0	20	24
1CT + 1MRI	0	1	0	0	1
1CT + 1ANGIO	0	0	35	10	45
2CT + 1ANGIO	1	0	0	0	1
1CT + 1PET	4	0	0	0	6
1CT + 2PET	1	0	0	0	1
2CT + 2PET	1	0	0	0	1
1CT+1PET+1MRI	1	0	0	0	1
2CT+2PET+1MRI	1	0	0	0	1

TREATMENT:

		MV	QS	SB	RM	TOTAL
How many patients had stereotactic biopsy in the frame?		9	25	0	0	34
How many patients had isotope placement in the frame?		0	18	0	0	18
How many patients had electrode placement in the frame:-	for Ix of epilepsy?	0	2	0	0	2
	for thalamotomy?	3	1	0	0	4
Patients for radio-therapy/surgery in the frame. How many had:-	1 treatment	0	0	93	12	105
	2 treatments	0	0	1	9	10
	3 treatments	0	0	0	4	4
	4 treatments	0	0	0	4	4
	5 treatments	0	0	0	6	6
	6 treatments	0	0	0	7	7
	7 treatments	0	0	0	4	4
	8 treatments	0	0	0	8	8
	9 treatments	0	0	0	5	5
	10 treatments	0	0	0	1	1
	more (please state)					
EXCLUSIONS						TOTAL%
How many patients were excluded from the series due to:						
1 Inability to fit into the frame?		0	1	0	0	
2 Inability to tolerate the frame		0	0	0	0	
2° to pronounced gag reflex?		0	1	0	0	1.5%
2° to claustrophobia?		0	0	0	0	
2° to pain in the teeth		0	0	0	1	

MATERIALS AND METHOD

	MV	QS	SB	RM	TOTAL%
Which dental impression material was used and in how many patients?					
- Acrylic sheet pressure formed over dental model	2	18	0	0	9%
- Polyethylmethacrylate PEM	11	2	8	18	20%
Panasil putty	0	0	92	11	49%
- Dental composition material	0	4	0	0	2%
- Light cured Acrylic (LCA)	0	8	0	34	20%
Which dental impression material did you find most satisfactory	PEM	LCA	Panasil	LCA	
In how many patients did you have the following problems with the dental impression ?					
- Abrasion to gums	0	4	0	0	2%
- Unable to remove impression due to setting on teeth	0	0	0	0	
- Rocking of impression on teeth	1	2	15	8	12%
- Damage to crowns	0	0	0	0	
- Chipping of enamel	1	1	0	0	1%
- Breaking of tooth	0	0	0	0	
- Other please specify	0	0	0	0	

How was accuracy of fit detemined (tick)	MV	QS	S.B	R.M	TOTAL%
Patients judgement of stability	√	√	√	√	
Technicians judgement of stability	√	√	√	√	
Ports to view occlusal surface	√	√			
Other please specify					
POSITIONING THE FRAME					
In how many patients was the frame fixed: - parallel to canthomeatal plane	13	17	90	63	88%
- parallel to Frankfort plane	0	0	10	0	5%
- parallel to another plane between CMP + FP	0	15	0	0	7%
FIXING THE FRAME					
How many patients had frame relocated under GA	2	30	3	0	17%
What was the longest period between fittings eg. follow up	7mths	6 wks	3 wks	2 mths	
How did you determine the accuracy of relocation					
1 Rely on correct location of dent tray		√			
2 Take AP and Lat. xrays and superimpose	√		√	√	
3 Displacemnt skin mark with stereoguide		√			
In how many patients was adjustment of impression necessary between fittings	0	0	0	0	0
In how many patients has it been necessary to adjust the position of the head rest during treatment or follow up due to:					
- change in hair thickness?	0	0	0	0	0
- steroid / radiotherapy induced induced swelling of scalp	0	0	0	0	0

PATIENT TOLERANCE	MV	QS	SB	RM	TOTAL%
How many patients found wearing the frame: Comfortable	4	2	30	23	28%
a little uncomfortable	8	23	58	34	59%
very uncomfortable	1	5	10	6	11%
painful	0	2	2	0	2%
Generally, how long after fixing the frame did patients complain of discomfort	45 min	45 min	40 min	45 min	
Of those patients who found wearing the frame very uncomfortable or painful the prime site of discomfort was					
one or two teeth	0	1	0	0	4%
all teeth	0	1	0	2	12%
the gums	0	1	0	0	4%
the occiput	1	4	8	4	65%
the top of the head	0	0	4	0	15%
What is the longest time a patient has continuously worn the frame	4 hrs	2 hrs	2 hrs	105min	
On how many occaisions did you remove the frame during imaging because of:-					
discomfort	0	0	1	0	1%
Claustrophobia	0	0	0	0	
Vomiting	0	0	1	0	
epileptic fit	0	0	0	0	

Discussion

PATIENTS AND PROCEDURES

At the four hospitals where a prototype Relocatable Frame was used a total of 208 patients were investigated and or treated under stereotactic conditions for a range of cerebral pathologies. These included 96 primary brain tumours, 22 secondary brain tumours, 84 arteriovenous malformations, 2 cases of epilepsy, and four patients with Parkinson tremor. The age range of the patients was from 2 years to 75 years. Seventeen of the patients were under 14 years of age.

Two hundred and ninety two radiodiagnostic imaging procedures were performed under stereotactic conditions. All the patients had at least one CT scan performed in the frame and 30% had further imaging such as repeat CT, angiography, MRI, or PET under the same stereotactic conditions at a later date.

Fifty eight invasive stereotactic procedures were performed in the frame including 34 biopsies. 18 patients had interstitial brachytherapy for recurrent gliomas, 2 had electrode placement for the investigation of epilepsy and 4 had thalamotomy for Parkinsonian tremor.

One hundred and sixty three patients had stereotactically focused irradiation therapy to AVMs or tumours, and received a total of 372 treatments. One hundred and five had a single treatment (radiosurgery) and 58 had multiple treatments (stereotactic radiotherapy).

In this large clinical series only three patients were excluded. One patients head was too large to fit into the BRW frame, a second patient had such a pronounced gag reflex that they were unable to tolerate having a dental impression made. The third patient was excluded due to poor dentition and painful teeth when pressure was exerted.

MATERIALS AND METHOD

The Dental Impression

The formation of a rigid and accurate dental impression is the key to precise and stable relocation of the frame, but it is not an easy technique to master. As a result each centre using the prototype adapted the method and tried different impression materials to suit there own requirements. The various materials and methods are described below.

1. Pressure formed Acrylic impression:

The steps in forming an acrylic impression are:-

i. An alginate impression is taken of the upper teeth. Alginate is a conventional impression material formed of the sodium salt of alginic acid. It is provided as a powder which is mixed with a measured quantity of water and spatulated into a thick paste which is then placed into the impression tray and the whole inserted into the patients mouth and pressed on to the upper teeth. Within 2-3 minutes the impression sets to a rubbery consistency and is then withdrawn from the mouth.

ii. Plaster of paris is poured into the impression which forms a model of the patients upper teeth and palate. The undercuts which are predominantly on the buccal surface of the teeth are now carefully filled with additional plaster of paris.

iii. The prepared model with the undercuts eliminated is placed in a pressure forming machine Druformat (Dreve Dentamid GmbtH. Max Planch Strabe 31, 4750 Unna. Germany). A three millimetre Perspex sheet (Bioglass H Dreve. Dentamid GmbH) is placed on a moveable carriage in the machine. It is heat softened under a lamp and then brought down over the model and forced over its surface with air pressure to conform precisely to its numerous contours. When the Perspex has cooled the acrylic impression so formed is withdrawn from the dental model, trimmed and then bonded with cold cure acrylic cement to the bridge shaped supporting element of the dental piece.

This technique is very time consuming and requires the facilities of a dental laboratory. Each impression takes a number of hours of a technicians time to make. The accuracy of the impressions fit on the teeth is very good, although being made of 3mm thick Perspex, the impression is prone to distortion under load unless appropriately reinforced by building up its thickness with additional cold cure acrylic cement.

2. Polyethylmethylmethacrylate PEM.

The single stage formation of a dental impression using PEM has previously been described. The prime advantage of using this material is that an accurate and rigid dental impression can be formed within a few minutes. As mentioned previously however, the technique requires a degree of expertise and careful timing. If the impression is withdrawn from the mouth too early the material remains relatively fluid and is likely to distort prior to setting. If the material is left too long in the mouth it will set hard and may be impossible to remove without drilling it off the teeth. The impression may require some pre fitting adjustment to provide additional clearance of the undercuts. (a high speed drill is used for this purpose).

3. Viynylpolysiloxane putty (Panasil putty)

Equal volumes of the base putty and hardener putty are mixed and placed in the dental tray. Perforations in the tray lock in the material. The patient bites on the material and it is allowed to set in the mouth. It sets to a firm rubber like material in 2-3 minutes. When the impression is withdrawn from the mouth the elastic nature of the material enables it to spring out of the undercuts.

The taking of an impression using Panasil putty is simple, however this advantage is outweighed by the disadvantage of its flexibility- which in my view makes it an unsuitable impression material for accurate serial relocations on the upper jaw.

4. Dental composition material

Dental composition material is formed from a mixture of waxes and resins with an inert filler a well known example is Stent . At room temperature dental composition is hard but when placed in hot water above 70°C it softens to form a putty like material. When in its softened state it can be placed into a dental tray and an impression taken of the patients upper teeth. Like the PEM material it is withdrawn from the mouth before it sets hard, thereby clearing the undercuts and allowing its subsequent repositioning on the teeth. the advantages of the material are that it is simple to use, and if for any reason one is unhappy with the impression taken then by placing the tray in hot water, the material will resoften and allow another impression to be taken. One disadvantage of this material is that its degree of shrinkage on setting tends to make the fit unacceptably loose on the teeth. A further disadvantage is that the material is very brittle and will shatter if dropped or may fracture if the patient bites hard on the impression. I feel these factors make composition material unacceptable for this use.

5. Light cured acrylic

The light cured acrylic material used was ethoxylated Bisphenole A, Butandioldimethacrylate, Tetrahydrofurfurylmethacrylate. This is currently available for denture relining under the product name " Lightdon - u/hard" (Dreve-Dentamid GmbH).

The required quantity of Lightdon u/hard paste is placed into a dental tray and a dental impression formed by the patient biting into it. The impression is then removed from the teeth which automatically clears the undercuts. Lightdon u/hard will remain as a paste until cured and so unlike PEM there is no time limit to forming the impression. One can therefore repeatedly take an impression until the desired result is achieved. The impression is the placed in a light box (Polylux Unit: Dreve-Dentamid-GmbH) for 10 minutes until the material is hardened.

Lightdon u/hard will form a chemical union with the acrylic dental tray to form an extremely rigid combined structure.

Blobs of Lightdon u/hard are placed over the built up sections on the under surface of the tray and impressions of the cusps of the lower premolars taken when the patient bites on the tray. When light cured and refitted in the mouth the patient can then bite firmly on the impression seating it evenly on the upper teeth.

The accuracy of the fit can be determined by applying a blue indicator paint "Fixtector" (Prodent GmbH .6380, Bad Homburg. W.Germany) to the occlusal surfaces of the upper teeth. The impression is then repositioned and if accurately relocated the paint, which forms a layer 5 microns thick over the teeth, will be evenly deposited over the impressions occlusal surface. Irregularities in the impression will be observed

as areas where no contact has occurred. These can be corrected by placing more Lightdon u/hard paste into the impression and reapplying it to the teeth. When subsequently removed, light cured and repositioned a near perfect fit should be achieved.
Light cured acrylic is undoubtedly the impression material of choice however it did not become available until 1991 and as a result was not used from the outset.
In the early stages of the frames development and for the first two patients I used pressure formed acrylic impressions and then progressed on to the use of PEM, due to the time consuming nature of the former method. Having developed a degree of expertise in taking impressions I found its use satisfactory. In only one patient were there any problems and this was due to the chipping of the enamel from a front incisor. The cause may have been from too tight a fit of this incisor in the impression in addition to weak or cracked enamel.

The three other groups using the frame found PEM difficult to use. The group at Queens square reverted to using impressions formed from an acrylic sheet until light cured acrylic became available. Four of their patients received gum abrasions from the acrylic sheet impressions which was due to the inclusion of the soft tissues in the impression. One patient in this group also had chipping of a flake of enamel from an incisor.

The group at St. Bartholomews hospital opted for Vinyl polysiloxane putty, and at the time of completing the questionnaire had not tried using the light cured acrylic. The Panasil putty was simple to use and there were no cases of damage to teeth or gums, however it provided a less rigid means of fixation with reduced accuracy of location.
The group at the Royal Marsden Hospital used Panasil putty on 11 patients and proceeded to use Light cured acrylic on 34 patients In none of this latter group were there problems with the impressions.

In all groups the accuracy of the dental impression's fit was checked at the time of relocation by both the patients and the clinicians judgement of the stability of the frame on the teeth. The exception to this was where the frame was relocated on anaesthetized patient. In these cases which included 2 in my personal series and 30 in the Queen Square series the accuracy of location was assessed by viewing through ports the occlusal surface of the premolar teeth in contact with the impression.
In the St. Bartholomews and the Royal Marsden groups viewing ports were not used and all patients had AP and Lat. xrays performed in a treatment simulator prior to treatment. These were compared with previous films to ensure that relocation was generally within 1mm for all cases.
The longest period between frame relocations was seven months and it was not found necessary to adjust the dental impression between fittings for this patient or any other.

The Localiser Unit

In clinical practice problems were encountered with the localiser unit. The first being the release of noxious fumes from the cold cure acrylic cement as it was used to bond the dental piece to the positioning plates. It is recommended that the cement is used in a fume cupboard but this is not always practicable. The second and potentially more serious problem is that if dropped the Perspex localiser unit is likely to break due to its brittle nature. If a patient was between radiotherapy treatments and their unit broke then all the previous imaging data and planning would immediately be worthless and would require repeating. One localiser did break when it was dropped but fortunately the patient had completed treatment in the frame.

Head Rest and Straps

There were no particular problems with the fixation method regarding the head rest and straps. There were no known errors due to incorrect reading of the vernier scales on the headrest slides. The position of the head rest did not have to be altered for any patient during a treatment as a result of change in hair thickness or scalp thickness secondary to radiation therapy or steroids.
When the straps were tightened the combined tensions in the coronal straps and the posterior sagittal straps held the frame perfectly rigid. The anterior sagittal strap was therefore redundant and was removed.

PATIENT TOLERANCE

The degree to which a patient can tolerate fixation in the frame is dependant on a multitude of variable factors. These include the patients anxiety level, pain threshold, the sensitivity of the teeth and their expectation of what they will experience. Other factors may include the degree of tension applied to the straps and how evenly the force is distributed on the teeth and occiput (which is dependant on the accuracy of the impressions). Finally patient tolerance will depend upon the duration of frame fixation.

Quantifying the degree of tolerance is difficult because it is of course entirely subjective, but within the limitations of this study it was found that patients generally tolerated the frame well. They would find it comfortable after initial fixation but after approximately 45 minutes the majority (72%) would be aware of discomfort to a variable degree. 11% found it very uncomfortable and 2% found it painful. In only one of the 208 patients who have worn the frame was it necessary to remove it during a procedure because of discomfort.
Most stereotactic imaging or therapeutic procedures last for about 45 minutes, however a number of patients wore the frame for four hours (for diagnostic PET scan).
Of the patients who found wearing the frame very uncomfortable or painful 65% had discomfort at the

occipital protuberance and 15% at the top of the head where the central strap connector pressed into the scalp. The scalp presumably becomes relatively ischaemic at these points of continual pressure. Very few patients complained of pain in the teeth although most were aware of a generalised ache in the upper dentition.

One patient vomited while in the frame during radiosurgery treatment. When the frame was detached from a bracket on the treatment couch it was possible to turn the patient on their side and clear the airway with the frame remaining in situ. The dental impression does not limit access to the mouth and therefore removal of the frame is not necessary. The frame can however be removed within a few seconds if required.

CHAPTER 7

FRAME MODIFICATIONS

Second Prototype

Third Prototype

Fourth Prototype

FRAME MODIFICATIONS

All the original objectives in designing a non invasive relocatable head fixation device have been met by the first prototype frame. Never the less the prototype in the form described would be unsuitable for mass production and general use due primarily to the choice of materials from which it is constructed. Tufnol and acrylic were selected as construction materials for the first prototype because as non conductors they cause no artefact on MRI images. Tufnol however is difficult to machine and lacks the stiffness and durability of the metals. It was therefore possible to bend the headrest and base plate with the application of moderate force. The base plate was only stiffened when it was fixed to the metal BRW base ring.

The construction of the localiser unit from acrylic components that could be bonded together fulfilled its purpose of accommodating the desired range of head sizes and frame positions. A significant disadvantage of using acrylic was that brittleness made it vulnerable to fracturing if dropped. If this were to happen in a clinical setting, then all the image data relating to that patients position in the frame would be rendered useless.

To fit the head into the confines of the BRW stereoguide required the fine adjustment of head position that was possible with the localiser unit. In 1989 the CRW (Cosman - Roberts - Wells) stereoguide was introduced (Radionics Inc. Burligton Mass). This has a much larger working space within it. It soon became apparent that the vast majority of patients could be fitted into the CRW system via the Relocatable Frame with the dental impression held at a fixed position. Differences in head size could then be accommodated by adjustment of the head rest slides.

In the clinical study 87% of patients had the frame fixed parallel to the canthomeatal plane and there was no reason why the remaining 13% could not have been fitted into this same orientation had they not been constrained by the BRW working space. There is in fact little clinical indication to place the frame parallel to the Frankfurt plane. Even for CT - directed thalamotomy the only imaging requirement is that the axial slices are truly horizontal. The angle of pitch of the CT slices is less important because the images have to be resliced along the plane of the AC-PC line. Positioning the frame parallel to the canthomeatal line for thalamotomy is therefore perfectly adequate because the frame can not be accurately aligned with the AC-PC line using external landmarks. {The relationship between the AC-PC line and the Frankfurt plane varies between 11.5° and 18.5° (Van Manen 1967).

The Second Prototype Frame.

The second prototype frame (fig.56), or first production model, the GTRL (Gill, Thomas Repeat Locator; Radionics Inc. Burlington, Mass.) was designed to have the dental impression held at a fixed position. When located on the upper dentition the frame would assume an orientation approximately parallel to the canthomeatal plane. Provision was also made for adjustable fixation of the impression in exceptional circumstances.

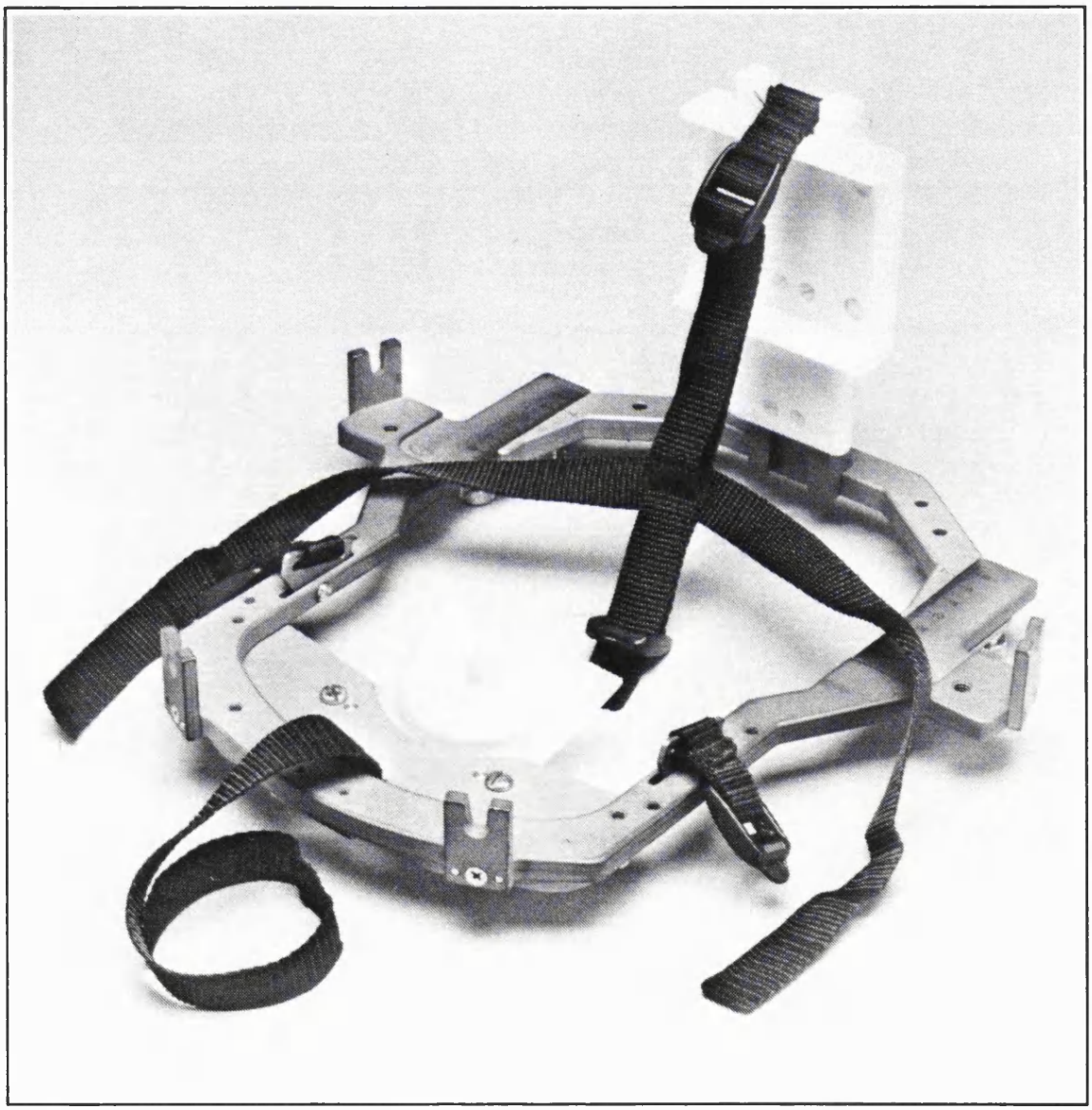


Figure 56 The second prototype Relocatable frame. (GTRL)

The form of the base plate was essentially the same as that of the first prototype, but was constructed from anodised aluminium. For a production version it was felt that aluminium's advantages of durability, good

machining characteristics, light weight and resistance to distortion outweighed its disadvantages of causing image artefact on MRI. These latter effects were minimised because the ring formed by the U-shaped baseplate and the head rest bracket was electrically broken by the insulation provided by their anodised surfaces of contact. This prevented the formation of major eddy currents in the MRI.
The effects of local eddy currents in the base plate appeared to have no influence on the field of view because the frame was set low on the head. (MRI compatibility was tested in a 0.15 Tesla MRI scanner at RPMS, Hammersmith Hospital,London, and on a 1.5 Tesla scanner at the Brigham Hospital, Boston , Mass).

The headrest tray was formed from acetal which causes no artefact on biomedical images, and the head straps made of woven nylon with moulded nylon buckles. The coronal and sagittal straps were sutured together at their meeting point rather than secured via a plastic connector. This reduced local pressure on the scalp when they were tightened because the load was spread over a greater surface area.

An acrylic dental tray is fixed to an aluminium bracket anteriorly in the frame. Dental trays are provided in three sizes - small - medium - and large. Each tray is integral with an acrylic block in which it is set at an angle of 20°s (fig.57).
The block has location holes through it for fixation to the bracket. The tray has built up sections on its under surface in the region of the premolar teeth so that when the patient bites on the tray the occluding force is directed centrally. The palatal section of each tray is excluded because the vast majority of patients have teeth and this is a more comfortable arrangement as the tongue can be brought up to the hard palate.

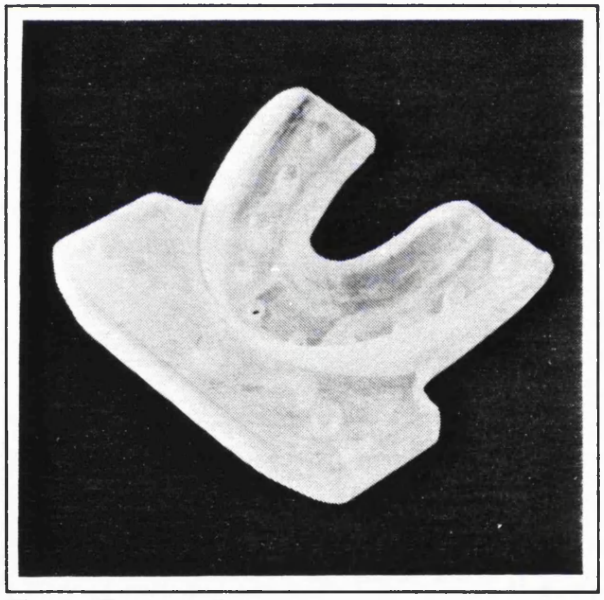


Figure 57 An acrylic dental tray

For those patients who are edentulous an acrylic palatal dome may be bonded to the existing dental tray prior to loading it with light curable acrylic paste and taking an impression of the upper jaw.Acrylic was used to cast the dental trays because it forms a chemical union with the light cured acrylic impression material to form an extremely robust combined structure. Acrylic can also be worked with simple hand held tools so that adjustments can be made to a standard dental tray if required.

If necessary provision can be made to position the frame in any desired orientation on the head using an aluminium localiser unit as shown in (fig.58). This overcomes the problem with bonding acrylic components together and the concern with breaking the localiser unit if dropped. The patients standard dental tray is

bolted to the bridge shaped supporting element and the frame positioned around the head. The lateral edges of the supporting element are then bolted to the positioning plates thereby recording the frames position for that patient. The localiser unit can be stored until the patient is to be repositioned in the frame.

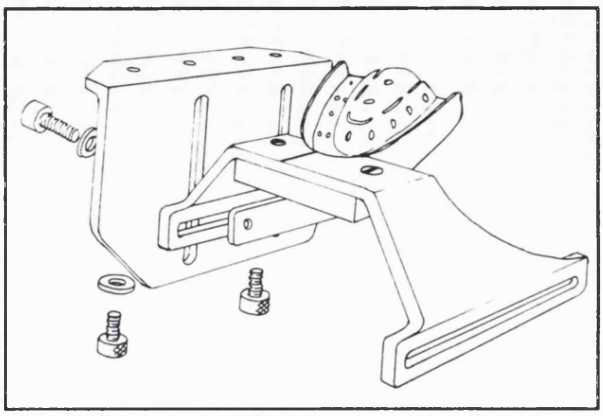


Figure 58 Aluminium localiser unit

The second prototype was used on a number of patients for biopsy,stereotactic radiotherapy and radiosurgery. It was simpler to apply than the first prototype and provided a more rigid fixation. The rather complex localiser unit was never used because all patients fitted into the frame with the standard fixed position of the dental tray. However some additional adjustment of the AP position of the dental tray would have been helpful because in patients with larger heads the AP adjustment on the head rest bracket tended to be set at its most posterior limits and occasionally the head rest clashed with the BRW fiducial system. A further disadvantage which also applied to the first prototype was the need to stack the BRW base ring onto the base plate and then, if a biopsy was to be performed, stack the CRW arc on to these.(fig 59) This was rather a cumbersome arrangement and led to the design of the third prototype

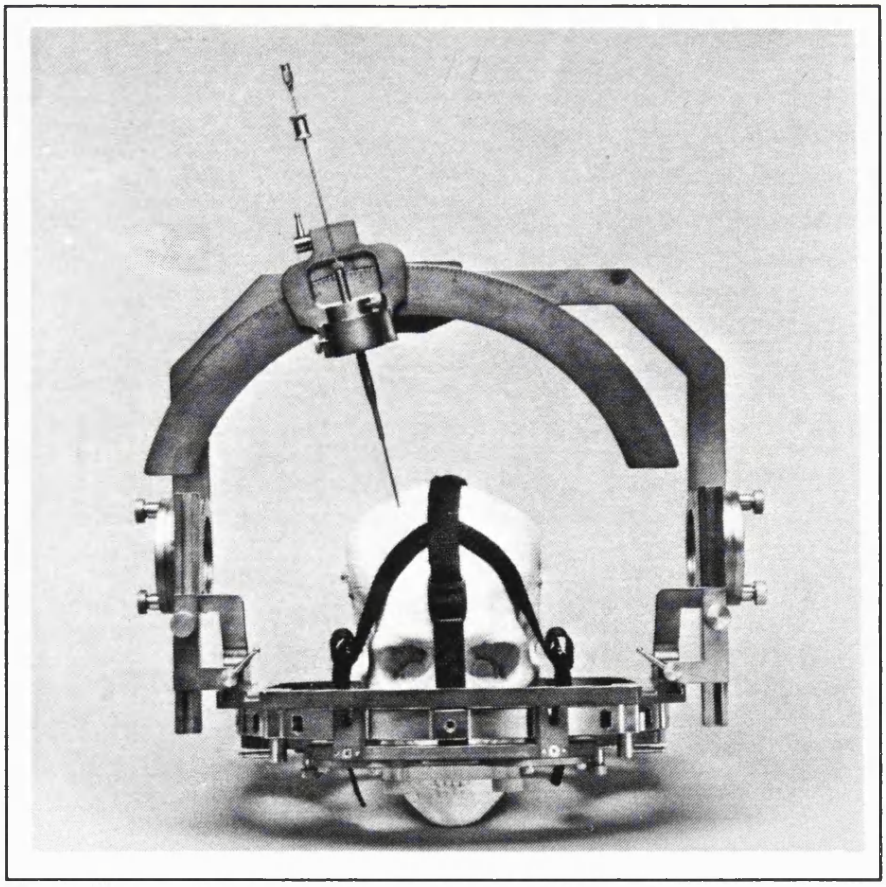


Figure 59 Stacking of CRW stereoguide on the BRW head ring on GTRL base plate

The Third Protype

The third prototype the GTRL II is shown in (figures 60 and 61). It is in the form of a ring that comprises two interlocking U sections that slide apart on dovetail slides but do not separate. The anterior U section has medially placed fixation points for the dental tray and laterally positioned fixation points for the coronal head straps. On the under surface of the lateral limbs are lock nuts to lock the AP slide in different positions. The posterior U section contains three cam locks which accept and lock the three fixation ball posts on the BRW localiser ring or stereoguides. It has a posteriorly placed head rest tray whose height is adjustable on a lockable slide. The frame has two laterally placed wings accommodating fixation holes so that it can be fixed within scanners or on an operating table via an appropriate holder. Additional fixation points are provided on the under surface of the frames on each side of the posterior cam lock. These are in the same position as the fixation points in the conventional BRW head ring. The positions of the AP and vertical slides are recorded on engraved millimetre scales.

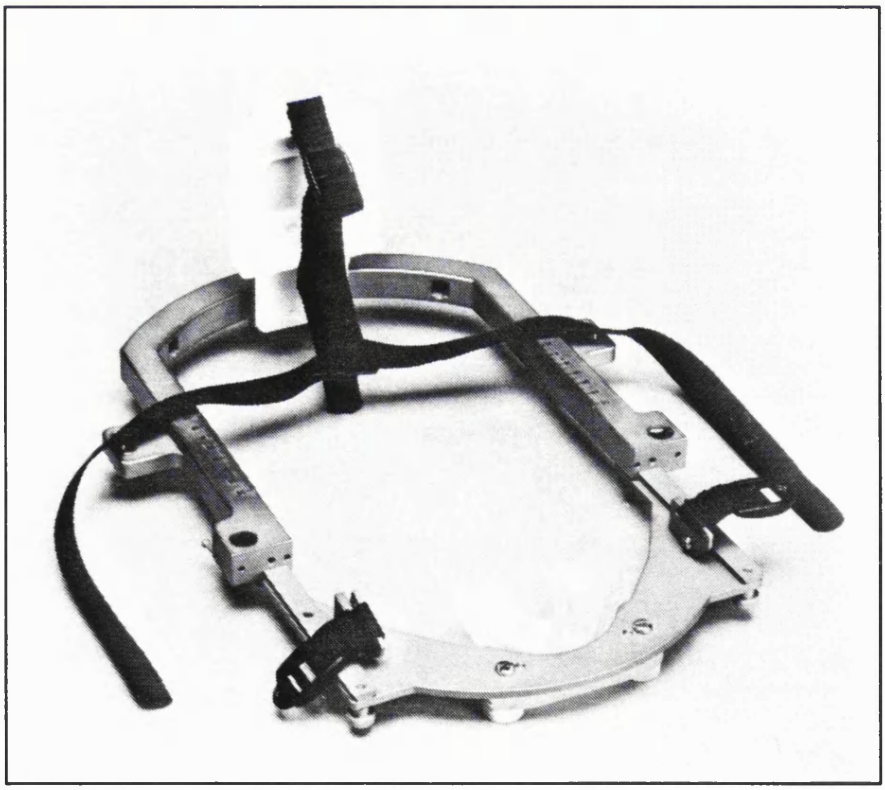


Figure 60 GTRL II, U sections separated

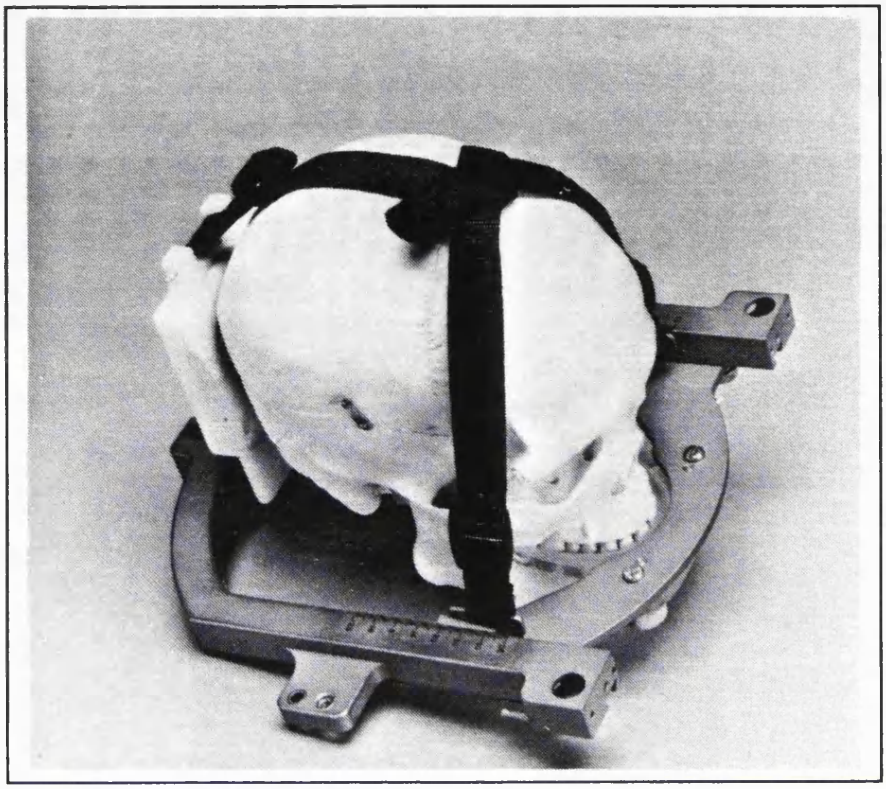


Figure 61 Skull fixed in GTRL II

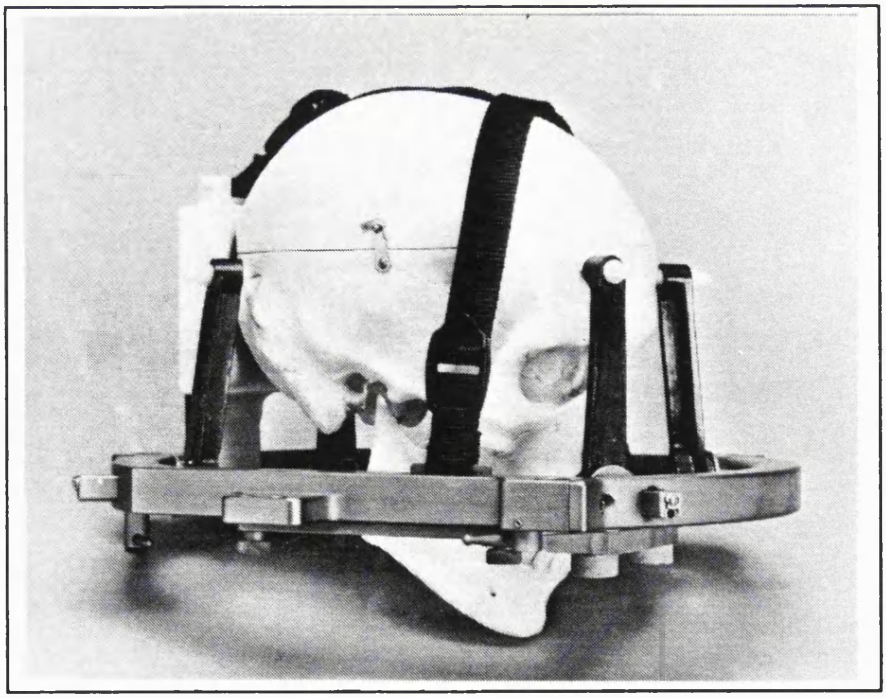


Figure 62 GTRL II - conventional head fixation with pins

Provision is made for conventional head post fixation that may occasionally be required for stereotactic craniotomy when it is necessary to remove the head straps from the operating field. Two mounting holes for the head post screw drives are positioned in the posterior U section and diametrically opposed to these, two further mounting holes are positioned in a bracket that attaches to the anterior limbs of the posterior U section, see (fig.62)

The method of head fixation is as follows

1. A dental tray of the appropriate size is selected for the patient and an impression of the upper jaw is made using Light cured acrylic, as previously described.
2. The dental tray is bolted to the fixation points in the anterior U section.
3. With the U sections of the frame maximally distracted it is placed over the patients head and the patient bites on the impression.
4. The U sections are brought together so that the head rest meets the occiput. The height of the head rest tray is adjusted so that its lower lip engages just beneath the occipital protuberance.
5. The sections are then separated and the head rest tray loaded with vinyl polysiloxane putty. When brought together again an impression is formed of the occiput which sets to a hard rubber.
6. The AP slides lock nuts are tightened and the head straps connected and tightened firmly.
7. The positions of the AP and vertical slides are recorded prior to removing the frame so that it can be precisely repositioned at a later date.

The third prototype has been entirely satisfactory in practice. The advantages of effectively incorporating the BRW head ring into the frame rather than stacking it on top of the base plate are that the arrangement is less cumbersome and the frame is considerably lighter than the combined weights of the previous base plate and the BRW head ring. It also makes the relocation of the frame for imaging or stereotactic procedures simpler and quicker.

A major concern with this method of head fixation is that as it becomes more widely accepted, particularly for focused radiotherapy, a time will come when an error will be made in reading the AP and vertical scales. This would be immediately noticed if check AP and Lateral films were repeated each time the frame was applied. However as confidence in the accuracy of the system has increased a number of centres have stopped performing such check films. A significant error in relocation could result in serious consequences if high dose radiation was mis-targeted.The only way to eliminate errors in reading scales is to remove them all together. It was this consideration that led to the development of a further prototype.

The Fourth Prototype

The fourth prototype (GTRL III) is made from anodised aluminium and is shown in (fig. 63) The frame is an octagonal ring formed in two sections that slide apart on rods but do not detach. The rods project from the posterior section that carries the head rest and slide in acetal bearings in the larger anterior portion that carries the dental tray. The rods are threaded at their anterior ends and engage in threaded inserts in the anterior portion of the frame when the sections are brought together. The sections can therefore be locked together by rotating the rods around their long axes.

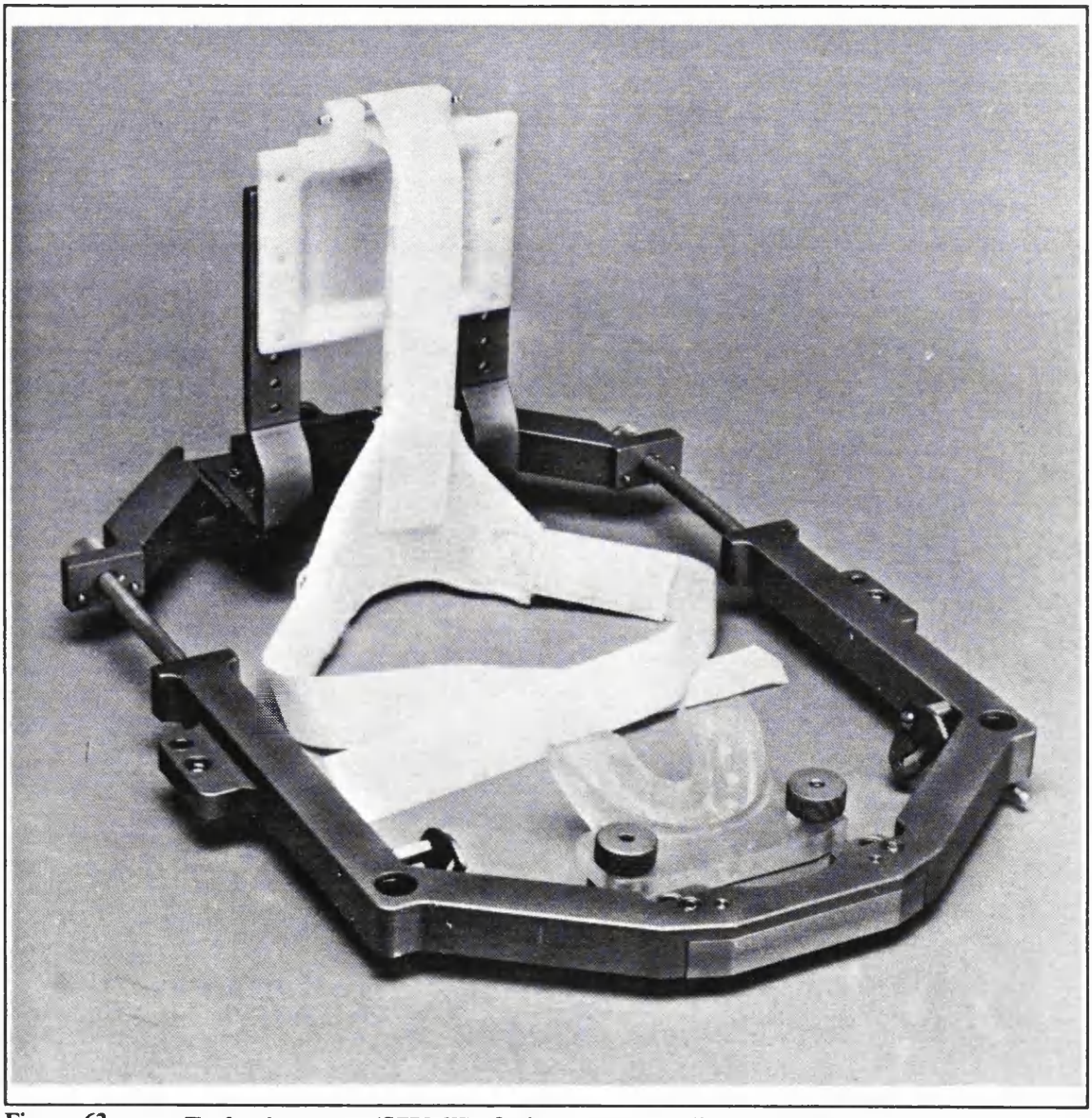


Figure 63 The fourth prototype (GTRL III) : Sections separated on slides.

The frame is held during imaging or stereotactic procedures by brackets which attach to laterally placed wings in the mid transverse plane of the frame. The anterior section has two laterally placed cam locks and the posterior section a centrally placed cam lock, which together provide fixation points for the BRW localiser ring or stereoguides. A standard acrylic dental tray is fixed to the anterior section by one of a series of brackets of variable length or angle, (fig. 64).

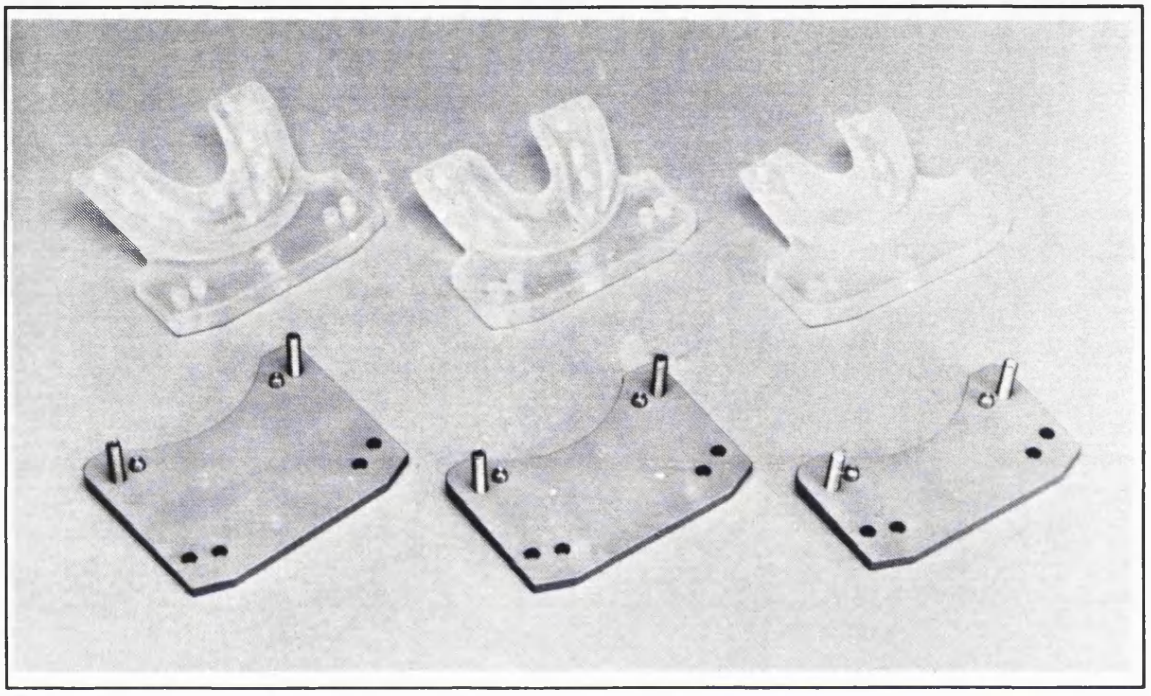


Figure 64 Range of sizes of dental trays and fixation brackets.

The headrest assembly (fig. 65) comprises atray that is formed of acetal and is fixed to the posterior section of the frame by two laterally placed L shaped aluminium brackets via an intermediate locking plate. Tapped holes in the L brackets enable the headrest tray to be positioned at different heights and fixed with screws. The head rest can be adjusted antero posteriorly by the L bracket sliding in slots in the intermediate locking plate. The desired position is fixed by bolting the brackets to the locking plate. The head rest assembly can be detached from the frame by unbolting

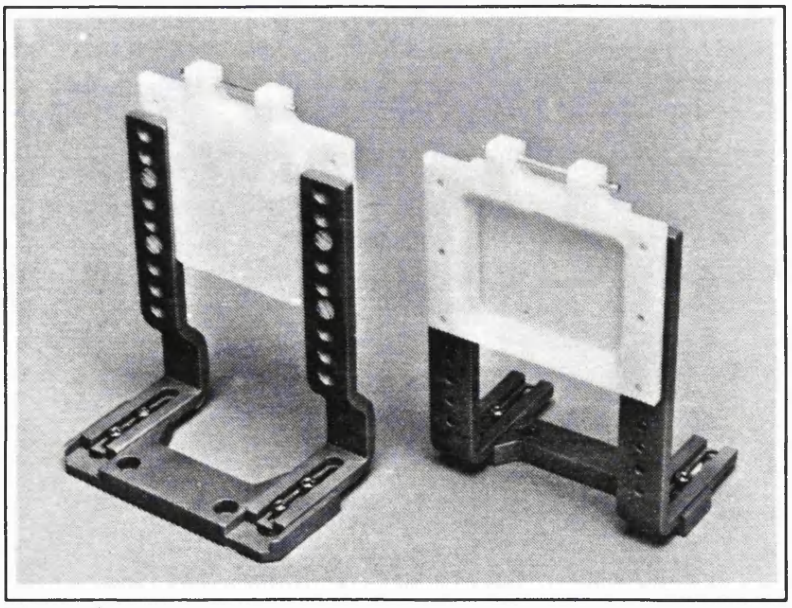


Figure 65 Head rest assembly

the intermediate locking plate from the posterior section of the frame. The head strap arrangement is unchanged from previous designs.

The method of fixation is as follows

1. A dental tray of appropriate size is selected for the patient and an impression of the upper jaw is made using Light cured acrylic as previously described
2. The dental tray is bolted to a dental fixation bracket of a length that will position the patients head centrally in the frame. Four standard lengths of bracket are provided. the standard dental tray is set at an angle of 20° to its plane of fixation, and so when bolted to a straight bracket and located on the head the frame will be positioned approximately parallel to the canthomeatal plane. By employing a bracket angled down at 10° the frame can be positioned approximately parallel to the Frankfurt plane. A range of lengths of 10° brackets are provided.
3. The dental fixation bracket with attached tray are fixed to the anterior section of the frame. The intermediate locking plate is bolted to the posterior portion of the frame and the two L brackets loosely secured with bolts.
4. The two sections of frame are separated by sliding them apart. The frame is then placed over the patients head and the patient bites on the impression. The two sections are now brought together and locked. (fig. 66)

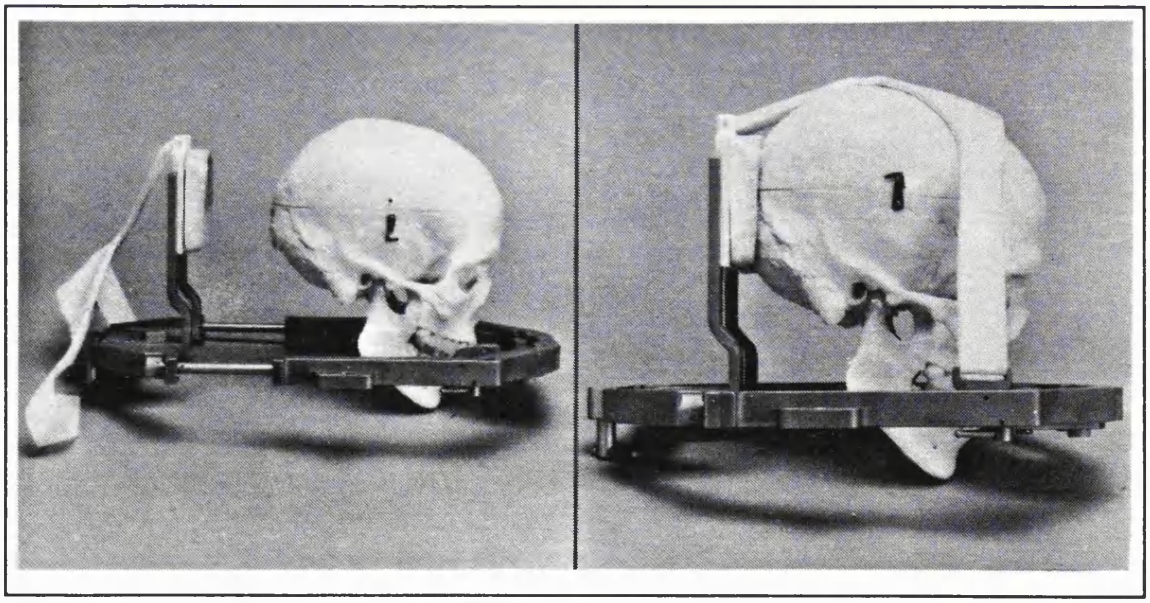


Figure 66 GTRL III - Method of head fixation.

5. The headrest tray is fixed at the desired height so that its lower lip will engage just beneath the occipital protuberance. The head rest tray is loaded with polysiloxane putty, polyethelyne film is placed over the putty and the tray slid forward to engage with the occiput. The impression so formed sets hard in 2 - 3 minutes.

6. The AP position of the head rest is fixed by tightening the bolts which clamp the L brackets to the locking plate.
7. The head straps are now tightened.

The frame is removed by releasing the head straps, unlocking the two sections of the frame and sliding them apart. The impression can then be removed from the teeth and the frame lifted over the head. The patient specific dental tray with the fixation bracket and the head rest assembly are removed and stored for that patient until relocation is required.

This design enables the patient to be accurately repositioned in the frame without the need to record numbers or set slides to calibrate positions. Its disadvantage is the need to store more components for each patient, however with the exception of the cast acrylic dental impression they are all reusable when the patient has completed a course of investigation and treatment.

CHAPTER 8

CONCLUSIONS

CONCLUSIONS

1 A practical means to integrate the spatial information from multiple brain images with stereotactic procedures has been provided by the development of a non-invasive Relocatable Stereotactic Frame. (S.S.Gill 1987)

2 The key to achieving non-invasive and yet rigid fixation of a stereotactic frame to the head, which is accurately relocatable, is to employ a precise dental impression that is firmly applied to the upper jaw as the prime means of location and fixation.

3 The described technique of non-invasive stereotactic frame fixation has a repositioning accuracy that is greater than any method previously reported ($<$ 1mm of displacement of any point in the head in each cardinal axis between frame repositionings).

4 Using the Relocatable Frame to reproducibly position the head in a variety of biomedical imagers (eg., PET, CT and MRI) geometric correlation can be achieved to within the voxel size of each imager.

5 The accurate geometric correlation of structural with functional brain images using the non-invasive method of head fixation has important application in basic neurological research. In the clinical setting it can be of significant value in diagnosis and treatment planning.

6 Serial brain images acquired many weeks or months apart in the Relocatable Frame can be accurately correlated allowing pathological change and response to treatment to be objectively monitored.

7 The rigidity with which the Relocatable Frame can be fixed to the head makes it suitable for stereotactically guided functional and non-functional neurosurgical procedures. The advantage of the Relocatable Frame in these circumstances is that image acquisition and surgical planning can be performed at some time prior to surgery at the convenience of the clinician. The stereotactic procedure can then be performed quickly and efficiently on a routine list after relocating the frame.

8 The Relocatable Frame facilitates biopsy from regions of interest selected from any one, or combination of, biomedical images. Biopsy material can be examined histologically or biochemically by radio-immuno assay, or alternatively put into cell culture for in-vitro

experimentation. This allows both functional and structural pathological change to be exactly correlated with the display screen intensities seen on any biomedical imager.

9 The Relocatable Frame has been shown to have particular application as a head holder for fractionated stereotactic radiotherapy. Its advantages of accuracy of repositioning and good patient tolerance make it the head fixation method of choice for this purpose.

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APPENDIX I

DESIGN OF LOCALISER UNIT

DESIGN OF THE LOCALISER UNIT

For the Relocatable Frame to accommodate a wide range of head sizes, the surface area of the positioning plates must be of a size that will ensure full contact with the lateral edges of the dental piece throughout this range. To calculate the dimensions of the positioning plates that are required one must first quantify the cephalometric proportions of heads at the extremes of the range. Assuming that the frame is fixed centrally around the head and in a standard orientation for stereotaxy then the relationship between the upper dentition (or dental piece) and the base plate (or positioning plates) can be determined for these extreme head sizes from their cephalometric data.

1. Quantifying the cephalometric proportions of extreme head sizes:

The largest probable head size that would be fitted in the frame was selected as a mean adult size (18yrs) + 2SD (m=f). The smallest probable head size was selected as a 10 year old's - 2SD (m=f). The cephalometric data for these head sizes were obtained from the 'Bolton Standards of Dentofacial Development and Growth (Broadbent et al. 1975).
The Bolton study was performed between 1927 and 1974 at the Health Science Centre at Case Western University in Cleveland. It includes over 22,000 recordings made from over 5,000 individuals and is the largest longitudinal study of its type. The population analyzed were Caucasian North American children, adolescents and young adults.

'Normal Standards' (Bolton Standards) of cephalometric proportions for each age group were derived from a subgroup of the population whose cephalometric recordings most closely conformed to the statistically derived means. These individuals (16 males and 16 females) had serial cephalometric recordings made on a six-monthly basis for the first four years of life, and thereafter on an annual basis to adulthood.
In addition to conforming closely to the mean cephalometric proportions these individuals were selected for having excellence of static dental occlusion, a good health history, and having aesthetically favourable faces as viewed by those performing the study. The cephalometric measurements of these individuals were averaged to form standards for the hermaphrodite population.

The cephalometric measurements for an average 10-year old - 2SD., were derived from a precise tracing of the Bolton Standard for a 10-year old (male/female average), which was photographically reduced to 0.92 of its original size. This magnification factor was calculated from the Bolton Population data by taking the mean measurements, of a 10yr old's skull (m=f) from the Bolton Point to the Nasion (Bo-Na), minus 2SD, and dividing it by the mean Bo-Na distance for a 10yr old. (See table (A1) of landmark definitions , and figure A1 of cephalometric measurements).

Table A1, CEPHALOMETRIC MEASUREMENTS: Landmark definitions

Na NASION	The junction of the fronto-nasal suture at the most posterior point on the curve at the bridge of the nose.
S SELLA TURCICA	The centre of the pituitary fossa of the sphenoid bone. Determined by inspection.
ANS ANTERIOR NASAL SPINE . . .	The tip of the median, sharp bony process of the maxilla at the lower margin of the anterior nasal opening.
PNS POSTERIOR NASAL SPINE . . .	The most posterior point at the sagittal plane on the bony hard palate.
Gn GNATHION	The most anterior-inferior point on the contour of the bony chin symphysis. Determined by bisecting the angle formed by the mandibular plane and a line through Pogonion and Nasion.
Pg POGONION	The most anterior point on the contour of the bony chin. Determined by a tangent through Nasion.
Me MENTON	The most inferior point on the symphysial outline.
UIE UPPER INCISOR INCISAL EDGE.	The incisal tip of the maxillary central incisor.
Bo BOLTON POINT	Point in space, about the centre of the foramen magnum, that is located on the lateral cephalometric radiograph by the highest point in the profile image of the post-condylar notches of the occipital bone. Since the post-condylar notches are close to the median sagittal plane, their shadows generally register on the lateral film as a single image.

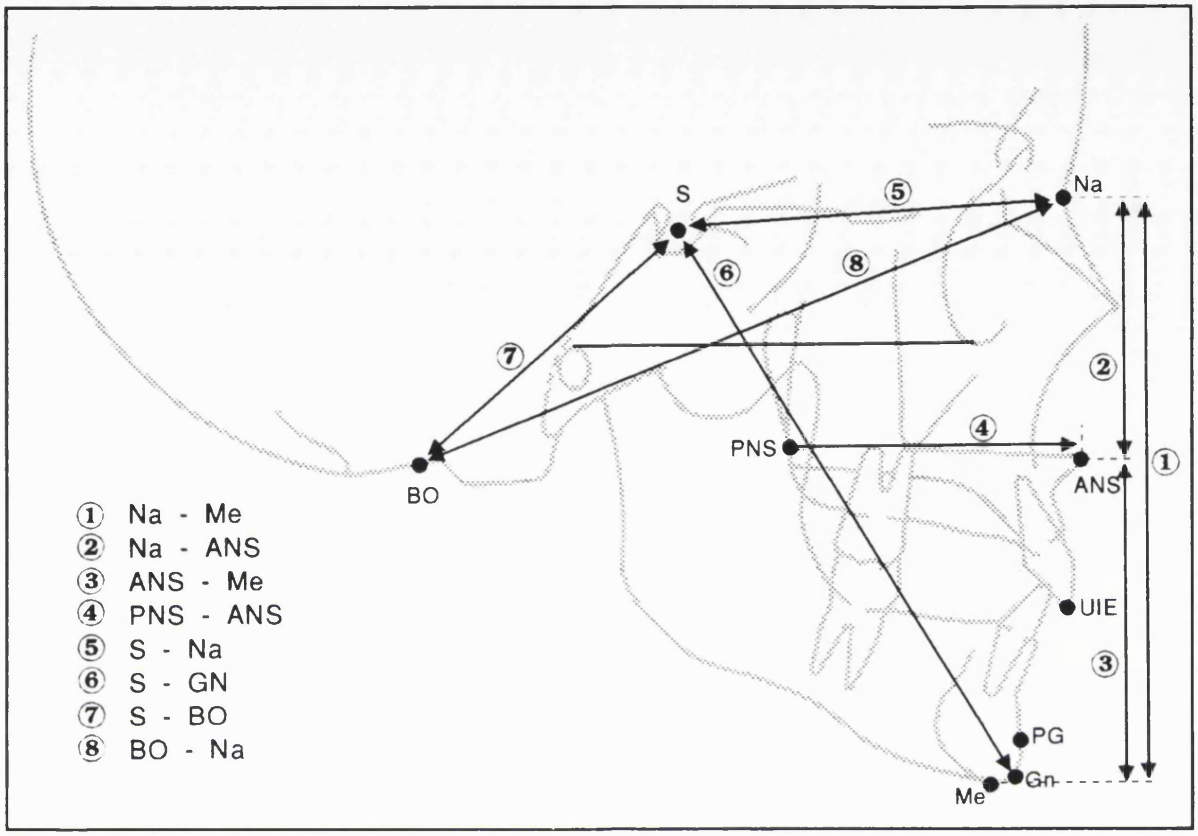


Figure A1 Cephalometric measurements

Cephalometric measurements were then made from this template and compared with the mean measurements for a 10yr old - 2SD that were derived from the 'Bolton Population' (see table A2). This showed that there was a good correlation between the two sets of data; ie that thee cephalometric proportions of the reduced template gave an adequate representation of the head proportions of an average 10yr old - 2SD as derived from the 'Bolton Population'.

Table A2

Mean cephalometric measurements from 'Bolton Population' for 10yrs - 2sd (m=f) V_o measurements from 'Bolton Standard' Template for 10yrs (m=f) reduced x .92

Measurement (mm)	1 Na-Me	2 Na-ANS	3 ANS-ME	4 PNS-ANS	5 S-Na	6 S-Gn	7 S-Bo	8 Bo-Na
Population mean 10yrs - 2SD	94.6	42.5	48.5	46.9	62.7	111.8	53.2	110.6
Standard 10yrs reduced x .92	95.0	42.5	51.0	47.0	62.5	103.0	53.5	110.5
Difference	-0.4	0.0	-2.5	-0.1	0.2	8.8	-0.3	0.1

The cephalometric measurements for the adult skull (18yrs) + 2SD., were derived in the same manner. The magnification factor in this instance was 1.1, and again there was good correlation between the Bolton Population and the template measurements. (see table A3).

Table A3

Mean cephalometric measurements from Bolton population for 18yrs + 2SD (m=f) V. measurements from 'Bolton Standard Template for 18yrs (m=f) magnified 1.1

measurement (mm)	1 Na-Me	2 Na-ANS	3 ANS-Me	4 PNS-ANS	5 S-Na	6 S-Gn	7 S-Bo	8 Bo-Na
Population mean 18yrs + 2SD	133.8	61.5	66.4	62.6	80.4	145.1	69.4	140.1
Standard 10yrs mag x 1.1	131.0	60.5	69.0	62.5	80.0	143.0	69.0	140.0
Difference	2.8	1.0	-2.6	0.1	0.4	2.1	0.4	0.1

2.Establishing the relationship between the upper dentition (of heads at the extremes of the normal range) and the base plate:

A fixed reference point on the head that bears a constant relationship to the frame must be chosen from which to measure variation in the position of the teeth relative to the base plate. The reference point chosen was a point 1.5 cm anterior to the external auditory meatus along the Frankfurt line. This point (the pre-meatal point) is approximately half way along the axis of the head when the nose is included. When the head is placed centrally in the frame a line passing transversely through both pre-meatal points (the pre-meatal line), will be in the mid-transverse plane of the base ring.

The pre-meatal point was taken as the point at which the Frankfurt line crosses the canthomeatal line. To calculate the position of any target in the brain using the BRW system, the base of the skull must be at a level 3cm above the top surface of the base ring. The fixed position of the pre-meatal line was therefore chosen to be in the base ring's mid-transverse plane 3cm above its top surface. This allows only one degree of freedom of movement of the head relative to the frame, which is a variation in the degree of pitch with the head rotating about the pre-meatal axis. Because the localiser plates are fixed vertically to the underside of the base-plate, the distance between the top of the localiser plates and the accessible stereotactic space is 6cm, which is the thickness of the base plate (1cm), plus BRW base ring (2cm), plus the inaccessible stereotactic space (3cm). Thus the distance between the pre-meatal line and a point on the under surface of the base-plate in its mid-transverse plane (the base-plate reference point), will remain constant at 6cm, irrespective of the degree of pitch of the head. The tip of the upper incisor was taken as a reference point on the upper dentition of each skull. The relationship between the incisor tip and the

base-plate reference point was measured with the frame set parallel to the Frankfurt plane, and again with the frame set parallel to the canthomeatal plane (see Fig. A2).

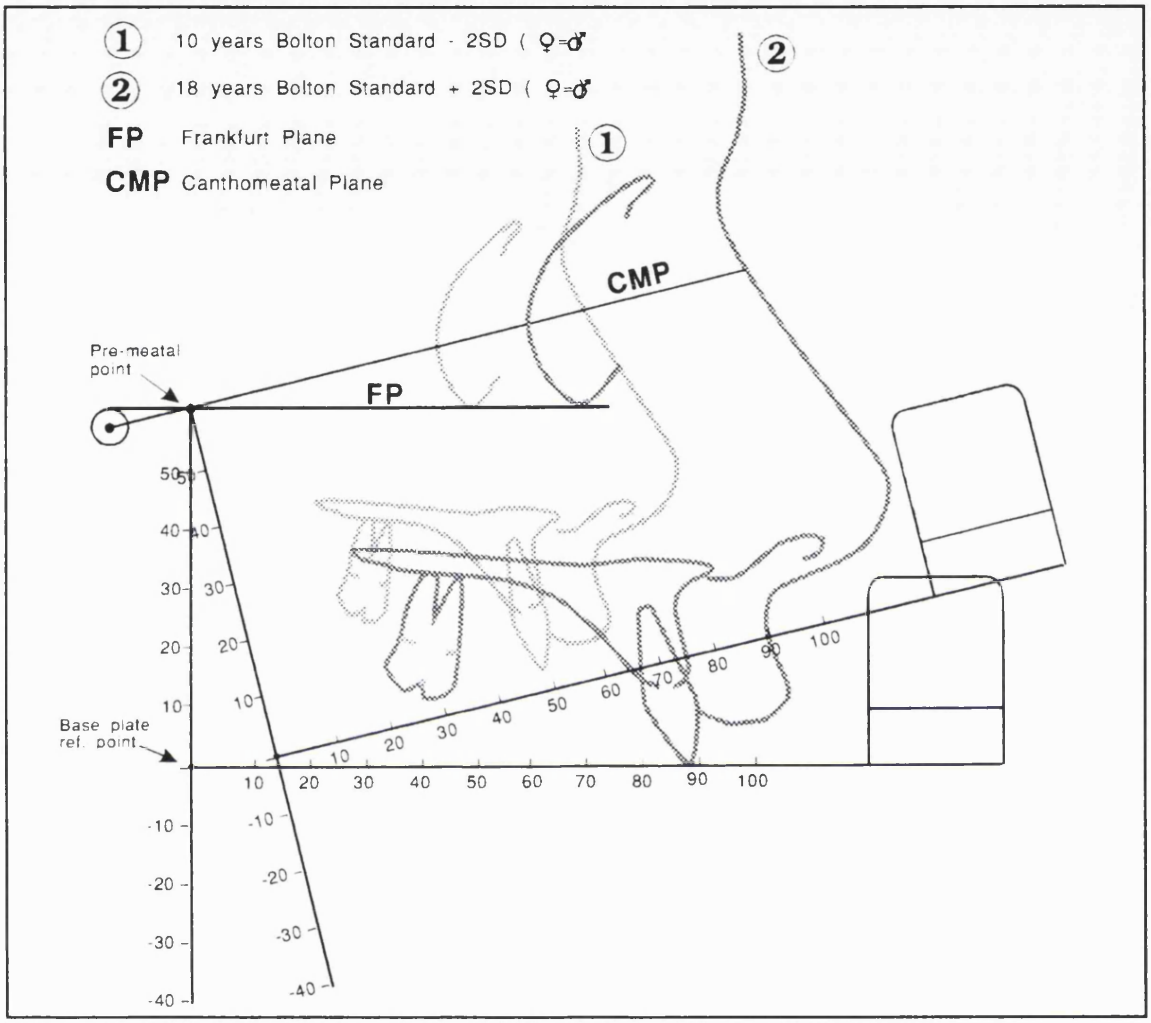


Figure A2 **The relationship between the upper dentition (of heads at the extreems of the normal range), and the base plate when set parallel to the Frankfurt and canthomeatal planes.**

Measurement of the incisor tip position relative to the base-plate reference point was made in the vertical direction, along the axis between the base-plate reference point and the pre-meatal point. Measurement in the horizontal direction was made along the under-surface of the base-plate.

When the frame is positioned parallel to the Frankfurt plane, the incisor tip of the largest head is at the level of the lower surface of the base-plate, however, the incisor tip of the smallest head is 17mm above the lower surface of the base plate. Similarly, when the base- plate is positioned along the canthomeatal plane the incisor tip of the largest head is 8mm below the under-surface of the base-plate. The incisor tip of the smallest head is 4mm above the under-surface of the plate.

3. The geometry of the dental piece

To fix the position of the dental impression relative to the base plate for heads at the extremes of the range, the dental piece must be capable of projecting both above and below the level of the base plate. For example to fix the smallest defined head it must project above the bottom surface of the base plate (or top surface of the positioning plates) to a height of at least 17mm. It was therefore necessary to construct the supporting element of the dental piece in the form of a bridge so that its lateral edges would remain in contact with the positioning plates throughout the range.

The angle between the occlusal plane and the Frankfurt plane is approximately 10°s (see fig A3). For most purposes the frame is positioned on the head parallel to the canthomeatal plane. The angle between the canthomeatal plane and the Frankfurt plane is ≈ 12°s. The relationship between the occlusal plane and the canthomeatal plane is thus ≈ 22° (10°±12°). The bridge shaped supporting element was therefore designed to hold the dental tray at an angle of 20°s to its lateral edges.

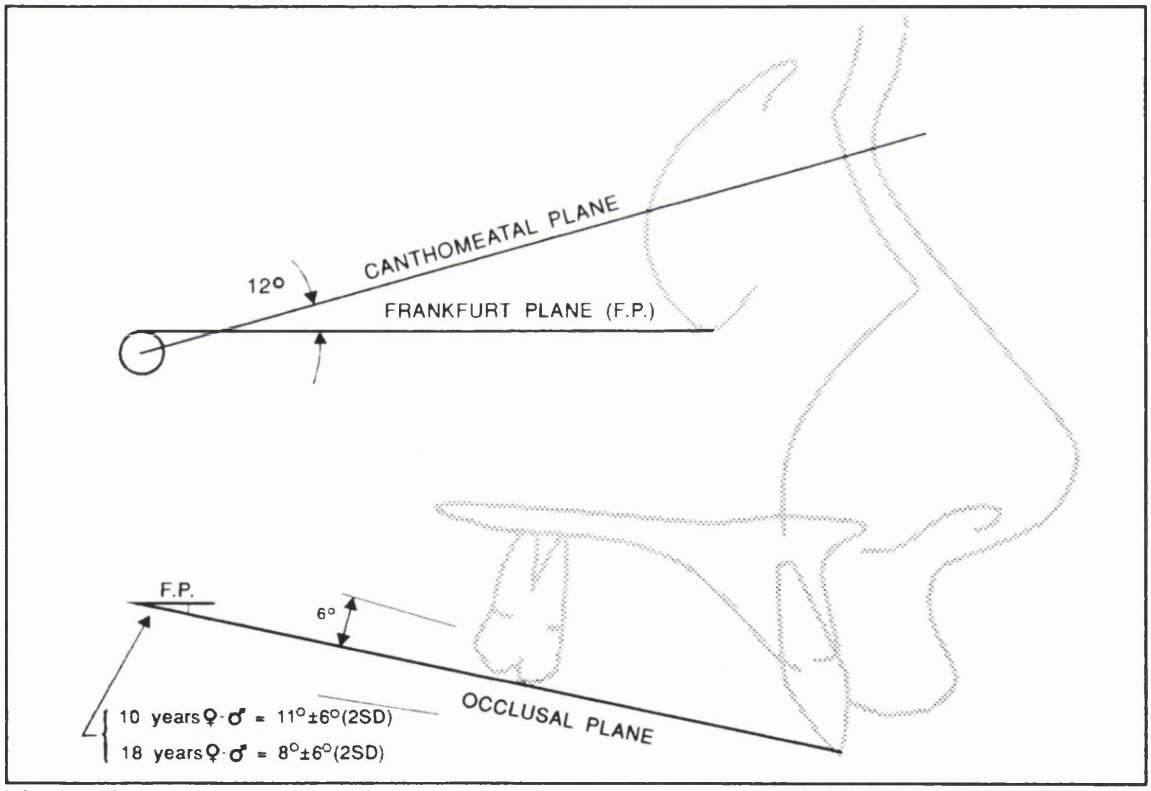


Figure A3. Angular relationship between the occlusal plane and the Frankfurt and canthomeatal planes.

4. The surface area of the positioning plates

The projection of the lateral edges of the dental piece onto the positioning plates for the largest and smallest head sizes are shown in (fig. A4) when the frame is orientated along the Frankfurt plane and in (fig. A5), when orientated along the canthomeatal plane.

A further factor to take into account in determining the desired surface area of the positioning plates is variation in the occlusal angle between individuals. The mean angle between the occlusal plane and the Frankfurt plane in the Bolton study for a 10-year old child (male/female) is 11°s $\pm$ 6°s (2xSD), and for an adult (18 years male/female) is 8°s $\pm$ 6°s (2xSD). This variation when projected onto the positioning plates via the dental piece is also shown on (fig A4, and A5).

The required dimensions of the positioning plates that would ensure full contact with the lateral edges of the dental piece throughout the likely range of head sizes and positions were thus determined from the scale drawings.

The described method of determining the required surface area of the positioning plates is based on cephalometric data from the Bolton study. Although the study was the largest of its type with a data base of over 5,000 individuals, they were all white North American children, adolescents and young adults, and will therefore only give an indication of the variance in a similar population. The study does not give an indication of inter-racial differences, or of a true cross-section of the population. Such data would, however, be unethical to collect as it would require a randomised cross section of the population to have AP and lateral radiographs performed in a cephalometer.

Figure A4

SURFACE AREA OF POSITIONING PLATES

(Frame positioned parallel to Frankfurt plane)

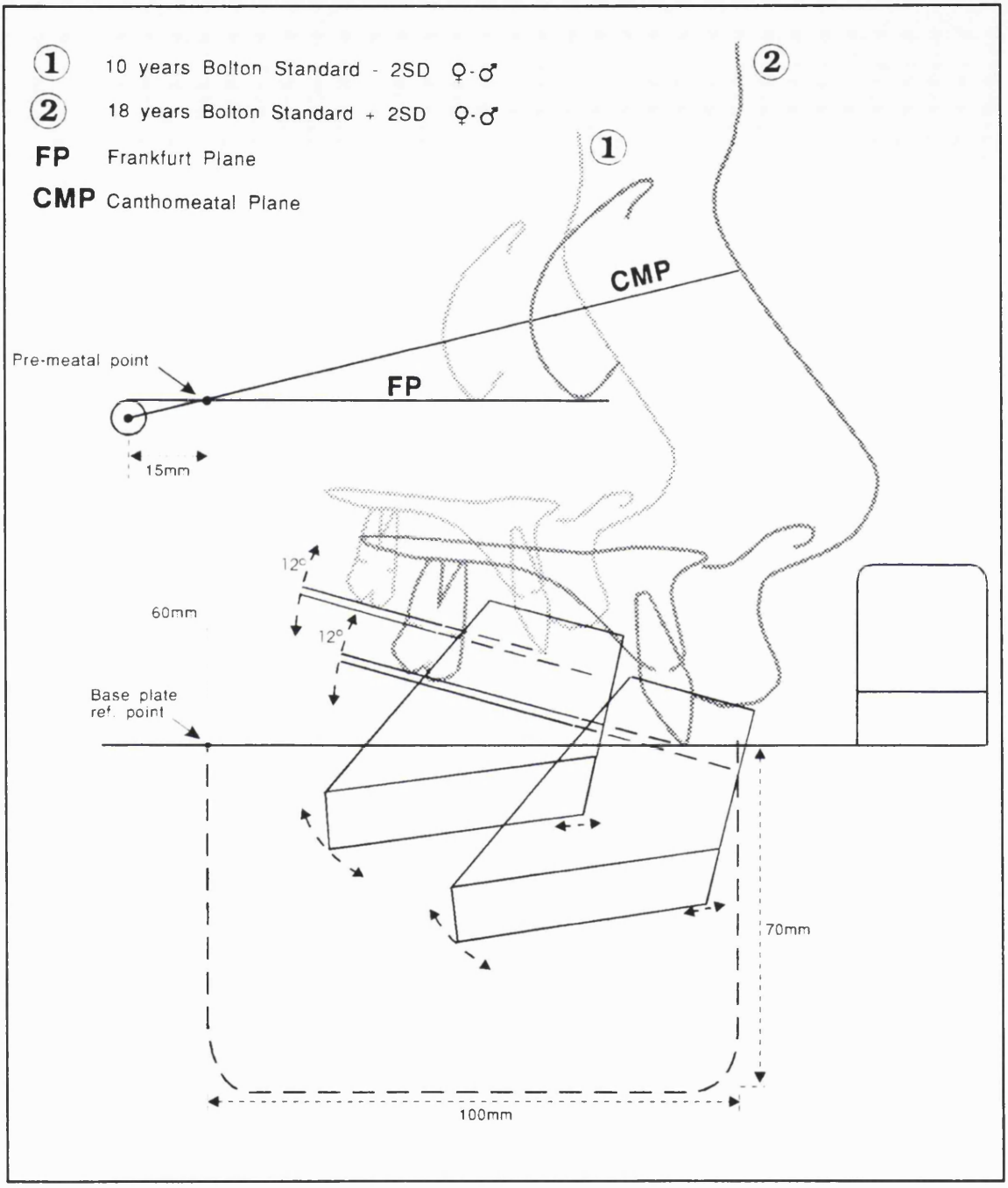
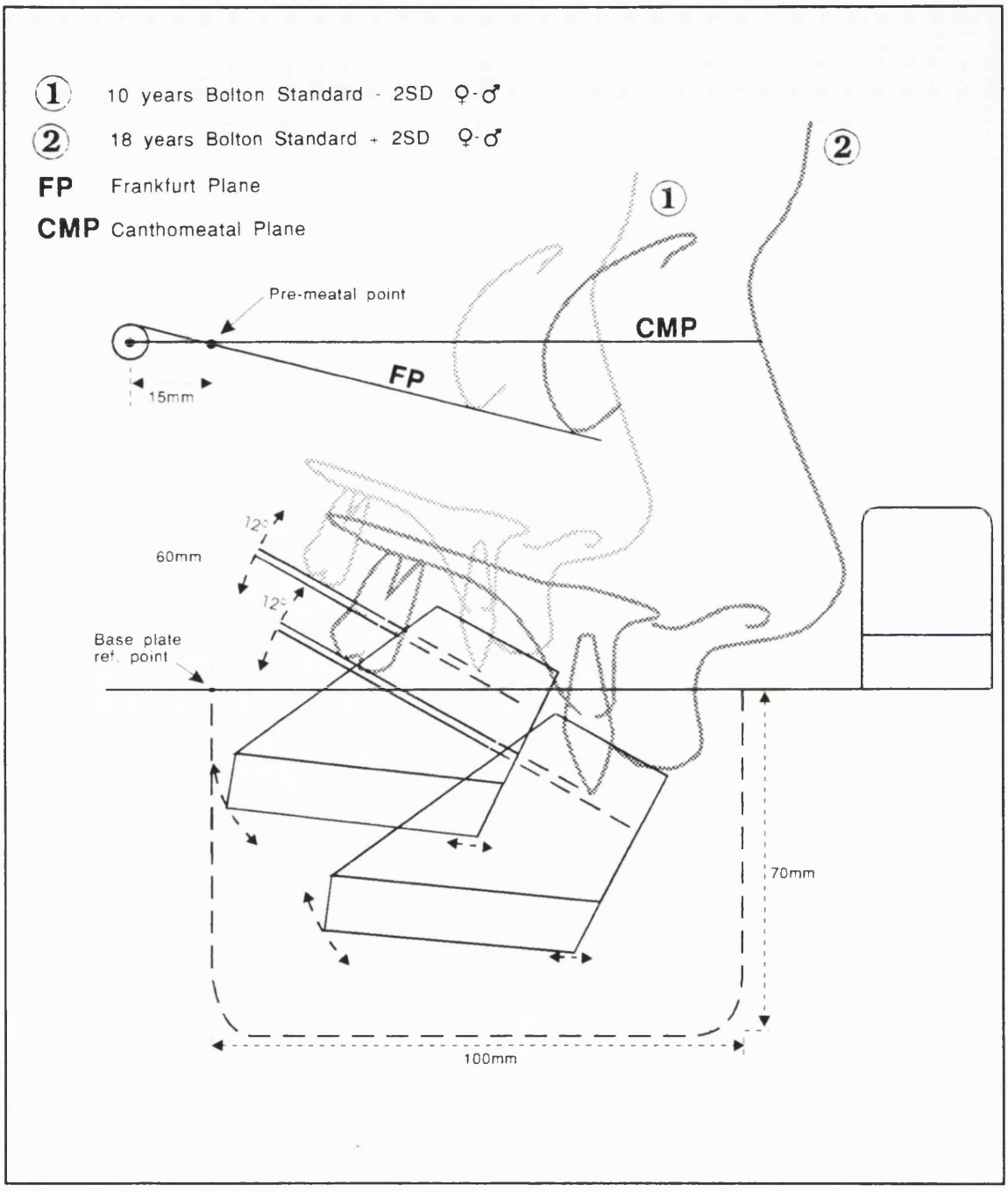


Figure A5.

SURFACE AREA OF POSITIONING PLATES:

(Frame positioned parallel to canthomeatal line).



APPENDIX II

BRAIN TUMOUR LOCALISATION AND PROLIFERATION:

A COMPARITIVE STUDY OF PET USING FLUORINE 18-FLUORODEOXYURIDINE, CT SCANNING, HISTOLOGY AND KI67 ANTIBODY.

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Summary

6 patients with primary brain tumours (5 high grade gliomas, 1 lymphoma) were preoperatively assessed with positron emission tomography (PET) using F^{18}-Fluorodeoxyuridine and enhanced computerised tomography (CT) scans. The patients were imaged in a relocatable stereotactic frame and biopsy coordinates were generated from the CT and PET scans. Serial biopsies of 1cm were taken from the edge through the tumour. Histological examination was performed to detect viable tumour and its extent, and proliferation was assessed using Ki67 antibody labelling.

The PET and CT scans were reconstructed along the plane of trajectory allowing pixel by pixel comparison and subsequent comparison with the biopsy results. One patient also had a magnetic resonance (MR) scan.

In all 6 patients there was an accurate correlation between viable tumour and increased signal on the PET images but not all CT enhanced scans. In the MR examination no differentiation could be made between peritumoral oedema and active tumour.

The areas of highest uptake of the isotope generally corresponded to areas of increased Ki 67 labelling and higher tumour grade.

Such findings may be important for the accurate definition of tumour volume and for the succesful treatment planning of primary brain neoplasms.

Introduction

In the treatment of primary brain neoplasms, whether surgical resection or radical radiotherapy, a knowledge of the full extent of the tumour is necessary. Studies correlating histology with computerised tomography (CT) have shown that although the enhancing rim generally represents the markedly cellular area of gliomas (Burger et al 1983), isolated tumour cells may extend several centimetres beyond the enhancing rim (Bergstrom et al 1983, Mosskin et al 1987, Burger et al 1988). Magnetic resonance Imaging (MRI) will demonstrate some low grade tumours not visible with CT, but again isolated tumour cells are found beyond the T1 and T2 defined areas (Kelly et al 1987). Positron emission tomography has beeen used to define active tumour notably with ^{18}F-fluorodeoxyglucose (FDG) (Patronas et al 1983, DiChiro 1987, Doyle et al 1987) and ^{11}C-methionine (Bergstrom et al 1983, Erikson et al 1985, Lilja et al 1985, Mosskin et al 1987). Although FDG appears superior at tumour grading (DiChiro 1987) it rarely defines tumour extent, whilst ^{11}C methionine allows a more precise deliniation of viable tumour tissue than CT and MR scanning (Mosskin et al 1987,1989). An 'in vivo' and non invasive measurement of tumour proliferation is particularly attractive in brain neoplasms.

Fluorodeoxyuridine (FUdR) is a halogenated pyrimidine developed as an anti neoplastic agent. In animal studies using ^{18}F-FUdR up to 24% of the label is seen in the nucleotide fraction at 2 hours (Abe et al 1983) and autoradiographic representation of ^{18}F-FUdR has been shown to be similar to thymidine distribution in an experimental brain tumour model (Kameyama et al 1987). Clinical studies have been reported revealing a clear cut difference between high and low grade gliomas attributed to differences in nucleic acid metabolism (Kameyama et al 1987/1990).

Ki67 is a mouse monoclonal antibody raised against a nuclear antigen expressed by proliferating human cells (Gerdes et al 1983) which has proven useful in the grading and determination of the proliferative potential of human brain tumours (Zuber et al 1988, Deckert et al 1989, Parkins et al 1991).

The aim of this study was to compare PET, using ^{18}F-Fluorodeoxyuridine (FUdR), and CT in assessing tumour extent as defined on multiple biopsy specimen. In addition, tumour proliferation rate as measured 'in vitro' by Ki 67 antibody labelling was correlated with uptake of the isotope, an 'in vivo measurement'.

Material and methods

Six patients with a clinical history strongly suggestive of primary brain tumours and positive CT scans, who were to undergo stereotactic biopsy were selected for this study (table1).

Permission to carry out this research was obtained from the ethics committee of Queen's Square and Hammersmith hospital. Authoritisation for the use of radionuclides was given by the Administration of Radioactive Substances Advisory Committee. All patients gave informed consent.

Scanning

Both scanning and surgical biopsy were carried out using the Brown Roberts Wells stereotactic system (BRW, Radionics Inc. Burlington Mass). This was non- invasively fixed to the head via an intermediate relocatable base plate, the Gill-Thomas repeat localiser (GTRL, Radionics Inc. Burlington Mass). The GTRL is located on the head by means of a patient specific dental impression of the upper jaw which facilitates repeated fixation that is reproducible within 1mm three dimensionally (Gill et al 1991). The GTRL was fixed to a bracket in each imager so that the axial slices taken could be directly compared.

CT scanning

All the patients were scanned with a GE 9800 CT scanner using contrast enhancement with a 2mm slice seperation through the tumour volume. In addition one patient had an MRI scan.

PET scanning

The patients were scanned with an ECAT 931-08/12 PET scanner (Spinks et al, 1988). 15 contiguous planes of data were recorded simultaneously over a transaxial length of 10.8 cm. Images were reconstructed using a 0.5 Hanning filter resulting in a spatial resolution of 8.4 x 8.3 x 6.6 mm FUHM (full width at half maximum) at the centre of the field of view (Spinks et al, 1988). Prior to the study, a transmission scan of 15 minutes was performed using an external ring source of germanium 68. This transmission scan was used for subsequent attenuation correction of all emission scans.

100-150mBeq of ^{18}F-FUdR (specific activity >95%) were infused over three minutes into a peripheral venous line. Arterial samples were withdrawn from a radial artery cannula at frequent intervals and counted in a well counter to determine the arterial activity.

Patients were scanned over a period of 2-3 hours. As they were being imaged in the relocatable frame, patients could be taken off and subsequently accurately repositioned to enable late scanning at 2 and 3 hours. Frames of 10 minutes were taken in the later stages.

Analysis

The CT and PET images were matched in a 3d computer matrix with reference to the BRW fiducial system. Added images from the PET emission scans obtained between 1-2 hours were used, as it was felt this would be more representative of the bound activity. Using image analysis software (Analyze version 2.0, BRU, Mayo Foundation, USA) thematched images were reconstructed along the plane of the biopsy trajectory to allow direct comparison between the two scans and biopsy data.

The pixel counts in the biopsied regions were compared to background normal brain to determine tumour/normal ratios.

The Spearman correlation test was used to study the correlation between tumour/normal ratios and Ki67 labelling index.

Stereotactic Biopsy

Using CT and PET generated coordinates, serial 1cm biopsies were taken from the edge through the tumour. 4-7 samples were taken. Biopsies were snap frozen using liquid nitrogen and stored at -20°C.

Ki67 labelling

Cryostat sections (5μ) were cut longitudinally and applied to albumin (2%) coated slides and stored at -20°C. Indirect immunochemical antibody staining was carried out according to Gerdes et al (1984). Frozen sections were warmed to room temperature and fixed in acetone for 10 min. The Ki67 antibody (Dakopatts Ltd, Copenhagen) was applied to each section at a 1:10 dilution for 30 min. After washing in phosphate buffered saline , a peroxidase conjugated rabbit anti-mouse IgG, was applied for 30 mins (1:20 dilution). Nuclei that had bound both antibodies were then visualised by production of a brown precipitate using the chromogenic substrate solution, diaminobenzidine (3mg/ml). Sections were counterstained with haematoxylin (10min) and the number of positively labelled tumour nuclei were counted, without prior knowledge of tumour diagnosis and the Ki67 index expressed as a proportion of the total (about1000 cells were counted). Neighbouring sections were cut and stained with H&E for pathological examination.

Results

The pictorial representations for patients 1, 2 are seen in fig 1 . The top left picture shows a 3-dimensional reconstruction of the tumour, using the PET emission data inserted into a shell generated from the CT data. The lower pictures show the CT and PET images reconstructed through the trajectory plane of the biopsy with the 1 cm serial biopsies indicated as a series of boxes. This allows direct comparison between the CT findings, PET tumour/normal ratios, histology and Ki67 labelling index. It would appear in patient 2 on the 3-d reconstruction that the biopsy tract has passed through a defect in the tumour. This was later confirmed histologically.

The results for all six cases are tabulated on table 2. It can be seen that there is general good agreement between histology, Ki67 labelling and the PET data.

There is a relatively good agreement between CT and PET. However on the biopsied sections, in three patients (pt 2,5,6) the CT enhancement is different to the PET signal. The areas of enhancement appear to be outside the histological proven tumour. Patient 2 is the most interesting in that although there is contrast enhancement on CT, there is no FUdR uptake in the biopsied area and at histology no evidence of tumour but abnormal vasculature. In patient 1, outside the biopsied area, the PET signal extended well beyond the area of contrast enhancement seen on CT (Fig 1).

There appears to be good agreement between histology and the PET signal. In cases 1,4, 6 there is a small increase in signal at the edge of identifiable tumour, where the histology is reported as hypercellular or reactive gliosis. These processes do involve some proliferation.

The correlation between Ki67 and increased isotope uptake as measured as PET tumour/normal ratio is shown on fig 2. There is a wide scatter of values but a trend would seem to exist (Spearman correlation 0.765 $p<0.005$). Fig 3 shows the PET, CT and MR data for patient 5. Although the MR scan shows a large area of oedema, PET appears the most accurate at determining active tumour.

A time activity curve (patient 5) is shown (Fig 4). It can be seen that tumour uptake continues to be seen over a period of time despite a fall in plasma activity, with little uptake in normal tissue.

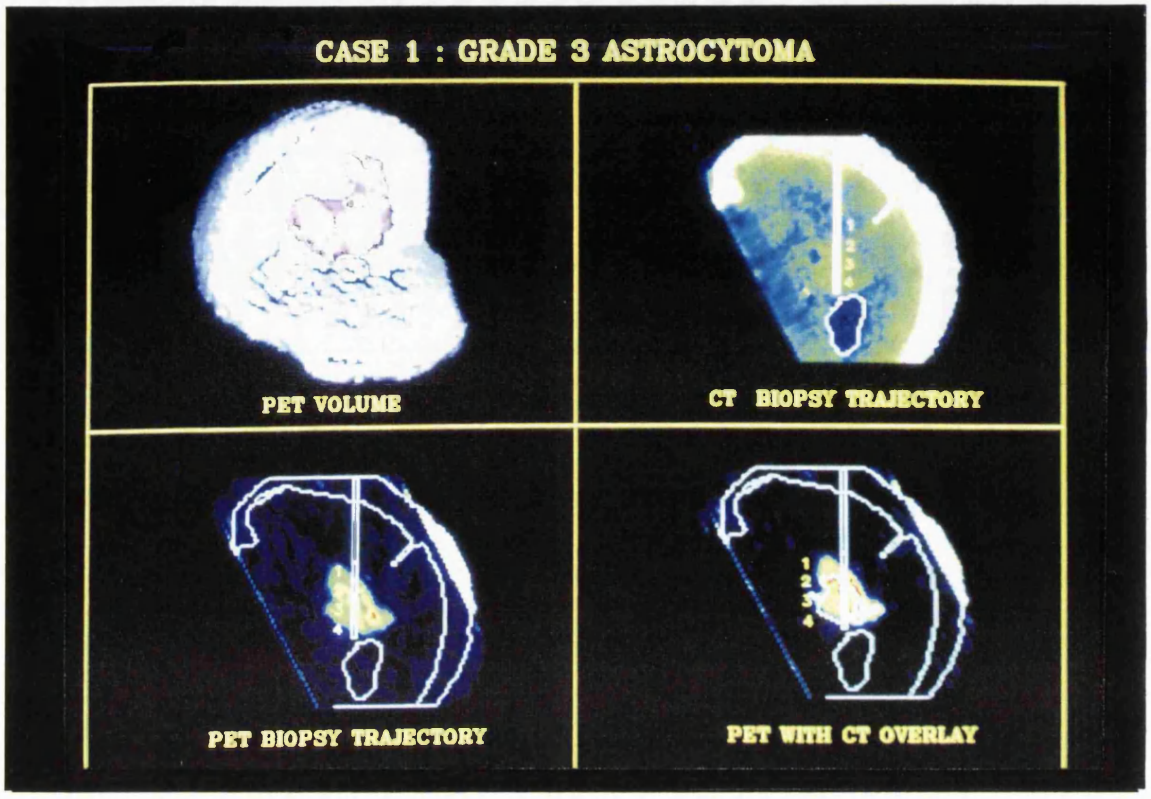

Figure 1 a - Patient 1: The top left picture shows the 3 dimensional reconstruction of the tumor using the PET emission data. The top right and lower pictures show the CT and PET pictures reconstructed through the trajectory plane of the biopsy. The serial biopsies are indicated as a series of boxes. In the lower right picture, it can be seen that the PET signal extends beyond the CT contrast enhancement.

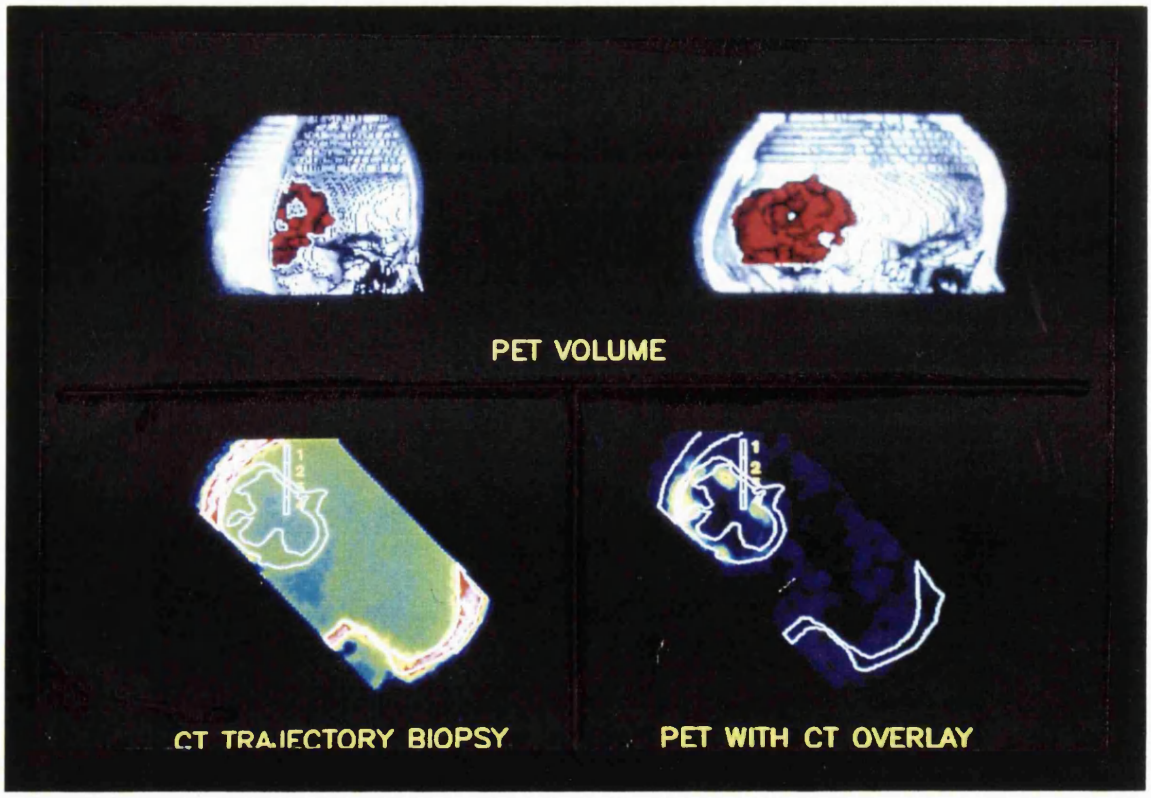

Figure 1 b - Patient 2: The top picture shows the PET 3d reconstruction of the tumour. A large central defect is noted. On the lower pictures, the biopsy tract is seen to pass through an enhancing rim in the CT images and the central defect of the PET data. Histologically only necrosis and abnormal vasculature were seen.

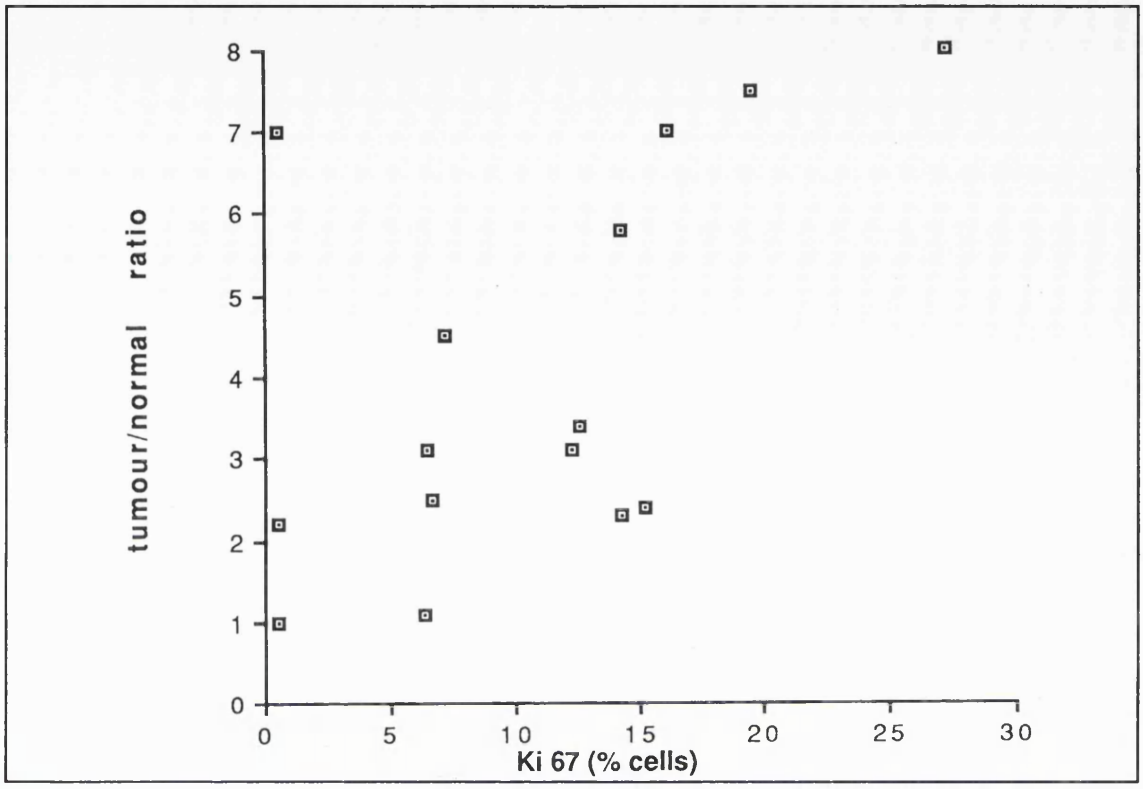

Figure 2 - Correlation of Ki67 antibody labelling of biopsy material with the PET isotope uptake, as measured by tumour/normal ratio of the same serial biopsy. (Spearman correlation 0.765 $p < 0.001$)

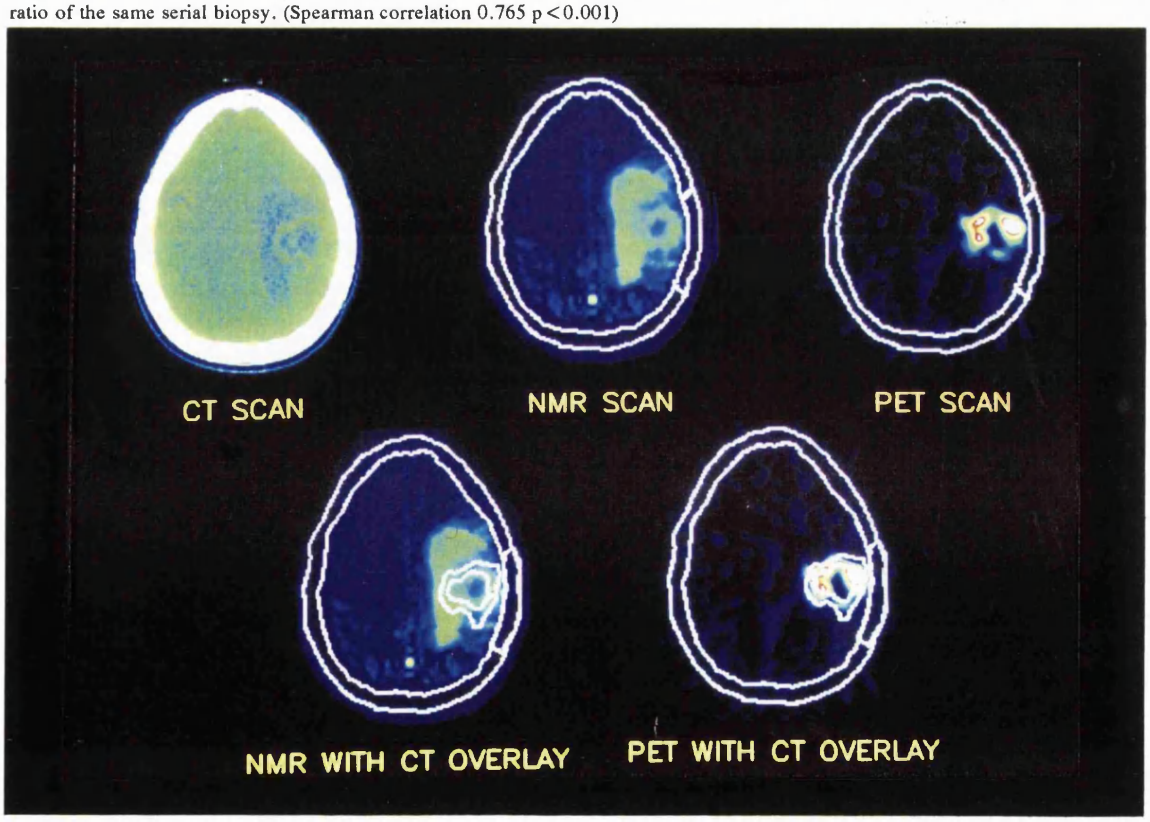

Figure 3 - CT, MRI and PET images for patient 5. The MRI scan shows the surrounding oedema, but the active tumour is seen on the PET image.

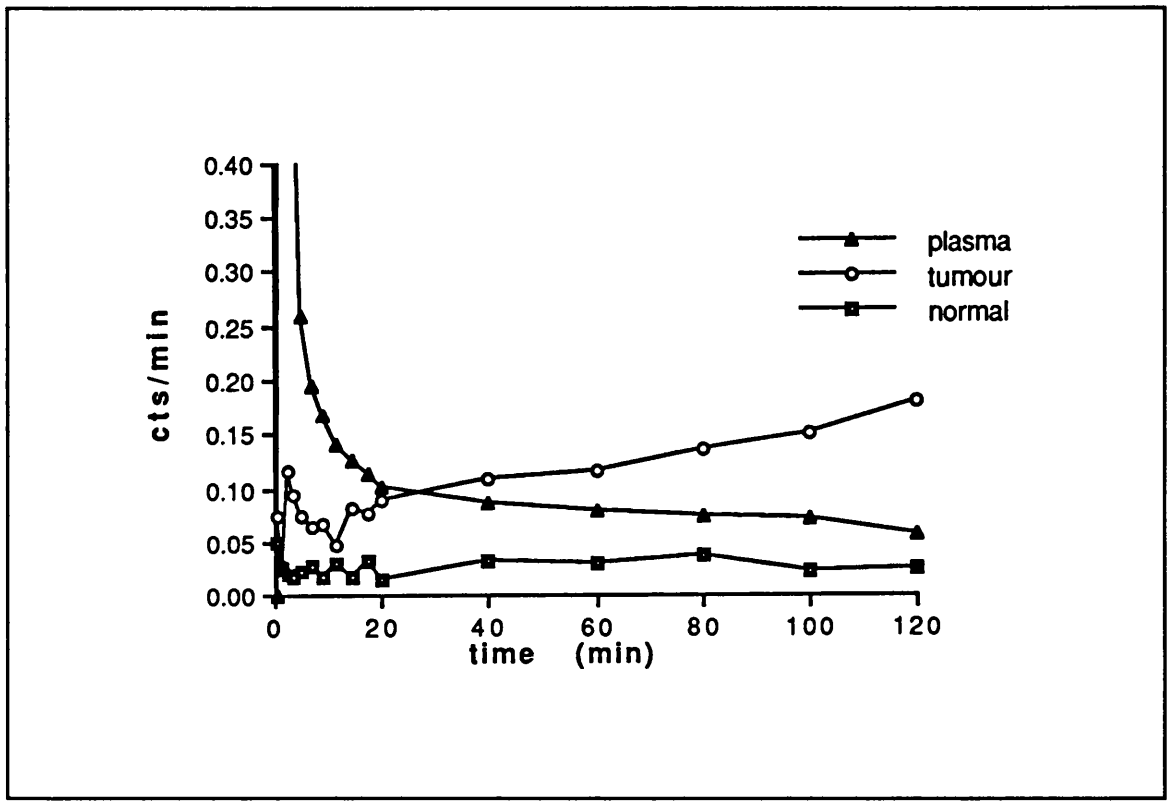

Figure 4 - ^{18}F-FUdR time activity curve for plasma, tumour and contralateral brain in patient 5. Tumour uptake of the isotope continues after 40 minutes.

Discussion

Conventional tests such as CT and MR cannot accurately predict tumour grade, determine tumour volume accurately or differentiate recurrent tumour from radiation necrosis (Burger 1983, Kelly et al 1987). From this small series of patients with high grade tumours, there would seem to be good agreement between the tumour edge as defined histologically and the PET signal following the administration of ^{18}F-Fluorodeoxyuridine. The discrepancies between areas of CT enhancement and PET would imply that this signal is more than merely disruption of the blood brain barrier. Furthermore the time activities curve (fig 5) suggest a continuous active uptake of the tracer rather than passive diffusion. In the one patient imaged with MR, PET appeared superior at defining active tumour.

In addition, this study has shown a positive relationship between Ki67 index and PET image intensity. Tumour heterogeneity was demonstrated, and areas with high labelling index (and presumed high proliferation) corresponded well to increased isotope uptake. However whether this truly represents nucleic acid metabolism is a matter of contention. The metabolism of FUdR is fast with a short half life (10 mins) and the rapid appearance of metabolites most notably β-alanine. This has a poor penetration through an intact blood brain barrier, but if this were disrupted would, like any false amino acid, be taken up actively by tumour tissue. Also β-alanine has been shown in vitro to have a specific transport mechanism in normal glial cells and has been considered as a possible neurotransmitter (Schonn and Kelly1975). In a high

concentration of glial cells as would occur in a glial tumour, uptake would be more marked. The continuing uptake into the tumour after 30 minutes is more compatible with this interpretation. However the signal intensity would still be consistent with increased amino acid metabolism and thus indirectly with proliferation and presumably tumour aggressiveness.

Mosskin (1987) has reported that PET scanning using methionine correlated well with histology in determining tumour extent and was more accurate than CT, but it was not always easy to distinguish the tumour edge and between tumour grades.

With FUdR, in view of low tracer uptake by normal brain (unlike methionine), background noise to signal is reduced, leading to a sharper contrast between tumour and normal tissue, than that seen with methionine scans. It has been suggested that this tracer may be the most suitable for the use of intraoperative probe for the detection of brain tumour tissue (Mazziotta et al 1991)

Fluorodeoxyglucose (FDG) is now widely used to define tumour grade and differentiate between tumour recurrence and radiation necrosis (Doyle et al 1987). FDG uptake is not always increased in high grade gliomas and does not deliniate accurately tumour volume (Tyler et al 1987).

In conclusion, PET scanning using 18F-FUdR appears to be more accurate in localisation of high grade gliomas than CT scanning . It could therefore be useful for planning of a localised treatment such as surgical resection or stereotactic radiotherapy in high grade tumours. It also appears to agree with tumour activity as measured by Ki67 labelling, and may be of prognostic value.

Acknowledgements

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TABLE 1- Patient Characteristics

patient	age	sex	diagnosis	survival
1	36	f	grade 3 astrocytoma	6 months
2	56	f	grade 4 astrocytoma	3 months
3	41	m	grade 2 NH lymphoma	6 months
4	39	f	grade 4 astrocytoma	>12 months
5	59	m	grade 4 astrocytoma	2 months
6	61	m	grade 3 astrocytoma	>12 months

TABLE 2 - Correlation between CT, PET, Ki67 labelling and Histology

CASE 1- grade 3 astrocytoma

	1	2	3	4
CT	+	+	+	=
PET(t/n)	2.2	3.4	4.5	0.7
Ki 67 (%)	<1	12.7	7.2	-
HISTOLOGY	infiltrated parenchyma	tumour mitoses+	tumour mitoses+	No sample

CASE 2- grade 4 astrocytoma

	1	2	3	4
CT	+	=	+	++
PET(t/n)	1	1	1.1	1
Ki 67 (%)	<1	<1	<1	<1
HISTOLOGY	normal parenchyma	normal parenchyma	pathological vessels	necrosis

CASE 3- grade 2 non hodgkin's lymphoma

	1	2	3	4	5
CT	=	=	+	+	-
PET(t/n)	1	1	8	7.5	1
Ki 67 (%)	<1	<1	27.3	19.5	<1
HISTOLOGY	reactive gliosis	reactive gliosis	tumour mitoses+	tumour mitoses+	reactive gliosis

CASE 4- grade 4 astrocytoma

	1	2	3	4	5	6
CT	=	+	=	=	+	+
PET(t/n)	1	3.1	1.1	0.5	3.1	2.2
Ki 67 (%)	<1	12.3	6.4	<1	6.5	<1
HISTOLOGY	reactive gliosis	tumour vascular	tumour necrosis	necrosis	tumour necrosis	reactive gliosis

CASE 5- grade 4 astrocytoma

	1	2	3	4	5	6	7
CT	=	++	-	-	-	++	=
PET(t/n)	1	2.3	2.4	1	1.4	2.5	1.4
Ki 67 (%)	<1	14.3	15.3	<1	<1	6.7	<1
HISTOLOGY	reactive gliosis	tumour vessels	tumour	necrosis	tumour necrosis	tumour vessels	reactive gliosis

CASE 6- grade 3 astrocytoma (oligodendroglioma)

	1	2	3	4	5	6	7
CT	+	-	=	=	+	+++	+++
PET(t/n)	1	2.9	7	7	5.8	3.1	
Ki 67 (%)	<1	<1	<1	<1	16.2	14.3	4.4
HISTOLOGY	normal cortex	oedematous parenchyma	tumour	infiltrated parenchyma	tumour mitoses+	tumour mitoses+	tumour mitoses+

For CT scan, - indicates hypodense, = isodense, + enhancement, ++ marked enhancement, +++ calcification

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