

Pediatric Brain Cancer Tissue Donation: Ask and You Shall Receive

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Citation

P A Clark, A Maheshwari, B Gleason, B Edmonds, J Schadt, M DiMuzio. *Pediatric Brain Cancer Tissue Donation: Ask and You Shall Receive*. The Internet Journal of Pediatrics and Neonatology. 2016 Volume 18 Number 1.

DOI: [10.5580/IJPN.39238](https://doi.org/10.5580/IJPN.39238)

Abstract

Tissue donation is a crucial element of cancer research and as a result of the lack of tissue samples, survival rates for brain cancer have not changed significantly in approximately fifteen years. Due to a particular shortage in brain tissue, children with central nervous system tumors do not have a favorable prognosis as compared to other types of cancers. With increased tissue donation, research in this field can function more efficiently to better understand pediatric tumor biology. This would almost certainly lead to the development of more effective therapies, and ideally, improvement in survival rates. Today, there is no standard method of approaching families of children with cancer for tissue donation. As a result, there are different levels of success for physicians. This paper will propose ways to encourage physicians to discuss the donation of biopsy and autopsy tissues with the families of children with cancer in the most effective, compassionate, and ethical manner. In order to reduce stress for families in such difficult decisions, it is important to outline the methods of approaching families. In addition, specific protocols for limited autopsy will be examined, as the samples recovered by these autopsies is the primary source of tissue used for research in this field. The ultimate goal of this paper is to increase the frequency of tissue donation in pediatric brain cancer through education of physicians, patients, and their families. A legal and ethical analysis of all potential solutions will be conducted, forming the basis of recommendations, and conclusions will be made.

INTRODUCTION

Cancer is the leading killer of children, yet there is a paucity of tissue samples with which to conduct research. Tissue donation is a crucial element of cancer research and as a result of the lack of tissue samples, survival rates for brain cancer have not changed significantly in approximately fifteen years[1]. Due to a particular shortage in brain tissue, children with central nervous system tumors do not have a favorable prognosis as compared to other types of cancers. With increased tissue donation, research in this field can function more efficiently to better understand pediatric tumor biology. This would almost certainly lead to more effective therapies, and ideally, improvement in survival rates.

One major challenge in conducting this research is that cancers in children and adolescents are relatively uncommon. Childhood cancers represent less than one percent of all new cases diagnosed in the United States each year. The shortage of samples makes clinical trials challenging. Certain challenges include the development of

less toxic treatments and limiting or mitigating the adverse effects of current and previous therapies. There is growing recognition of the harmful effects that treatments for childhood cancers can cause later in life. An increase in tissue donation can allow more research to be conducted in this area.

Medulloblastoma is the most common brain tumor in children. Approximately one out of every five pediatric brain tumors is a medulloblastoma. There are over 300 new cases in the United States each year, with most occurring between 5 to 10 years of age[2]. In the past 40 years, the mortality rate in medulloblastomas has only fallen approximately two fold. Improvement in survival rates will require increased understanding of the biology of medulloblastomas. The study of tissue collected by autopsy is the best source of this information[3]. There are currently treatments (including surgery, chemotherapy, and radiation,) which are effective in shrinking the primary tumor, however, recurrence and metastasis are common. According to one study only about half of patients survive for 5 years after diagnosis[4].

Today, there is no standard method of approaching families of children with cancer for tissue donation. As a result, there are different levels of success for physicians. We will propose ways to encourage physicians to discuss the donation of biopsy and autopsy tissues with the families of children with cancer in the most effective, compassionate, and ethical manner. In order to reduce stress for families in such difficult decisions, it is important to outline the methods of approaching families. In addition, specific protocols for limited autopsy will be examined, as the samples recovered by these autopsies is the primary source of tissue used for research in this field. The ultimate goal of this project is to increase the frequency of tissue donation in pediatric brain cancer through education of physicians, patients, and their families. An ethical analysis of all potential solutions will be conducted, forming the basis of recommendations, and conclusions will be made.

Medical Issues

After hematological malignancies, primary malignant Central Nervous System (CNS) tumors are the second most common childhood malignancies and the most common pediatric solid organ tumor.[5] They are one of the leading causes of death from pediatric cancer. Despite advances in diagnostic techniques, early interventions, and advances in treatment, they continue to have a high morbidity and mortality amongst children of all age groups. The etiology of most CNS tumors is still unclear, however, two extensively studied risk factors are exposure to ionizing radiation and genetic syndromes.[6]

As per data from Central Brain Tumor Registry of the United States (CBTRUS), the incidence of primary CNS tumors is estimated at 5.4 cases per 100,000 person-years for children and adolescents less than 19 years of age.² The estimated five-year survival rate for all primary CNS tumors is about 66 percent in pediatric patients. CNS tumors accounted for 29 percent of all childhood malignancies in children less than 15 years of age.³ The incidence of pediatric CNS tumors is greatest in children less than 1 year of age and between 1-4 years of age, males, and white and Asian/Pacific islander children as per CBTRUS statistics.⁵ [7] [8]

The two primary classifications of pediatric CNS tumors are the World Health Organization (WHO) classification based on tumor histology and the International Classification of Childhood Cancer (ICCC) based on primary tumor site and morphology. Our focus in this review will be on a specific

type of pediatric CNS tumor, Medulloblastoma, which is an embryonal CNS tumor and occurs only in the cerebellum. This is the most common malignant brain tumor in children and accounts for about 20 percent of all primary pediatric CNS tumors. The highest incidence is between 5-9 years old.

Clinical manifestation of CNS tumors is often nonspecific and can be mistaken for viral symptoms. This can frequently lead to misdiagnosis and late diagnosis when more apparent symptoms are visible. Symptoms are generally caused by local invasion of the tumor, compression of adjacent structures, or increased intracranial pressure (ICP). The most common symptoms and their frequency are headaches (33%), nausea and vomiting (32%), abnormal gait and coordination (27%), papilledema (13%) and seizures (13%)[9]. In infants and young children, due to their inability to express their symptoms, the most commonly seen signs with frequency are macrocephaly (41%), nausea and vomiting (30%), irritability (24%), lethargy (21%), abnormal gait and coordination (19%), and weight loss (14%)⁹. In older children, changes in personality and behavior or declining performance at school can be the first sign. Signs and symptoms are also greatly influenced by location of the tumor, which can also help in diagnosis. In medulloblastomas, clinical manifestations correlate with the specific site of the tumor whether midline or paramedian. Specifically, cerebellar signs including gait abnormalities, unsteadiness, incoordination along with nonspecific signs described above should raise suspicion and further testing should be initiated.

Initial diagnosis is made by neuroimaging, either magnetic resonance imaging (MRI) or computed tomography (CT). There have been multiple studies on timing of neuroimaging based on clinical judgment and now there is an evidence-based guideline, which can help physicians⁹. The criteria for brain imaging includes, but is not limited to, the following: persistent headache which wakes a child from sleep, occurs upon waking in any child less than 4 years, or is associated with confusion, disorientation, persistent vomiting upon waking, or visual or motor findings.

The initial test is normally a CT of the brain due to its cost-effectiveness, availability, and practicality with children. However, an MRI is the test of choice as it is more sensitive and detailed. If neuroimaging demonstrates a lesion, then the patient should be referred immediately to a neurosurgeon to establish a histopathologic diagnosis. Patients with medulloblastoma should also receive a spine MRI and lumbar puncture for CSF to evaluate the extent of the

disease, as the tumor generally metastasizes to the spinal leptomeninges.

Management approach for all pediatric CNS tumors is a multi-disciplinary approach to achieve the best results. It involves a combination of surgery, adjuvant radiotherapy, and single agent or combination chemotherapy. Risk stratification to devise an appropriate management plan is based on age, metastasis, histopathology, and molecular type of tumor. In medulloblastomas, approach to treatment is based on two primary factors: risk of recurrence and risk for treatment toxicity. Children are divided into three groups accordingly: children older than 3 years with average risk disease, children older than 3 years with high risk disease, and infants and children younger than 3 years of age.

Surgery is the first line of treatment to establish a tissue diagnosis and for near total or total resection, if possible. Radiotherapy use is dependent on multiple factors, which are primarily the specific histologic diagnosis of the tumor, age of the child and weighing the risks versus benefits of the acute and long term complications. Chemotherapy use is dependent again on the child's age and is usually used in combination with the above. Combination chemotherapy is often used in younger children to delay or avoid the use of radiotherapy due to the risk of long term complications. In medulloblastomas, maximal safe resection is an important goal of treatment although it is not always possible due to sequela post surgery[10].

With advances in treatments and early diagnosis, the prognosis for CNS tumors is improving, although is still poor. Five and ten-year survival for pediatric CNS tumors are 73 and 70 percent respectively[11]. Approximately 75% of children with medulloblastomas survive into adulthood. However, 20-30% will relapse following initial treatment[12]. Poor prognosis is associated with younger age, metastatic disease, relapse after resection and certain histopathologic types.

Children who survive a CNS tumor frequently have long term complications from either the tumor or the various treatments, which include chronic medical conditions, cognitive, psychological, and social effects. This can significantly impact quality of life. As per Childhood Cancer Survivor Study (CCSS), 82 percent of 2821 five-year survivors were reported having at least one chronic medical condition after treatments and are at high risk for developing a secondary cancer as well[13].

BENEFITS OF AUTOPSY TISSUE DONATION

Post mortem tissue collection by full or limited autopsy is a process that is currently conducted in the pediatric brain cancer field, as well as in nearly every other area of cancer study[14]. It is nearly universally accepted that the samples obtained through autopsy collection are of great value to researchers[15] [16] [17].

Biopsy tissue is generally collected in tiny amounts, only enough for diagnostic testing[18]. The collection of post-mortem tissue allows for greater amounts of tissue to be collected. The entirety of the tumor can be collected and examined, as well as any metastases and samples of healthy tissues. This is extremely valuable to researchers, particularly because it has been shown that metastases may vary genetically from primary tumors[19]. This variation creates a need for different treatment plans different than those used to treat the primary tumor. Additionally, it has been shown that metastases have caused up to 90% of cancer related deaths[20]. Therefore, metastatic tissue is extremely important to researchers looking for better treatment plans. Whole brain autopsy is also more valuable than post-mortem tumor biopsy due to the extensive amount of tissue collected, which allows the tumor biology to be studied on a macro and microscopic level[21]. In situations in which excision biopsy has been performed, autopsy donation might not be as beneficial as in cases where there has not been excision biopsy conducted. The tissue which has been excised can be of use in biological testing and in the event that there are no metastatic tissue, there is likely very little remaining tissue. Autopsy donation is still an option in this scenario, as the collection of remaining tumor tissue and comparable normal tissue would be of use to researchers. However, the comfort of the family is of utmost importance and if after an excision biopsy procedure this is not a procedure in which they are interested, it ought not to be pursued. Due to the rarity of excision biopsy in CNS tumors and the fact that metastases might be present after an excision, whole brain autopsy is the most valuable procedure in the vast majority of cases.

The large quantities of tissue collected in partial autopsy can be preserved in different ways that facilitate different types of analysis. Fresh tissue can be collected for study of cytogenetics or the establishment of cell lines (generally for mouse models.) Frozen tissue is useful for studying molecular genetics, and paraffin embedded tissue is useful for examination using light microscopy, immunohistochemistry, and fluorescence in situ

hybridization to detect tumor-specific translocations.

Additionally, autopsy allows for the collection of matched fresh, frozen, and paraffin tissues from primary tumor, metastatic tumor, and normal tissue[22].

Never before have researchers been able to utilize tissue samples for such specific tests, or obtain such accurate results. It has never been more important for researchers to have samples, because researchers today have the ability to analyze cancers in a variety of ways, but lack the specimens with which to conduct their research. Examination of autopsy tissue can provide insight as to the effectiveness of particular treatments. It can also provide families a source of comfort knowing that they and their child have made a contribution with a possibility of preventing another child and family from suffering as they have. Extremely powerful parent testimonies regarding the tissue donation process and how it affected them personally are available on countless websites and support groups. Such accounts can be found on the Kids vs Cancer webpage (www.kidsvcancer.org) as well as several websites dedicated to specific pediatric conditions. Nearly all parents in these accounts share how happy, relieved, and even proud they were to know that they and their child were able to contribute and hopefully prevent other families from enduring what they had.

BARRIERS TO TISSUE DONATION

Presently, tissue is donated almost exclusively when the process is initiated by the patient or his or her family. This is a result of a lack of awareness regarding this process, a lack of communication skills by physicians, and the discomfort and trauma that it is capable of causing for all involved. If physicians are not aware of the opportunity to donate tissue or its benefits, then they are less likely to broach the subject. In this case, if they do discuss it, they may not be enthusiastic or clear in their description. Additionally, many doctors do not approach families regarding tissue donation because they believe that the discussion will upset the family. Barriers originating with the family are also common. These include religious concerns, fear of disfiguration of loved ones, unawareness of wide range of benefits to clinical research, and potential additional costs[23]. Further barriers arise due to logistical issues, such as coordinating the autopsy if a child dies at home, coordinating transport of samples to a researcher, or funding.

Legal Issues

Prior to 2002, there existed little to no regulation from the

FDA in regards to emerging treatment procedures for pediatric oncology[24]. This lack of protocol was due to the scarcity of development on advanced cancer treatments specifically designed for children. Nearly all drugs available for the treatment of pediatric cancer were drugs originally developed for, and commonly used to treat adult cancer[25]. Thus, most FDA approved therapies for pediatric oncology involved the use of an adult-intended drug in lower dosage. This was permitted under an FDA ruling in 1994 that allowed drugs developed for adults to be used to treat children based on extrapolation from adult studies, in conjunction with child safety studies. Since 2002 however, the FDA has enacted programs to incentivize the development of pediatric-specific oncology therapies, as well as regulations that decrease the amount of time between the completion of a drug's trial and its becoming available for clinical use.

One such program is the Best Pharmaceuticals for Children Act (BPCA), which was implemented in 2002 as an extension of the FDA Modernization Act of 1997, and was made permanent in 2012. The BPCA incentivized the development of pediatric drugs by granting drug developers an additional six months of patent exclusivity for on-patent drugs already in use in pediatric studies. The BPCA also established a partnership with the NIH to promote and develop research in pediatric cancer therapies. This act allows the NIH to submit a proposed pediatric study request for a specific drug that outlines what clinical studies are necessary to enhance the pediatric labeling for that drug. The FDA will then send the proposed studies to the manufacturer of the drug and upon a response by the manufacturer, the NIH is cleared to conduct the necessary studies[26]. The BPCA also works in association with the NICHD to establish a list of pediatric drug therapies deemed most worthy of additional study which is updated every three years. The overall impact of the BPCA has been to increase the rate of labeling for pediatric-specific oncology therapies.

Another protocol developed by the FDA for increased production of pediatric therapies is the Pediatric Research Equity Act (PREA)[27]. Initially developed in 2003 and made permanent in 2012, this act imposes pediatric study requirements for the development of new therapies[28]. Under the PREA, applications for new drugs or biological licenses are required to enclose pediatric assessments that will be taken into account by the FDA in determination of approval. This act was designed to operate in conjunction with the BPCA in requiring manufactures who wish to

extend exclusivity to anticipate additional pediatric studies. These requirements apply to all new therapies seeking approval from the FDA unless a waiver has been obtained. The FDA only grants waivers if studies would be impractical to conduct, or if evidence exists suggesting that the new drug would have harmful effects or be ineffective in children, or if the proposed drug will not bring about any benefit over existing drugs currently used for its intended purpose[29]. In combination with the BPCA, the PREA defines the regulations in regards to obtaining FDA approval for drug therapies or pediatric use. In addition to the medical and legal aspects of the process of tissue donation, ethical consideration must be given. It is imperative that an issue with such powerful and widespread implications be examined ethically before any recommendations be made.

ETHICAL ANALYSIS

Survival rates for many pediatric cancers have improved significantly in the past decades, but unfortunately pediatric high-grade gliomas, a particularly aggressive group of brain tumors, have not benefitted from the same progress. Pediatric high-grade glioma patients, like those with astrocytoma or glioblastoma multiform, have five-year survival rates ranging from just 15-20 percent. As a result, pediatric brain tumors are the leading cause of cancer-related death in children under 14 years old, and overall survival statistics have not improved in nearly 40 years[30].

The major challenge facing patients, families, physicians and researchers in regards to pediatric brain cancers is that pediatric cancer is relatively uncommon. Childhood cancers represent less than 1% of all cancers diagnosed in the United States each year. With so few cases it is difficult for researchers to find the amount of tissue samples they need to conduct valuable research. This has challenged researchers in this field to find ways to work collaboratively to foster a strong national clinical research program in this area. Unfortunately, there have been serious barriers to bring about this collaboration. It has become almost imperative that children's cancer centers and national research programs must collaborate now and in the future to ensure that clinical trials enroll sufficient numbers of patients. We cannot allow competition, egos, lack of funding and fear of failure to stand in the way of this valuable research. Ethically, creating new therapies for children with brain cancer in order to improve their quality of life and survival is imperative for the children, their families and society as a whole. It will be argued that—according to the ethical principles of respect for persons, beneficence/nonmaleficence, and

justice—action must be taken immediately to address the concerns surrounding the lack of tissue donation for pediatric clinical trials. Such action will not only save lives, but will also do much to conquer cancer.

RESPECT FOR PERSONS

This principle incorporates two ethical convictions: first, that persons should be treated as autonomous agents; and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy[31]. Respect for human persons refers to the right of a person to exercise self-determination and to be treated with dignity and respect. All people deserve autonomy and to be treated with dignity and respect. Failure to provide any person with adequate health care, which includes clinical research, violates this basic right of respect for persons. Clinical research will increase our understanding of the biology of brain tumors, which will inform future research, and hopefully should result in the development of new, more effective therapies, which can be lifesaving.

Second, as an autonomous agent an individual has the right of informed consent. Since children are minors, unless emancipated, parents have the right to know all information about their child's diagnosis, prognosis, treatments and care plan. The elements of informed consent include professional disclosure, patient comprehension of the information, patient voluntariness and competence to consent. This means that parents have the right to know from their physicians that tissue donation is essential to help bring about a cure for the various types of brain tumors. Unless physicians provide parents with full knowledge of possible research protocols and the huge benefits they can provide, physicians are not giving these families informed consent. To make themselves aware of possible research protocols means primary care physicians have to be in dialogue with clinical researchers. This will entail working collaboratively and establishing a national directory of research protocols not only nationally but worldwide. Informing parents about these research protocols and having conversations about the need for tissue donation may be difficult for physicians, patients and families but unless these conversations are initiated and continued during the course of the illness, the research teams will never have the tissue needed to fight this cancer. Physicians may need to be trained on when and how to communicate the need for tissue donation but this can be

accomplished by following the recommendation that are being proposed in this paper. For informed consent to occur physicians must have the knowledge needed of what is available in regards to research opportunities and families must be reassured about the scientific research, emotional benefits and practical issues that may follow regarding the process of an autopsy or biopsy.

Children are minors but in the field of pediatrics physicians and bioethicists believe that children have the right of assent in regards to medical treatments and procedures. Assent is when an individual who lacks decisional capacity, or decisional authority, agrees to go along with a proposed medical intervention for him or herself. It should include the following four elements: First, helping the child achieve a developmentally appropriate awareness of the nature of his or her condition. Second, telling the child what he or she can expect with tests and treatments. Third, making a clinical assessment of the child's understanding of the situation and the factors influencing how he or she is responding (i.e., voluntariness). Fourth, soliciting an expression of the child's willingness to accept the proposed treatment or procedure. Regarding this final point, we note that no one should solicit a patient's views without intending to weigh them seriously. In situations in which the patient will have to receive medical care despite his or her objection, the patient should be told that fact and should not be deceived[32]. The problem is that many physicians lack the training on how to raise the topic of clinical research with children. Many clinicians believe that children and adolescents would not understand the implications of a biopsy or an autopsy to retrieve tissue and that such a conversation might even psychologically harm the child. In a recent article published in *Pediatrics* a study found that children living with a life-threatening illness want to be able to choose and record (1) the kind of medical treatment they want and do not want, (2) how they would like to be cared for, (3) information for their family and friend to know, (4) how they would like to be remembered. The final aspect includes the bequeathing of one's belongings, being able to donate one's body, and how a child would like to be remembered in the future by family and friends[33]. Children may be vulnerable individuals but they have the ethical right to know and understand their diagnosis, prognosis, treatments and care plans. After understanding that tissue from their brain tumor could help them and others in the future, they may become the biggest advocates for clinical research. Children in these clinical situations have come to know other children with cancer that they meet while in the hospital or during treatment. There is

a bond that grows between these children and the common foundation is to do what they can to fight this dreaded enemy. Children are fighters and they are compassionate. Their illness opens their eyes to see that their tissue may not only help them but could help others who have the same cancer.

The failure of physicians to be proactive in addressing the medical needs of this most vulnerable population in regards to tissue donation is causing needless suffering and possibly even more deaths. Wiener et al. argue that "the complexity of the therapeutic relationship that involves the medical team, parents or guardians whose views may themselves differ, and a patient whose capacity to make medical decisions is somewhere along a continuum of complete dependence to complete independence, cannot be underestimated." [34] To deny parents and children the right to decide to allow for tissue donation that may help them and others clearly violates the ethical principle of respect for persons and our responsibility to help others in society.

BENEFICENCE/NONMALEFICENCE

The principle of beneficence involves the obligation to prevent, remove, or minimize harm and risk to others and to promote and enhance their good. Beneficence includes nonmaleficence, which prohibits the infliction of harm, injury, or death upon others. In medical ethics this principle has been closely associated with the maxim *primum non nocere* ("Above all, do no harm"). Children and their parents have a right to know that despite the terrible nature of the child's illness, there is the potentiality of making an invaluable contribution to medical research and even the possibility of a cure for pediatric cancer patients with additional tissue and more clinical trials.

Physicians have, as moral agents, an ethical responsibility to treat their patients in a way that will maximize benefits and minimize harms. Failure to adequately communicate and educate patients and families about the need for tissue donation from pediatric brain tumor patients, for whatever reason, is not in the best interest of the patient, their families or the society as a whole. Literature and research studies have confirmed pediatric cancer remains the number one disease killer of American children, with about 35 children diagnosed every day. Survival rates have improved for some types of pediatric cancers, but 2,300 children die each year and thousands more experience adverse complications as a result of their treatments. The lack of age-appropriate treatment options, inadequate amounts of tissue donations

for clinical research, complex regulatory environments within pediatric cancer clinical trials, and gross underfunding is hindering progress to defeat this type of cancer. To maximize benefits and minimize harms, physicians must educate themselves about the need for tissue donation. Patients and families must understand the need for tissue donation and how it can impact their lives and the lives of millions in the future. The federal, state and local governments must comprehend the need for additional funding. And researchers have to facilitate collaboration among their colleagues in order to bring together the greatest minds to defeat this enemy.

It is clear, after reviewing statistics and studies and identifying the biases and stereotyping that exist in medicine and clinical research, that failure to increase tissue donation for pediatric cancer patients will bring about unnecessary risks, including more suffering and even more deaths. Physicians have a moral responsibility to do what is good for their patients. Should a physician be impeded in the exercise of his or her reason and free will because of fear or a lack of training on how to communicate the need for tissue donation for clinical research, then that physician has an ethical responsibility to overcome those impediments and do what is demanded by the basic precepts of medicine—seek the patient’s good. Hospitals and research universities also have a responsibility to their communities. If hospitals and research universities have the ability to increase collaborative approaches to clinical research, can optimize research funding programs, can educate physicians and other medical professionals on the need for pediatric tissue donation, then it is the ethical responsibility of hospital and university administrators and other health care professionals to formulate programs that address this immediate need. Failure to recognize this great need is a failure not only of the test of beneficence; it may also be a failure of the test of nonmaleficence.

JUSTICE

This principle recognizes that each person should be treated fairly and equitably, and be given his or her due. The issue of tissue donation from children with brain cancer also focuses on distributive justice: the fair, equitable, and appropriate distribution of medical resources in society. At a time when reforming healthcare in this country has become a high priority, failure to initiate preventative measures and clinical research that would save medical resources and possibly human lives in the long-run violates the principle of distributive justice. The principle of justice can be applied to

the issue of pediatric tissue donation under discussion in two ways.

First, pediatric tissue donation is vital if we are going to find a cure for the various types of brain cancers. There is a need for more tissue samples because there have been improvements in medical techniques and technology and as a result, additional tissue samples are needed to test these new procedures and new drugs. To obtain additional tissue samples there is a need to create new protocols that will educate not only primary care physicians, but pediatric oncologists, medical professionals in pediatric hospices, parents and patients. Tissue samples whether obtained by biopsy or autopsy must be cost effective so that children from low-income families may also participate in this tissue collection. This can be accomplished through a multi-faceted strategy that includes government agencies, private industry and philanthropic groups like the Swifty Foundation and other advocacy groups that integrate the power of public policy and funding potential to move this scientific research forward. On January 12, 2016, President Obama in his State of the Union Address announced the launch of a “moonshot” to cure cancer. This new one billion dollar initiative to cure cancer will ensure that all children are treated justly, no matter their race, religion, income group, etc. As part of this new initiative there should be a call by Vice-President Biden, who is designated the leader of this new initiative, for a national gathering of appropriate stakeholders in the area of pediatric cancer research that includes experts from academia, clinical medicine, government agencies, regulatory officials, biopharmaceutical executives and philanthropic advocacy groups, to collaboratively decide how tissue donation can be expanded so that it is cost-effective, easily accessible and includes children from all races, ethnic backgrounds and financial standing. President Obama’s concern to cure cancer and eradicate malaria in the world is a result of putting a human face to these diseases. Vice-President Biden’s son recently died of cancer and President Obama’s relatives on his recent trip to Africa gave him “a human understanding of the toll that malaria takes on communities.”[35] Putting a face to cancer, as Michael Gustafson has done in creating the Swifty Foundation, helps to raise awareness and increase funding for cancer research to improve the outcomes for the most vulnerable cancer patients. Justice in the fight against pediatric cancer will only be assured if there is a coordinated national collaborative group that will develop national protocols for the best interest of all children with pediatric brain cancer.

Second, the principle of justice also pertains to the fair and equitable allocation of resources. At the moment, there is not a national repository for pediatric brain cancer tissue. There are regional ones and even university/hospital specific repositories, but according to most researchers it is very difficult to obtain samples from these repositories in a timely, cost-effective manner. Until there is a cost-effective national repository that makes tissue samples and research data readily available to researchers around the world, we argue that the best process to increase clinical research in this area is to have a national/international directory of clinical researchers working on the various types of brain tumors (medulloblastomas, brainstem gliomas, cerebellar astrocytomas, etc). One option could be the establishment of a phone bank established that would operate 24/7 in order to advise physicians where to send the tissue and assist them in having the tissue delivered to the proper research laboratory. In addition, these various research laboratories can supply primary care physicians with the autopsy kits that will allow for a non-invasive way to gather the brain tissue in a cost-effective manner. With an increase of tissue samples from both the original tumors and tumors that reoccur after treatment with radiation, chemotherapy and various drugs, clinical researchers will be able to create new clinical trials that will assist children with brain tumors and hopefully not only benefit them and their families but society as a whole.

Americans espouse the belief that all men and women are created equal. Equality has also been a basic principle of the medical profession. If we truly believe in equality, we should insist that all men, women and children receive equal medical treatment and resources. Denying medical treatment to children because there is a lack of education about the need for tissue donation or a lack of national protocols that will make these tissue samples easily accessible and cost-effective to researchers is an unjust allocation of resources and violates a basic tenet of justice. Physicians, clinical researchers and the medical profession have an ethical obligation to use available resources fairly and to distribute them equitably. Failure to do so is ethically irresponsible and morally objectionable. To compromise the basic ethical foundations upon which medicine stands is destructive not just to children but to society as a whole.

To address these medical, legal and ethical concerns, we propose various recommendations to increase pediatric tissue donation in the United States. Unless we Americans address these needs for additional education and access to

pediatric tissue donations we will never attain the goal of eradication of pediatric brain cancer in the United States. Our model will not only save valuable medical resources; but has the potential to save precious human lives. If we do not make this a priority now, everyone will pay a price in the future.

Recommendations

Nearly all of the barriers identified can be eliminated through effective, compassionate, and ethical communication between physicians, patients and families. If doctors are aware of all the benefits of this process, such as the vast scientific research, ability of families to designate the extent of the procedure, the potential emotional benefit to patients and families, ability to accommodate religious beliefs, ability to have open casket, no cost to the family, then they will undoubtedly be able to communicate more effectively with families, making families feel better informed and more comfortable with their decision to donate autopsy tissue. Some systematic barriers can also be eliminated through communication facilitated by the Kids v Cancer Tissue Donation program. The head of this program will connect a patient's oncologist with a researcher(s) in need of tissue. The researcher will then provide the oncologist with their protocol for the recovery of tissue samples and the two will work out logistics ahead of time. The following are additional recommendation that are proposed:

First, doctors ought to address the topic of tissue donation with the patient and family in a general manner as a part of initial diagnosis. The most effective way to do this is to simply say that the majority of the information that has been obtained regarding this type of tumor has come from brain autopsy tissue, which has been collected and utilized by researchers. Many doctors who have experience in this field suggest this introduction and agree that this information is sufficient for the first conversation[36]. This approach is already taken by doctors working with DIPG. The prognosis for this particular cancer is dismal, prompting the early mention of tissue donation. However, DIPG patients are the most likely to donate tissue, with some doctors claiming donation rates as high as 75%. This is attributable to the early discussion of tissue donation, and the proactive nature of patients' families.

Second, the discussion of tissue donation is appropriate at diagnosis in all cases of pediatric brain cancer, but the timing of more serious discussion ought to vary based on the

specific cancer. Due to the prognosis of DIPG, it is appropriate that the subject of tissue donation be brought up at diagnosis, and that the subject be discussed in earnest shortly afterward. In other tumors, serious discussion ought to be left until the family is ready, or curative options have been exhausted. In the specific case of medulloblastoma, this conversation ought to occur in the event of metastasis or recurrence of the tumor. The prognosis is fairly good in medulloblastomas with regard to the primary tumor, however, the metastatic tumor is biologically different than the primary tumor and is much more difficult to treat. The presence of a nurse, social worker, chaplain, or any other member of the medical team who has intimate knowledge of the situation is recommended to add to the support and comfort of the patient and family. Patients and their families ought to know that though their child's illness is a terrible thing, they can make an invaluable contribution if they feel so inclined. However, it is important to treat each case as unique. Timing is dependent upon the family. If they seem interested and willing to discuss this topic, then the doctor has an obligation to discuss it. This is of the utmost importance because studies have shown that doctors were often surprised by the willingness of families to donate[37] [38]. Additionally, if families have the necessary information initially, they may decide to donate at a later time even they initially rejected the idea of donation. One innovative idea that has just been launched by the Pediatric Brain Tumor Foundation is the Star Portfolio that is a diagnosis kit for patients and families. This kit contains information about pediatric cancer treatments and centers. This diagnosis kit could be expanded to include the need for pediatric tissue donation, researchers working on the various types of tumors and how tissue donation can be initiated. This would be a valuable resource to patients and families.

Third, waiting to discuss tissue donation until after the loss of a child ought to be avoided at all costs. One study found that about half of parents felt that exposure to the concept of tumor donation and research at the time of diagnosis was helpful. Additionally, a large majority of parents believed that the subject of autopsy tissue donation might usefully be broached after a discussion regarding the exhaustion of curative treatment options. All parents felt that following death was the least desirable time to discuss a research-related autopsy[39].

Fourth, researchers and oncologists are encouraged to utilize the standardized method of autopsy tissue procurement published by Kambhampati et. al[40]. This protocol

describes the process of whole brain autopsy for the collection of fresh, frozen, and paraffin embedded tissues from both cancerous and healthy tissue. Additionally, it contains a protocol for conducting this procurement remotely in the event that a patient is not close to their team. If a team cannot be put together at the remote location, this protocol also outlines a method for removal and shipment of the whole brain from the participating institution to their team. This protocol provides an efficient method of collection of autopsy tissue. This is crucial due to the time sensitive nature of the procedure.

Fifth, consortiums and coalitions between hospitals ought to be established in order to encourage cooperation in research. By sharing data, advances can be made more rapidly than if researchers operated individually. In medical research there is often a desire to protect one's findings in order to publish new results in the hope of securing additional funding for future research. There is no place for such a silo mode of operation in the pediatric cancer field. Cooperative groups help to accelerate research. If researchers operate individually, treatments advance more slowly leaving hundreds of children with sub-optimal treatment options. Additionally, cooperation among institutions allows for greater access and more efficient handling of tissue samples. With an increase of tissue samples from both the original tumors and tumors that reoccur after treatment with radiation, chemotherapy and various drugs, clinical researchers will be able to create new clinical trials that will assist children with brain tumors and hopefully not only benefit them and their families but society as a whole. An example of this type of initiative is the Children's Brain Tumor Tissue Consortium (CBTTC) (www.CBTTC.org) at the Children's Hospital of Philadelphia. This initiative is an open-access, collaborative, multi-institute research program dedicated to the study of childhood brain tumors. Presently there are nine medical research centers involved in this initiative. The CBTTC operations center includes a state-of-the-art biorepository where tissue is housed at Children's Hospital of Philadelphia.

Sixth, it is imperative to communicate that an autopsy will be limited to the brain, that there will be minimal evidence of the operation, and that an open casket will be possible. The purpose is to extract tissue for research, not establish cause of death. Thus, the autopsy can be as minimal or as extensive as the family wishes. For example, while whole brain autopsy allows for the collection of healthy tissue, which provides valuable information to the

researcher, a family could ask that the samples taken be limited to the tumor. Conversely, if a child's cancer has metastasized, the family could consent to the removal of samples from the metastatic tumor as well.[41] Also, there is no expense to the family.

Seventh, doctors should identify potentially helpful online parent groups before treatment and share them with the family. Parent advocates have expressed the concern that families will be overwhelmed with emotion during the first conversation regarding tissue donation. While these recommendations hope to minimize that effect, it still remains a possibility. Relatives of other pediatric cancer patients are an invaluable resource for families in this situation. They can relate to and empathize with each other in a very unique and powerful way. The power of parent testimonials in these groups has been reported by numerous doctors, families and patients to be the single most important factor in their decision to donate tissue. Every family enduring the difficulties associated with having a child with cancer ought to be presented with the opportunity to engage in conversation with individuals with similar experiences.

Eighth, it is crucial to organize transportation ahead of time so that the movement from home to hospital to funeral home is easy and efficient. Participation in the Kids v Cancer Tissue Donation program is an effective manner in which to ensure that these logistics are handled with care and professionalism. In addition to coordinating all arrangements (before, during, and after the autopsy) with the funeral manager beforehand, suggestions made by parents who participated in an experimental autopsy protocol for DIPG patients included adjusting the weight of the head after a total brain autopsy (parents often lift their child after the autopsy to keep their child in their arms), and using skin colored stitches to reduce signs of autopsy[42].

Ninth, doctors and other health care professionals in the oncology field ought to be well educated about tissue and organ donation and trained in how to communicate that information. Studies have shown that when doctors were not well educated, they found approaching families to be extremely difficult. Without full knowledge of the protocols in place and huge benefits they provide, a clinician cannot effectively communicate the option of tissue donation to a family[43]. The distribution of educational materials to oncologists would be beneficial to this cause. Examples of helpful and practical educational materials are videos and brochures. A simple animated video aimed at both patients and their families explaining this process will soon be

available on the website of the Swifty Foundation. The Swifty Foundation is dedicated to educating patients, families and physicians using social media. They are initiating ideas such as white boards, role-playing techniques on YouTube to assist physicians in approaching patients and families about tissue donation, and testimonials from patients and families about the need for tissue donation.

Education is arguably the most crucial component of advancing research in pediatric brain cancer. Therefore, with educational materials available, families of children with cancer can investigate the option of tissue donation on their own, and oncologists will have an excellent resource to provide families inquiring about tissue donation and research in the pediatric cancer field.

Tenth, an excellent way to increase tissue donation levels is through connection with the National Disease Research Interchange. The NDRI has partnerships with every Organ Procurement Organization in the country and they work to distribute biospecimens to researchers in need of them. A partnership with organizations such as Kids v Cancer could potentially yield tremendous results. With such a partnership, OPO's can alert the NDRI when a pediatric brain cancer death occurs. They would then alert KVC, and a KVC representative would reach out to the family. The tissue would subsequently be procured by the OPO, sent to and processed by the NDRI, then sent to the KVC researcher. While this is a last minute system, it will dramatically widen the scope of potential donation candidates.

CONCLUSION

It is clear that in recent decades, the survival rates for pediatric brain cancers have not improved as much as families and doctors have hoped, nor as much as many other pediatric cancers. Testimony from researchers and doctors highlights the fact that research in this field cannot proceed as fast as possible because there is a lack of tissue available for use. This places a great burden on doctors, researchers and activists to attempt to rectify this situation. This paper highlights not only the causes of this shortage in tissue, but also proposes viable solutions. Additionally, the recommendations made are grounded in the ethical principles of respect for persons, justice, and beneficence and non-maleficence.

The value of strong communication skills and bedside manner during the discussion of any difficult medical news cannot be overstated. A doctor's ability to convey the

necessary information while simultaneously empathizing with the patient and monitoring their reaction is truly an art. The discussions which occur regarding tissue donation are certainly no exception. It is for this reason that communication skills and bedside manner are of paramount importance in the pediatric oncology field, as is education regarding the benefits of autopsy tissue donation.

Pediatric Oncologists should be universally aware of the previously discussed benefits of early conversation regarding tissue donation. This is imperative because pediatric brain cancer patients still have relatively poor prognosis. Autopsy donation allows for more tissue to be collected than at any other time. This is not an issue which can be ignored.

Educated, ethical doctors have the ability to change the face of cancer research simply by showing patients and families the vast benefits that can come from the terrible loss that cancer can cause. In addition to their own insights, medical professionals can utilize existing literature and organizations, parent support groups, and others in their field in order to ensure that the families of cancer victims have all the resources and information available during their difficult times.

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