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## Resected tissue banking and post mortem tissue/whole brain banking for the purposes of brain tumour research

an exploratory discussion from the patient and caregiver perspective  
intended to stimulate debate about these topics

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# Resected tissue banking and post mortem tissue/whole brain banking for the purposes of brain tumour research

an exploratory discussion from the patient and caregiver perspective intended to stimulate debate about these topics

## Background

Primary malignant brain tumours – which affect some 200,000 people around the world each year – combine the worst elements of cancer with the worst elements of neurological diseases to create a devastating and lethal illness that can affect anyone, male or female, from tiny babies to children to teenagers to young and middle-aged adults to the elderly. <sup>(1)</sup>

Despite some modest advances in the treatment of primary brain tumours in the last thirty years, a cure – or even a successful approach to managing brain tumours as a chronic disease – has frustratingly and continuously eluded researchers, clinicians and those involved in the management and care of this rare cancer patient population.

It is now recognised that one of the elusive keys to conquering brain tumours once and for all may well lie in the genetic makeup of individual tumours. A greater understanding of an individual's tumour tissue is critical to the shift encompassing new treatment approaches which use targeted and personalised therapies.

In addition, brain tumour tissue for research is needed to better understand the mechanisms of tumour growth and progression.

## Resected tumour tissue

There is an emerging and critical need to encourage the banking of brain tumour tissue which is removed from the brain during neurosurgery and to facilitate the exchange of tissue among researchers in order to more comprehensively understand the makeup of these neoplasms and create better treatments for them.

Following most brain tumour surgeries, only a small amount of tumour tissue is required for the pathological diagnosis of type and grade of neoplasm. Tumour tissue that is in excess of this diagnostic amount is often discarded, allowing precious research material to be wasted.

Properly consented, carefully catalogued, coded and optimally preserved brain tumour tissue will be the building blocks on which the next generation of treatments will be based. The ethical attainment and ongoing management of samples together with rigorously enforced quality assurance measures will hopefully ensure that resected brain tumour tissue can be used for discovery and validation studies which will benefit those patients whose lives are already touched by a brain tumour and patients who are diagnosed with this disease in the years to come.

## Resected brain tumour tissue for research purposes

Although we have not carried out a comprehensive, formal, international survey of patient attitudes to donating their surplus resected brain tumour tissue (i.e. the brain tumour tissue removed during neurosurgery) to brain tumour research, we understand from anecdotal evidence that this is something which many patients would wish to do.

Their reasons for this might be altruistic. But they might also wish to themselves - in their own lifetimes - benefit from the greater knowledge that will be obtained if there is more tissue available for research.

So it may not be unreasonable to expect that brain tumour patients who donate their surplus resected tumour tissue to research today may, even in the space of a few years, themselves benefit from the knowledge gained from the study of their own donated tissue and be able to enjoy extended survival.\*

**We would strongly support urgent efforts to raise awareness in the relevant geographic areas of the crucial necessity for resected brain tumour tissue to be used for ethical and approved research programmes into the causes of and treatments for brain tumours.**

**In addition, we would urge institutions which treat brain tumour patients to standardise neurosurgery consent forms so that as many brain tumour patients as possible have the opportunity, under the protection of informed consent, to donate their surplus resected tumour tissue to brain tumour research (including genetic research). \*\***

## Post mortem brain tumour tissue banking (PMBTTB) and post mortem whole brain banking (PMWBB)

Of course, in the case of some rare tumours, such as primary central nervous system lymphoma (PCNSL<sup>\*\*\*</sup>) and diffuse intrinsic pontine glioma (DIPG<sup>\*\*\*\*</sup>) which generally cannot be resected and for which there may be very little biopsied material, the problem remains of how to advance knowledge through the use of tissue research when tissue availability is almost non-existent.

\* There is also the question of the right of donors to access useful genetic information obtained from a study of their tissue and which may be of use to them in accessing clinical trials based on genetic markers. It is worth noting that some clinicians and researchers have been lukewarm to this suggestion, citing the alleged variability of analytical laboratories. But if that is the case it begs the question: why, if genetic testing may still be variable and not yet wholly validated, are patients being screened out of trials as a result of these analyses?

\*\* One specialist in the UK with whom we are in contact emailed us to say: "It is my impression that the consent forms for neurosurgery across the UK are very variable as to whether they also record consent for the research use of resected material. A nation-wide standardised approach to this topic would be very helpful."

\*\* Primary central nervous system lymphoma (PCNSL) – "PCNSLs usually arise in the supratentorium within the deep white matter of the cerebral hemispheres or in the basal ganglia, but periventricular locations are not uncommon...these tumors are often multiple and multifocal, simulating metastatic tumors...PCNSLs are generally high-grade tumors with very poor 5 year survival rates..." (Textbook of Neuro-Oncology, Mitchel S Berger and Michael Prados, Elsevier Saunders, 2005, page 38). "Like most diseases of the brain, the symptoms are dictated by the location of the lesion and the amount of local mass effect on surrounding areas. PCNSL usually presents as a brain tumor, with the most common complaints being headache and personality changes..." (Berger/Prados, page 301). "Unlike most primary brain tumors, surgery is not helpful therapeutically, because most [PCNSL] tumors are deeply situated and often wide-spread microscopically. Furthermore, attempted resection may lead to increased neurologic morbidity." (Berger/Prados, page 304)

\*\*\* Diffuse intrinsic pontine glioma (DIPG) – "The majority of (pediatric) pontine tumours are diffuse intrinsic brainstem gliomas, which are usually high-grade, locally infiltrative, and have a uniformly poor prognosis. Histologically, these tumors are (usually) either anaplastic astrocytomas (World Health Organization [WHO] grade III) or glioblastoma multiforme (WHO grade IV)." Mark Kieran, MD, PhD and Karen Marcus, MD, <http://www.uptodate.com/patients/content/topic.do?topicKey=~.mRcz8tSL28gkJ> accessed 18 February 2010.

In terms of addressing the particular challenge of unresectable brain tumours, there is a possible way forward, but it is much more controversial than donation using resected material.

These other methods of tissue donation (or banking) are (a) the removal of a person's brain tumour post mortem (post mortem brain tumour tissue banking – PMBTTB) which can be used for research purposes, or (b) the removal post mortem from a brain tumour patient of the whole brain, known as post mortem whole brain banking (PMWBB). These procedures would be done following informed consent for an autopsy.

There is a clear distinction between resected brain tumour tissue for research purposes and post mortem tumour or whole brain banking, with the former being a more straight forward and far less controversial process.

The issues posed by post mortem tumour and whole brain banking can present an ethical minefield. Indeed following deep concerns raised by events at the UK's Bristol Royal Infirmary and the Royal Liverpool Children's Hospital (Alder Hey) between 1999 and 2000, the Kennedy and Redfern inquiries at these two institutions determined that tissue and organs from deceased children had often been removed, stored and used without proper consent.

As a result of this scandal the UK Human Tissue Act 2004 put into place specific statutory requirements for obtaining, storing and using human tissue for research. <sup>(2)</sup>

Apart from the ethical considerations attached to post mortem tissue banking, there are also other practical issues, some of which are listed below:

1. **How** can brain tumour patients – particularly those with rare neoplasms which might be inoperable (such as brain stem tumours like diffuse intrinsic pontine glioma, DIPG, in children or primary central nervous system lymphoma, PCNSL, in adults) – best be approached regarding the subject of PMBTTB or PMWBB?
2. **Who** is the best person to speak to patients and their families about this: the neurosurgeon, the neuro-oncologist, the specialist neuro-oncology nurse, other professionals?
3. **When** is the best time to speak to patients and families about the possibility of PMBTTB or PMWBB: prior to initial neurosurgery, post-neurosurgery, at some other stage during a patient's brain tumour journey, nearing end-of-life?

Surrounding these questions are various other issues:

- the need for and means of obtaining tissue material when a brain tumour – due to its location in an inoperable area of the brain – can only be biopsied and a very small amount of tissue obtained
- the challenges of obtaining consent from brain tumour patients at a stage at which they may not be mentally or emotionally able to provide informed consent or may be too upset or too much in shock. Patients may also be young children who are unable to give consent themselves

- societal, religious and cultural attitudes towards removing an organ following death, and the importance of maintaining human dignity and spiritual integrity and bodily “wholeness”
- whether a biopsy on an inoperable brain tumour – with all its attendant risks - should be carried out not for therapeutic reasons but for altruistic reasons connected to research and helping patients of the future (see discussion on DIPG tumours below)

Additionally there are practical issues such as:

- cost of procedures involved with PMBTTB or PMWBB
- the establishment (availability) of specific research projects and programmes which would make use of PMBTTB or PMWBB
- whether, specifically for PMBTTB or PMWBB, there should be central brain banks or banks held at individual specialist centres of excellence
- procedures for international (cross border) transfer of material
- an evaluation of exactly what the benefit would be in gaining donations of whole brains of brain tumour patients
- how such programmes would be funded
- how such programmes would be publicised

It is beyond the scope of this informal report to consider issues surrounding societal, religious and cultural attitudes towards PMBTTB or PMWBB. Suffice to say that in any possible future approaches to patients and families, these important factors would need to be taken into account and respect for an individual’s beliefs carefully considered. Neither does this paper include a discussion of the need for healthy donor brains for comparative studies.

## Post mortem brain tumour tissue banking and post mortem whole brain banking for DIPG pediatric brain tumour patients

Nowhere, perhaps, is the case for post mortem brain tumour tissue or whole brain banking more urgent than in the desperate plight of children suffering with a type of brain stem tumour called a diffuse intrinsic pontine glioma (DIPG). We are aware, however, of a recent Canadian breakthrough in identifying possible pathways for targeted treatments for this devastating disease. <sup>(3)</sup>

The Minutes of the April 27<sup>th</sup>, 2009 Joint Meeting of the Pediatric and Oncologic Drug Advisory Committees of the US Food and Drug Administration (FDA) provide a startling insight into the tragic circumstances of DIPG. <sup>(4)</sup>

“Approximately 200 children per year [in the US] are diagnosed with DIPG. The mean age at diagnosis is 7 to 9 years. Children under the age of 3 years and young adults over the age 18 may have a better prognosis. Symptoms at presentation are often mild, and may include diplopia, cranial neuropathies, long tract signs, ataxia, hemiparesis, weakness, and obstructive hydrocephalus for a few months’ duration. The diagnosis is made based on a characteristic appearance on an MRI scan. The pons is diffusely infiltrated, and it is difficult to separate normal and abnormal tissues. Basilar arteries are frequently encased by the tumour. Surgical resection is impossible, and biopsy of the lesion is only recommended currently for atypical cases. Steroids are the mainstay of initial therapy, followed by focal radiation therapy. Most DIPGs respond to radiation with initial improvement clinically and radiologically. However, the neurological findings return and worsen within several months. Death often occurs as a result of a respiratory event. Over 90% of patients die within two years, and the median survival is 9 to 10 months. Previous attempts to improve the outcome by intensifying therapy have been unsuccessful. No treatment has shown any benefit over conventional radiation, despite multiple studies using chemotherapy and radiation at different time points.”<sup>(5)</sup>

For further insight into the devastating nature of DIPG tumours, and the human toll on the child, family and caregivers, there are a number of DIPG brain tumour websites on the Internet.

For an illustration of one child’s battle against diffuse intrinsic pontine glioma – and the brutality of the disease – visit <http://www.justonemoreday.org/aliciasJourney.html> which charts young Alicia’s journey with DIPG in a powerful photo montage.

Some parents of DIPG children believe that progress with research into DIPG is hindered by the lack of the availability of biopsied brain tumour tissue. Some parents believe that the potential side effects of a non-therapeutic biopsy to harvest tissue for research are no worse than those side effects which occur as a result of treatment. Other parents feel strongly that while there should never be an obligation to participate in DIPG research which requires non-therapeutic biopsied material from their child, parents should as a matter of course, be fully informed of the need for such research.

With regard to post mortem tissue donation, the FDA report referred to above states:

“Some ambiguity existed among Committee members about whether avenues for studies using autopsied tissue had been thoroughly pursued. Some members noted that, at the time of death, children have generally received radiation, steroids, and frequently experimental chemotherapeutic regimens. Therefore, the specimens could be tainted by the effects of radiation necrosis or clonal selection. Additionally, the biology of tumor types frequently changes over time. Others believe that the potential adverse effects of pre-mortem radiation and chemotherapy would not present critical obstacles to post mortem investigation...Some members noted that many parents were unwilling to consent to autopsy and that there is an inevitable time lapse between death and tissue recovery...There was also a discussion of whether readily available tissues from other pediatric or adult astrocytomas could be used in lieu of DIPG

samples. Some Committee members were concerned that these tumors varied greatly based on appearance and response to treatment, and hence may not be a good surrogate. Others thought that enough questions remained pertaining to these tumor types that there was not an immediate need for DIPG tissue.”<sup>(6)</sup>

Additional ethical questions which arose during the FDA meeting included:

- “how direct benefit should be assessed...
- whether voluntary consent was possible in the face of a devastating diagnosis
- at what age children might be capable of assenting to a non-therapeutic procedure based on altruism
- the professional responsibility of physicians (i.e., whether recommending or performing a non-therapeutic brain biopsy can be consistent with the professional obligation to act in the best interest of the patient)”

Dr Loice Swisher, herself the mother of a daughter with a brain tumour, and a US Food and Drug Administration (FDA) patient representative on pediatric brain tumours, is very involved in advocacy work for DIPG patients and their families in the United States.

Of the DIPG situation in America, Dr Swisher says:

"Parents and advocates are also frustrated here with the fact that there has been no change in prognosis over the last three decades with this disease that devastates children and their families. They are equally frustrated by the fact that prior post-mortem donations are 'sitting in the freezer' waiting for enough specimens to be collected at that location to allow for effective analysis. Currently, molecular tumor analysis and targeted therapies are areas of utmost interest in oncology. Unfortunately those dealing with pediatric DIPG are not truly able to participate in conferences or discussion regarding tumor genomics as there is only one published study at this time on molecular analysis of this tumor type - and that was of only 11 specimens."

Further, Dr Swisher also said:

"Parents are willing to do the hard job of educating other parents about the need for post-mortem donation for this tumor. There has been a concerted effort from the DIPG parent-advocate community to identify researchers and in fact to do designated donation to further active DIPG research in hopes of altering the course of this disease so it will not be another 30 years before there is change."<sup>(7)</sup>

Background on some of the research being carried out into DIPG at various US institutions, together with a FAQ on post-mortem banking of DIPG tumour tissue can be found here: <http://www.justonemoreday.org/Research/TumorTissueAnalysis.html>

In summarising the challenges of DIPG research, Dr Darren Hargrave (Oak Foundation Consultant Pediatric Oncologist in Drug Development and specialist in pediatric neuro oncology at the Royal Marsden Hospital, Sutton, UK) said:

“Brainstem glioma remains a tumour with a dismal prognosis but relatively little is known about the underlying biology and progress will require a concerted effort to collect tissue by biopsy and autopsy to allow appropriate analysis to identify and validate targets. A new era of molecular based therapies offers the promise of major benefits in the management of pediatric glioma but translating this promise into reality will require further understanding of the biology driving these tumours.”<sup>(8)</sup>

## Challenges of post mortem brain tumour tissue banking and post mortem whole brain banking

The question of post mortem whole brain banking was the subject of a recent draft discussion paper by the International Brain Tumour Alliance and the Astro Fund for the purposes of use in an advisory committee tasked with creating national guidelines for the treatment of four rare brain tumours.

**Clearly, the subjects of post mortem whole brain banking and post mortem brain tumour tissue banking are very complex.**

**There are important underlying ethical imperatives to make the best possible use of donated tissue. Therefore, it is crucial to first identify the specific needs of researchers in this field for post mortem brain tumour tissue and post mortem whole brains. This is particularly relevant for rare brain tumours such as PCNSL in adults and, as previously discussed, DIPG in children, where neurosurgical options are at best limited and at worst not possible at all, resulting in a dearth of material from these tumour types which can be used for research purposes. If a real need is quantified, then a plan to address that need can be developed.**

**But there must be a genuine, secure and workable system in place which is ready to receive and act on post mortem whole brain and tumour tissue donations from brain tumour patients.**

Following the IBTA’s informal discussions with pathologists, researchers, clinicians, patients and others, here are some additional points to consider about post mortem whole brain banking and post mortem brain tumour tissue banking:

### **A. Determining specific need and use first**

It is important to first determine specific uses for PMBTTB or PMWBB in the context of brain tumour research.

What is to be done with the material determines the type of material to collect. Research studies which will involve the use of the whole brain need to be identified and formulated first. In doing this, one must also take into account the condition of the material obtained. Whole brain post mortem tissue from brain tumour patients will, in general, have been heavily pre-treated with radiotherapy and chemotherapy, so tissue

may be changed by prior treatment. This was a concern voiced by the delegates at the April 2009 FDA DIPG meeting. <sup>(9)</sup> This in itself might be a rationale for a research study, i.e. how new types of therapies (such as bevacizumab [Avastin], for example) might affect brain tumour and normal brain tissue.

PMWBB could be useful for assessing tumour growth and especially infiltration. This type of study could be helpful in identifying pro-infiltrative molecules which could possibly be targeted by mono or combination therapies. One clinician we spoke to said: “For example, EGFR amplification in glioblastomas is much more pronounced in the infiltrative component, suggesting it plays a role in this process.” <sup>(10)</sup>

Another use for whole brain banking would be to possibly identify pre-neoplastic changes in normal brain tissue.

But there is also the issue that some whole brains wouldn't be suitable for further research, for example, in late stages of the disease where there is uncontrollable brain swelling and rupturing.

## **B. Funding**

Because the families of deceased patients who donate whole brains or brain tumour tissue are not expected to pay for any aspect of the procedure to remove them post mortem, the full cost of this is borne by brain banks. The UK Parkinson's Brain Bank online information sheet states, for example, that “The Parkinson's Brain Bank covers all the costs for the transport of the donor's body to the hospital where the tissue will be removed, the tissue removal and the return of the donor to the undertakers responsible for the funeral. Funeral expenses, however, remain the responsibility of the family – the same as if a donation was not made.” <sup>(11)</sup>

Information sheets such as this one, as well as others (for example the online information sheet for BrainNet Europe) also tackle other challenging queries which might come from potential donors and families such as “Will a post mortem donor be disfigured by the procedures involved with the donation?” the answer to which is “No” or “Will this procedure delay funeral arrangements?” the answer to which is “No”.

Storage costs in a freezer are also expensive and obviously whole brains take up much more room than smaller tumour specimens.

Other costs involved in the collection and research use of post mortem brain tumour tissue or whole brains from brain tumour patients might include service support fees for bereavement specialists or other staff who would assist with the consent process and brain tumour tissue or whole brain collection, the consultant's time for confirming pathological diagnosis, the technician's time for preparing the brain for banking, specialist research nurses, etc.

In speaking to various specialists, it was uniformly acknowledged that post mortem brain tumour tissue or whole brain banking would be an expensive endeavour. This cost burden might be reduced somewhat by having a national, central repository and efficient coordination between specialist centres which treat brain tumour patients. Post mortem whole brain or tumour tissue banking may, in the first instance, only apply

to some very rare tumours where it is extremely difficult or impossible to obtain tissue during life because of the tumour's location. This would possibly limit cost and logistic implications. But it was agreed that overall cost is a substantial problem.

It is estimated in Australia that the cost per whole brain donation is approximately AUD \$3,000. In the UK, cost is estimated at approximately GB £1200. In Canada, approximate costs are CAD \$700. This Canadian figure does not include the day-to-day cost of running a brain bank with a full-time facilitator. The Canadian Brain Tumour Tissue Bank has an annual budget of CAD \$85,000). <sup>(12)</sup>

One specialist commented: "...the idea of selective retention of a few defined brain slices in addition to the tumour was raised. This would be one way on cutting down on storage costs. However, at the moment, the money side is too prohibitive for us...to start whole brain banking. This hopefully will change in the future, but as banking is a long term commitment, it is difficult to rely solely on short term grants to keep it going."

Another specialist said: "In reality, to get post mortem tissue optimally you are talking about a few hours following death. It needs a pathology department which has the resources to process the patient post mortem as fast as possible." He then explained that this would mean pathologists being readily available throughout the night at all hours in some cases. "You would have to [then] negotiate costs with the pathology department." (We are aware that in the recent Canadian study involving the identification of promising pathways, the post mortems took place between 9 and 40 hours after death.) <sup>(13)</sup>

Other questions in relation to costs might be:

- Is fundraising by the voluntary sector required to meet these costs?
- What role, if any, should government agencies play in terms of funding dedicated brain tumour banks?
- To save on costs, could existing facilities and systems (i.e. for the neuro-degenerative diseases) be expanded?

## **C. Systems**

### **i. Guidelines**

None of the specialists we were in contact with were aware of any dedicated brain tumour banks which existed solely for the purpose of collecting post mortem tissue and/or whole brains affected by this disease. None were aware of any published guidelines on post mortem tissue and/or whole brain donation from brain tumour patients.

But the specialists pointed out that as well as following statutory requirements, there would need to be solid systems in place to deal with the practical issues described above, the costs and other issues.

One specialist gave us an example of a possible system based on one established by a Creutzfeldt-Jakob Disease model. <sup>(14)</sup> A dedicated agency deals with all aspects of the donation from coordinating contact with the family, to obtaining consent, to arranging for the transport of the deceased patient to contacting the local pathologist, to paying fees to the institution for handling the brain and also to paying fees to the pathologist.

Of course, C-JD presents a public health issue so tight control of any such donated tissue is of paramount importance. Brain tumours are obviously different but might be able to be subject to this type of agency system.

A specialist also mentioned that in order to avoid conflict of interest, a post mortem brain tumour tissue/whole brain bank should be what is called a “disinterested bank” where the people who run it don’t engage in tissue research but are instead “gate-keepers” who provide a “firewall” of protection. Confidentiality and anonymity are maintained by coding tissue donations.

## ii. Timings

Donation of the brain: **Assuming that a clear and specific need was first established for post mortem brain tumour tissue or whole brain donation from brain tumour patients** any system would need to take into account optimal time requirements for the removal of the donated tissue or brain from the deceased in order to ensure the donation was as fresh as possible.

Once a person dies, brain tissue begins to deteriorate immediately. Preferred time frames are fast – opinions included the necessity of removing the brain anywhere from a few hours post mortem to 24 hours maximum. (See comment above regarding the Canadian experience.)

Consent. The required legal processes for obtaining consent and getting all the necessary documents in place is complex. Assuming that a clear and specific need was first established for post mortem donations from brain tumour patients, there are models for consent forms which are used for neuro-degenerative disease whole brain banking which could perhaps be adapted. Indeed one specialist with whom we were in contact said that they were considering modifying consent forms used for dementing illnesses, alcoholism, Multiple Sclerosis and normal controls. Another specialist brought up the issues of “consent” and “intent” which are different from each other, a consent being “signed” by the patient and an “intent” being signed by the next of kin or nominated individual. It was felt that ideally, it was important to arrange consents/intents well in advance but that the patient and next of kin/nominated individual should be aware that they could change their minds at any time.

Communication with patients, family and others: Assuming that a clear and specific need was first established for post mortem donations from brain tumour patients, the question of when to bring the subject up with patients brought the following responses from the specialists we contacted:

- a) "It's wise to try and make the necessary arrangements for donation as far in advance as possible. Each person and situation is different so this needs to be done on an individual basis. It's very important to be sensitive to the patient and family and to approach this at an appropriate time for them. Perhaps the best person to do this is the clinician or specialist nurse."
- b) "I think this is best done by raising the issue of support for research, and by providing an information leaflet that describes the various options available. Further information, on a website, and details of how to become a donor can be included on the information leaflet. Since the reactions of individual patients and families is very variable, I think that these approaches are best made by someone who knows the patient and in whom the patient has trust, for example a neuro-oncology nurse...A flexible approach to suit the needs of various patients and their families is required, taking into account a whole range of factors including religious beliefs."
- c) "How and when do you bring this subject up in the family? How do you bring up the question, especially where a child's death from a brain tumour is involved? My clinical colleagues are reluctant to do this. If they want a post mortem whole brain for their own research, this is unethical and immoral...To me it is much easier for a physician when patients come to you to ask if they can donate their brains for research rather than the other way around of a physician asking for a brain." (We understand that a forthcoming report of a Canadian study of parents' attitudes identifies strong support for the concept of post mortem banking.)
- d) "It is very unusual for brain tumour patients to be autopsied. Brain tumours are such terrible tumours, that to add that extra process seems to be adding pain to the family where there is too much of it already. But ideally you would have a system whereby consent is obtained for autopsy restricted to the brain. The brain would then be removed and cut into in such a way that some can be frozen and the tumour part of the brain saved in formalin. The pathology department then has responsibility to generate a report on that brain...The difficulties are whether the tissue [post mortem] is good enough. But the rarer the tumour, the more the researchers will be prepared to give it a go even though tissue might be suboptimal."
- e) "Of course, certain tissues [from some of the rarer brain tumours such as PCNSL, DIPG, etc] cannot be obtained in a conventional way [i.e. during resection when the patient is alive] for research purposes. The ideal is that there is a system in place that rare brain tumours are collected via autopsy."

The following responses were from a group of brain tumour patients and their relatives who were discussing PMWBB at a recent support group meeting at the Royal Marsden Hospital in Sutton, Surrey, UK.

- f) All agreed it was a difficult/sensitive and complex topic with no "right or wrong" response.

- g) No one was aware of the need for organ donation. They assumed, because the brain was “damaged”, it would be of no use. This assumption relates to their concepts held about healthy organ donation. All patients were organ donors.
- h) They are aware of the importance of research and would value being able to contribute. No one thought there was a “right” time to introduce the topic verbally/within a consultation.
- i) The topic relies on open/explicit discussion with patients and their families.
- j) The general consensus was: there could be a short written explanation, with a name and contact number, e.g. of the brain bank. This could be included in the initial information packs patients and families receive, i.e. the earlier the topic is introduced the better.
- k) They thought the context of research would facilitate discussion.
- l) They were curious about how the MS Society or the Parkinson’s Disease Society broach the subject.
- m) If interested, ideally they would want to discuss it with a professional they knew and trusted.

Questions arise from the above comments:

- Should the public at large be “educated” about brain tumour tissue research and if so, how? Or should this be targeted only at the brain tumour community?
- Would professional organisations such as societies for neuro oncology, neuro pathology or neurosurgery take the lead on providing information or would this be passed to the voluntary sector?
- How many brain tumour post mortem donations would need to be made in order for *meaningful* data to be obtained?

#### **D. Comparisons with brain banking for neuro-degenerative diseases**

Our enquiries to various specialists revealed that none knew of a dedicated brain tumour-specific, post mortem whole brain banking facility. While there are brain banks specifically for resected and biopsied brain tumour tissue (such as the one funded by the Brain Tumour Foundation of Canada and the Neuro-oncology Bank at New York University) most brain banks hold specimens largely relating to the neuro-degenerative diseases such as Parkinson’s Disease, Alzheimer’s, Huntington’s, Multiple Sclerosis, etc.

For example, Brains for Dementia Research [BDR] is a network of brain bank facilities across England and Wales in the United Kingdom which is jointly funded by the Alzheimer's Society and the Alzheimer's Research Trust. The BDR links five leading centres based in London, Oxford, Newcastle, Manchester (all in England) and Cardiff (in Wales). <sup>(15)</sup>

Another example is the Corsellis Brain Bank (held by the West London Mental Health Trust in the UK) and which has been collecting cases for 50 years. Corsellis now holds 8,600 brains and sections from various disorders and control cases. They state that they hold "...for the majority of cases, paraffin-embedded blocks, histologically stained slides and wet tissue held in 10% formalin (4% formaldehyde v/v)." A summary of cases in their collection can be found via the weblink at the end of this paper. It is stated in the list that 305 cases are "CNS tumours – all types" and "CNS tumours – benign". Over 1500 cases are for neuro degenerative diseases. The remainder cover personality disorders due to brain disease or damage, schizophrenia, depressive disorders, epilepsy, 1850 cases of "no psychiatric or organic brain disorder" plus a large range of other samples. <sup>(16)</sup>

There is also BrainNet Europe (BNE), a consortium which allies 19 European brain banks. But again, this alliance appears to deal mainly with diseases such as Alzheimer's, Parkinson's, depression and schizophrenia. <sup>(17)</sup>

There would appear to be no such dedicated networks or individual banks specifically for post mortem brain tumour tissue and/or whole brain donations from brain tumour patients.

With regard to whole brain banking, and from the brain tumour patient and caregiver perspective, it could be difficult to translate the neuro-degenerative disease journey into one that may be relevant to brain tumour patients.

We feel that the biggest difference is that post mortem whole brain donation by a Parkinson's Disease patient, for example, is something that the patient and his or her family might think about for some time and become "comfortable" with, having been asked by their clinician to consider it as a possibility. That same extended survival period, indeed the luxury of time, does not exist in the brain tumour world in the majority of cases.

The much slower onset of Parkinson's versus the devastatingly rapid disease progression of malignant brain tumours might be likely to cause some difficulties as brain tumour patients and their families might be in a more fragile emotional state and therefore not be amenable to an approach for whole brain donation using a model from the neuro-degenerative disease world.

## **E. Untapped resources**

One specialist we spoke to said that one very big untapped research resource is the paraffin-embedded tissue in pathology departments. He said that researchers were not usually interested in formalin-fixed samples because, based on current assays, it was hard to analyse DNA and RNA in this tissue format. However, these samples are in abundant supply and frozen tissue is not.

He also felt that pathologists should be involved in the very early stages of trial design and planning. “If you were to put all your resources to best use it would include establishing decent liaison between all the professionals – surgeons, oncologists and pathologists so that tissue harvested at time of surgery was the best it could be [i.e. for use in trials].”

The specialist went on to say that this abundant supply of already-existing samples of the more common types of brain tumour could also be used to test techniques which could perhaps then be translated to the more limited supply of rarer tumour tissue.

## **General issues**

### **i. Existing facilities and projects**

It will be a difficult task to ensure that expectations of the possible benefits of banking involving post mortem removal match the needs of researchers and the stage which relevant research projects have reached. (That is, for projects not utilising previously banked material.) For example, a researcher may initiate a project based around the study of a very specific brain tumour and call for donated tissue. Word will spread but only a small percentage of potential donors might respond initially.

By the time the request has filtered to other potential donors the project might have been completed and those who intended donating for altruistic reasons might be quite disappointed.

### **ii. International collaboration**

Underlying the discussion on resected tissue banking and post mortem brain tumour/post mortem whole brain banking are the challenges relating to the question of the international transfer of material, particularly from areas where specific research is not currently taking place or envisaged. This will most likely involve the transfer of material within either North America or Europe, or the transfer of material from sources that are external to either geographic area e.g. the donation from a paediatric patient in Australia to a North American research institute (which has already taken place in at least one instance of a DIPG tumour).

International centralisation of information - via a dedicated website - relating to current research trials and proposed trials using or requiring post mortem material, together with details of how to donate tissue, might help ameliorate (to some degree) the challenges described above.

## **In summary**

- 1. There is an emerging and critical need to encourage the banking of brain tumour tissue which is removed from the brain during neurosurgery (resection) in order to more comprehensively understand the makeup of these neoplasms and create better treatments for them. In addition, brain tumour tissue for research is needed to better understand the mechanisms of tumour growth and progression. This need will vary country by country. The IBTA cautions against creating a disconnection between awareness of a need; the availability of banking facilities and research projects to make good use of donated tissue; and the expectations of parents (acting on behalf of their child in pediatric cases) and adult donors.**
- 2. There should be urgent efforts made to raise public awareness of the crucial necessity for resected brain tumour tissue to be used for ethical and approved research programmes into the causes of and treatments for brain tumours. In addition, institutions which treat brain tumour patients should standardise neurosurgery consent forms so that as many brain tumour patients as possible have the opportunity, under the protection of informed consent, to donate their surplus resected/biopsied tumour tissue to brain tumour research (including genetic research).**
- 3. Brain tumours such as DIPG and PCNSL – where there is little chance of resection – may present problems in terms of research due to the lack of material available to study. Therefore, it can be argued that the use of post mortem brain tumour tissue banking and post mortem whole brain banking may have an important relevance to these two tumour types in particular. More research is needed into the challenges of this type of tissue banking - for example, the identification of specific needs of researchers in this field; practicalities of post mortem banking, cost implications and most importantly, patient/family/caregiver input into this controversial area of tissue banking.**

## Notes:

1. In 2007 the International Brain Tumour Alliance (IBTA) commissioned research from the Central Brain Tumor Registry of the United States (CBTRUS) which projected that in 2010 the worldwide incidence of malignant primary brain tumours may climb to 220,568. See page 38, *The First Walk Around the World for Brain Tumours*, 2008, International Brain Tumour Alliance, ISBN 9780646494814
2. Human Tissue Act 2004 (c. 30), Explanatory Notes, Summary and Background, [http://www.opsi.gov.uk/acts/acts2004/en/ukpgaen\\_20040030\\_en\\_1.htm](http://www.opsi.gov.uk/acts/acts2004/en/ukpgaen_20040030_en_1.htm)  
Accessed 15 July 2009
3. *Journal of Clinical Oncology*, 10.1200/JCO.2009.25.5463 and online at <http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2009.25.5463> , Maryam Zarghooni, Ute Bartels, Eric Lee, Pawel Buczkowicz, Andrew Morrison, Annie Huang, Eric Bouffet and Cynthia Hawkins.  
Web version accessed 12 February 2010
4. US Food and Drug Administration. Minutes of the Joint Meeting of the Pediatric and Oncologic Drug Advisory Committees, April 27, 2009. See <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM171523.pdf> Accessed online 11 February 2010. A full transcript of this meeting is available from this website address: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/UCM171718.pdf>
5. *Ibid.*, Minutes, page 4, comments by Dr Kenneth Cohen (Johns Hopkins University School of Medicine) in his summary of information on the current clinical management of children diagnosed with DIPG.
6. *Ibid.*, Minutes, page 7
7. Email exchange with Dr Loice Swisher, 18 February 2010
8. *British Journal of Neurosurgery*, August 2009; 23 (4): 351-363, Dr Darren Hargrave, Pediatric Oncology Unit, Royal Marsden NHS Foundation Trust, Sutton, UK
9. *Op cit.* FDA Minutes, page 7
10. Email correspondence with Dr Michael Buckland, quoting Okada et al, *Cancer Research* 63, 413-416, January 15, 2003
11. Parkinson's Disease Society online FAQ sheet, [http://www.parkinsons.org.uk/research/parkinsons\\_brain\\_bank\\_donation\\_questions.aspx](http://www.parkinsons.org.uk/research/parkinsons_brain_bank_donation_questions.aspx)  
Accessed 17 July 2009

12. Personal email correspondence with Dr Michael Buckland, Sydney, Australia; Mrs Jennifer Wilson, Senior Research Nurse for the Cambridge Brain and Tissue Bank, Cambridge UK and Dr David Ramsay, Brain Tumour Foundation of Canada's Brain Tumour Tissue Bank. Dr Ramsay's quoted fees are based on amounts the CJD surveillance group pays his institution for removing the brain and providing a provisional diagnosis. Fee for prosector and attendant = CAD \$250; fee for autopsy room = CAD \$300; pathologist's professional fee = CAD \$150.
13. Journal of Clinical Oncology, 10.1200/JCO.2009.25.5463 and online at <http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2009.25.5463> , Maryam Zarghooni, Ute Bartels, Eric Lee, Pawel Buczkowicz, Andrew Morrison, Annie Huang, Eric Bouffet and Cynthia Hawkins.  
Web version accessed 12 February 2010
14. Creutzfeldt – Jakob Disease Surveillance System (CJD-SS), <http://www.phac-aspc.gc.ca/hcai-iamss/cjd-mcj/index-eng.php>  
Accessed 11 August 2009
15. Brains for Dementia Research (BDR),  
<http://www.brainsfordementiaresearch.org.uk/site/index.php>  
Accessed 11 August 2009
16. Personal correspondence (email) from Dr Michael Maier, Curator, Corsellis Brain Bank and Dr Matthew Williams, Manager, Corsellis Brain Bank.
17. BrainNet Europe (BNE), <http://www.brainnet-europe.org/> accessed 11 August 2009

## APPENDICES:

The following appendices have been uploaded to the IBTA website at [www.theibta.org](http://www.theibta.org) and can be accessed via these specific links:

<http://www.theibta.org/AppendixA.doc>

<http://www.theibta.org/AppendixB.doc>

<http://www.theibta.org/AppendixC.pdf>

<http://www.theibta.org/AppendixD.pdf>

<http://www.theibta.org/AppendixE.doc>

### Appendix A

Sources of information and research for this informal report. The opinions expressed by the individuals mentioned in this Appendix are not necessarily those of the IBTA and/or the Astro Fund nor are the opinions of the IBTA and/or the Astro Fund which are set out in this draft discussion document necessarily those of the listed individuals.

See <http://www.theibta.org/AppendixA.doc>

### Appendix B

List of website links, see <http://www.theibta.org/AppendixB.doc>

### Appendix C

UK Parkinson's Disease Society's Brain Donor Register consent form and accompanying documents, see <http://www.theibta.org/AppendixC.pdf>

### Appendix D

Cambridge Brain Bank Consent Forms and Information Sheet, see <http://www.theibta.org/AppendixD.pdf>

### Appendix E

Corsellis Brain Bank Summary of Cases, see <http://www.theibta.org/AppendixE.doc>