

Pediatric Post-Mortem Tissue Donation: The Ethical Responsibility of Physicians

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Abstract

Post-mortem tissue donation represents a driving force in progressing research into pediatric brain cancer treatments. As of now, cancer is the second biggest killer of children around the world taking over 1000 lives under the age of 15 each year.⁶ One major barrier to increasing research is the lack of pediatric brain cancer tissue that is being donated to research. This low frequency of donation can be attributed to a variety of contributing factors but, oftentimes physicians are simply not initiating these conversations due to the emotional distress on the patient and family. This paper will introduce a range of resources aimed at aiding clinicians in carrying out these conversations and assisting families through the process. This paper will further discuss the ethical responsibility of the clinician to encourage this process as an option for the patient and the family.

INTRODUCTION

In the current era of cutting-edge healthcare, research physicians have developed multiple methods and techniques to better understand pathological processes which contribute to a vast array of medical conditions. Studying various biopsy and surgical specimens renders a unique perspective but, oftentimes patients with complex and rapidly progressive cancers are unable to survive and offer a unique opportunity for the process of post-mortem tissue donation to occur to better understand their conditions and help future individuals with similar conditions. Despite its major prevalence and poor prognosis, pediatric cancer research is drastically under-funded, with only 4% of the National Cancer Institute's research fund being spent towards pediatric cancer research.¹⁻² Brain cancer generally functions differently in children than in adults because children are constantly growing and developing, likewise affecting the development of their tumors.³ The scarcity of pediatric tissue donations is one of the largest obstacles in improving pediatric brain cancer research. With the pressing need for increased research in pediatric brain cancer in order for improved treatment and prognosis, post-mortem tissue donation is essential. This knowledge is vital in conducting clinical trials and advancing more effective cancer treatments.⁴ Although post-mortem tissue donation gives hope for the future of pediatric brain cancer research, the

conversation to initiate the process is not always being carried out due to the emotional tension of the situation as well as a diffusion of responsibility among physicians.

In the process of pediatric post-mortem tissue donation, the first step involves empathetic discussion with the family members and patients. Given the lack of medical and cultural awareness about post-mortem tissue donation, these discussions help in not only education but also are imperative for obtaining consent for the procedures involved in tissue harvesting. Even though many families may not consent to the process, it is vital for them to know about the implications as well as the benefits associated in advancing current modalities and research with post-mortem tissue donation. An important facet to this discussion involves the timing of the conversations. Based on a opinion survey involving a multi-institutional post-mortem CNS tumor collection program, Gift From A Child (GFAC) and 120 parents who lost their children to brain cancer, it was noted that the ideal time is usually when the care is being transitioned to hospice or when the prognosis is grim as this provides the families with enough time needed to contemplate the process but is not short sighted.⁵ Another topic of discussion that needs to be emphasized to the families is that hospitals in conjunction with various nonprofit organizations will bear the cost and obtain consent for the process and it is not a binding contract. Post-mortem

rapid tissue donation programs involve harvesting live tissue from patients right after death and have become quite prevalent in major academic health institutes but viable tissue can often be obtained until several hours as well. Programs such as GFAC of the Swifty Foundation have multiple resources such as websites, information videos, other parents who have lost their children to brain cancer, ancillary staff as well as families considering brain tissue donation. Establishing proper channels and pathways for post-mortem tissue donation, specially trained staff and distribution of appropriate rapid autopsy kits is imperative for a smooth workflow needed to execute the process. The logistics include transfer of the patient from the place of death to health institutes with the necessary infrastructure to conduct autopsies and harvest brain tissues and transfer of the necessary samples obtained to centers equipped to store and pursue further research is imperative. Once the autopsy is completed, various incisions are sutured and the body is then directed for the final rites based on the family and next of kin's wishes.¹ Post-autopsy communication with the family is equally as important in order to maintain transparency, accountability and in cases when interested, sharing the research findings is crucial and oftentimes helps families achieve a sense of closure. This paper will explain the physicians' ethical responsibility to inform patients and their families about the opportunity and benefits of donating and provide a clear pathway to aid in carrying out these emotionally difficult conversations.

MEDICAL ANALYSIS

Epidemiology

Cancer is the leading cause of death by disease in children.⁶ In the United States, one out of every 285 children are diagnosed with some form of cancer before the age of 20.⁷ Approximately 10,470 new pediatric cancer cases are expected to be diagnosed in the year 2022, and 1,050 of these children are likely to die as a result of their disease.⁶ The most common types of cancer amongst children ages 0 to 14 are central nervous system tumors, leukemias, and lymphomas.⁶ Central nervous system cancers consist of brain and spinal cord tumors, masses of abnormal cells with uncontrolled cell growth.⁷ In recent years, central nervous system cancer has surpassed leukemia as the primary cause of cancer related death in children, yet no drug is available to specifically treat pediatric brain tumors. There are over 4,000 pediatric diagnoses each year, making up a fourth of all childhood cancers, and 29.9% of total childhood cancer deaths are the result of brain cancers.⁸

According to the Central Brain Tumor Registry of the United States (CBTRUS), between 2014-2018, the annual incidence of malignant and non-malignant central nervous system (CNS) tumors in children and adolescents between the ages of 0-19 years old was 6.21 per 100,000.⁸ This makes primary brain cancers the second most common type of cancer in the pediatric population and the leading cause of mortality among all childhood cancers. Despite these statistics, many questions still surround the multifactorial causes of pediatric brain tumors, the best courses of treatment while minimizing side effects, and determinants of prognosis.

The first step in treating any illness is to recognize the signs and symptoms of its presentation so that it can be addressed. This can be challenging with pediatric brain tumors as their clinical presentations vary widely depending upon the age of the child and several tumor characteristics such as type, location, and rate of growth. Furthermore, symptoms may be non-specific including symptoms like headache, nausea, vomiting, or increased intracranial pressure.¹⁰

Doctors have thus realized that in brain tumors, as with any other malignancy, early detection leads to better outcomes. Unfortunately, physicians have inadequate understanding about the biology, pathology, and thus exact etiology of brain cancer in children. This has limited our efforts in developing an efficient screening test to diagnose and treat these tumors at an early stage. Most patients end up seeing a doctor after they have developed significant neurological manifestations.¹⁰

Pathology

Brain tumors can be categorized using the World Health Organization (WHO) classification which grades tumors on a scale of grade I-IV, with grade I being the least malignant and grade IV being the most malignant. Distinctions in grading can also indicate specific treatment plans. In the following section, each group of CNS tumors will have a variety of subtypes at different grades. They have been listed from the most common to the least common. These are just a few common varieties of brain tumors and not an in depth review.

Gliomas: Gliomas are tumors that arise from the abnormal growth of the glial cells including astrocytes and oligodendrocytes. These account for almost 50% of central nervous system tumors in the pediatric population.⁹

a. **Pilocytic astrocytomas:** Pilocytic astrocytomas are the

most common low grade (Grade I), well circumscribed gliomas which originate from astrocytes, commonly found in the cerebellum. Given that these tumors are well circumscribed, surgical resection can be curative for 90-95% of cases with malignant transformation occurring only in about 5% of pilocytic astrocytomas. Even as this cancer is curable, there are several long term sequelae such as intellectual impairments, hearing and vision loss and endocrinopathies.³

b. High grade gliomas: Glioblastoma multiforme (Grade IV) is the most common high grade glioma in the pediatric population. These tumors are often located in midline structures making them difficult to resect. Standard treatment remains surgical resection followed by irradiation and chemotherapy with temozolomide. Extent of surgical excision of tumor cells is the greatest predictor of survival. In cases where $\geq 90\%$ of tumor cells are resected, the progression-free survival (PFS) is approximately 35% whereas in partial resections, the PFS is approximately 17%. The overall survival of pediatric GBM varies from 10-73 months. Given that survival based on surgery shows a poor prognosis, much research has been focused on novel pharmacological treatments targeting different aspects of cancer cells such as cell growth, proliferation and metastasis. However, a systematic review published in 2022 showed that no novel approach led to improvements in progression-free survival or overall survival

Embryonal Tumors: Embryonal tumors are derived from fetal (embryonal) cells within the brain. The most common tumor within this group is medulloblastoma which makes up almost 20% of all childhood brain tumors.

a. Medulloblastomas: Medulloblastomas (Grade IV) are located almost exclusively within the cerebellum. They most commonly affect children ages 1-9 years. Treatment for all genetic subtypes is surgical resection, radiation therapy and chemotherapy. Based on level of resection, patients are categorized as average-risk disease or high-risk disease which determines their prognosis. Average-risk carries a five-year disease-free survival of approximately 80% while high-risk falls around 60-65%.² Outcomes are poorer in children below age three as they have a five-year disease-free survival of approximately 41% in non-metastatic cases and 25% in infants with metastasis. Even with survival, a common side effect of treatment of medulloblastoma is posterior fossa syndrome which occurs in approximately 25% of cases.³ This syndrome is characterized by progressive mutism, ataxia, emotional lability and axial

hypotonia. Despite its common presentation, etiology of the syndrome remains unclear.

After diagnosis of the tumor, several factors must be considered when choosing the most appropriate treatment option. In general, surgical resection, chemotherapy and/or radiation therapy are used to target pediatric brain tumors. Even though these are standard of care, they carry many risks. For example, radiation therapy in children often causes long term neurocognitive impairments, endocrinopathies, behavioral changes, growth abnormalities and increased chance of malignancy. As such, treatment of such tumors is often combined with usage of molecular profile of tumors for more targeted irradiation, sensitization to radiation, immunotherapies and even stem cell replacement.¹⁰ Despite these advancements in treatment, response to treatment and sequelae after treatment still vary greatly amongst patients even with the same tumor type. Even after diagnosis, the treatment remains challenging. Long term effects on cognitive function and development can be as severe and debilitating as the effects of the cancer itself.

DONATION PROCESS

The process of tissue donation starts when the patient is declared to have died. This death can occur inside or outside the hospital. If the patient dies while being cared for in the hospital, the physician involved in the care of the patient usually alerts the concerned authorities (organizations like the SWIFTY foundation, gift of life etc.) about the death of the patient. The representatives of these organizations, who have special training in this matter, usually approach the immediate next of kin or health care representatives of the patient and put forth the option of post-mortem tissue donation. The process and procedure is discussed in detail and all their questions are answered.

Procedure of donation process-How donation occurs

If and when the family consents, tissue collection can occur either in the hospital or the funeral home before or during the embalming process as per the family's wishes and facilities available. The consent from the patient or next of kin is key. Post-mortem tissue donation cannot happen without written and informed consent. This consent can be revoked at any time in this procedure. The tissue is collected with the utmost care by specialists trained in this field, so as to prevent any distortion to the external appearance of the deceased. The body is then prepared so it looks as if nothing ever happened and is returned to the morgue or funeral home as per the wishes of the family. Precautions and checkpoints

are taken at each of the steps in this procedure to ensure that the body is treated with dignity and respect. The collected tissue is immediately transported to the recipient hospital or research institute where it will be stored and used for further research.

Need for tissue donation

The revised 5th edition of classification of tumors of the central nervous system (CNS) released in 2021 by the world health organization (WHO) incorporates molecular biology of CNS tumors, thus changing the way oncologists approach and manage these tumors.¹¹ Post-mortem tissue donation has helped researchers make significant strides in understanding the molecular biology and genetics of brain cancer, facilitating these discoveries and continues to do so in various ways. Various mouse models replicating the cancer cells harvested from post-mortem donors has led to the development of patient derived xenografts (PDX) and cell line derived xenografts (CDX). These are being used to develop new treatments and predictive models which model the behavior of these cancer cells in vitro. Unfortunately, these methods have their own limitations. Recent article by Ledford et al, showed how the tumor cells in these mouse models tend to change their characteristics, genetic composition and behavior when introduced in mice.¹² This has limited the direct applicability of drugs that are effective in mouse models to patient care. All of this points towards one thing, studying tumor tissue obtained from real patients is indispensable in studying brain cancer. When it comes to tissue donation, any amount of tissue and any tissue can be important in advancing science. If the collected sample includes the whole brain, it can be used to study the etiology, genetic mutations and the complex, intricate relationship that the tumor has with normal surrounding brain tissue. If the sample is just the tumor itself, it can be used to study the genomics of the mutated cancer cells. Even if the sample that can be collected is the cerebrospinal fluid (CSF), it can be used to develop molecular diagnostics to detect cancer early in the brain by detecting the abnormal DNA in the CSF.¹³

Myths and misconceptions

1. Willingness to go for post-mortem tissue donation affects the care that I get while I am alive.

The process of post-mortem tissue donation only starts after the patient dies. There is no change in the treatment options and the utilization of available treatment resources. Further,

there are two teams, one for treatment and one for tissue harvesting to ensure that this would not happen.

2. Post-mortem tissue donation is not allowed in my religion.

Most religions of the world allow post-mortem tissue donation. We encourage you to speak with your priest or pastor for further clarification about this matter.

3. An open casket funeral is not an option after post-mortem tissue donation.

Brain tissue is collected using a standard post-mortem craniotomy incision. This is performed by an expert pathologist who is trained to perform autopsies. Adequate care is taken so as to ensure minimal changes to the external appearance.

4. Personal health information about the patient is made public after post-mortem tissue donation.

All samples and information collected are stored in a secure database and are de-identified so that the patient's name and personal information is never released to the general public.

5. Patients wake up from a coma, is that possible with brain death.

Science has proven that brain death is an irreversible condition and is equivalent to death.

6. The patient is not eligible for post-mortem tissue donation because of his illness.

Post-mortem tissues can be collected from most of the patients after their death. We encourage you to speak with the representatives, if you have any doubts. In cases of cancer, study of actual brain tissue is of crucial importance.

7. I cannot afford the cost of post-mortem tissue donation.

The family does not bear any cost or expenses in the process of tissue donation. Costs are covered by the agency who is collecting the tissue or the organ. Sometimes funeral expenses can also be covered.

When to approach families for tissue donation

The process of post-mortem tissue donation begins after the patient is declared dead. This is the most challenging time for any family who is grieving but it is critical to begin the discussion regarding tissue donation at this time itself. It is usually the representatives of the health care agencies who

initiate and conduct this discussion with the patient's family. Unfortunately, the physician or oncologist who has been treating this patient for months or years, who the family knows and trusts, is asked to stay out of this discussion.

The causes of this are multifactorial. Having this discussion requires a certain expertise. It has been proven before that having trained experts conduct this discussion ensures uniformity and has better success rates than having an untrained practitioner go through with it. It also frees up physicians to focus on the care of other patients under their care.

This might be a fallacy that needs to be fixed though. The solution might involve having physicians go through with the necessary training to conduct these kinds of discussions as they are the first point of contact with the patient and their families. The discussion can then be carried forward by the representatives of the organizations who will be collecting the actual tissue samples. This will save the shock that the family faces when they are expected to talk with a stranger in possibly one of the toughest times of their lives.

The approach also needs to be individualized. Some families and patients themselves are much more aware and accepting of their clinical diagnosis and prognosis. These patients are open to have discussions about palliative care including hospice. In these patients, it might be appropriate to introduce this discussion about post-mortem tissue donation after the patient and family has chosen hospice care. It might even bring some solace to the patient that they will be contributing to science and medicine even after their death and will help decrease the sorrow and hopelessness that might be experienced in such situations.

It is the opinion of the authors that physicians should take on a more central role in the process of post-mortem tissue donation. They are fighting cancer side by side with the patient when the patient is alive. Why should they leave their side after they pass?

EDUCATIONAL RESOURCES

Resources for the Family

By donating, families can undoubtedly further pediatric brain cancer research greatly but, it also adds an additional sense of purpose and closure to this child's life. The tailored materials on the GFAC website consist of video testimonials, printed pamphlets, and informational papers (this one included) which can further aid the understanding

of what goes on in tissue donation after getting informed by a physician. Families are able to hear firsthand from others that have gone through this process from a wide selection of family donation stories present on the website. These stories serve as a comforting resource for individuals to hear about the reasoning that other families went about the tissue donation process and how it has helped them heal and come to the realization that their child's life still has a deeper purpose following their death.

Another vital tool for families contemplating this process is the Swifty Foundations support services, "Family Support services offer a variety of resources, free of charge, to meet the needs of all who are touched by the premature death of a loved one".¹⁴ Some of these resources include over the phone family support counselors, personalized one-on-one support sessions with a counselor in the area, and the ability to receive referrals to other support groups or counselors.⁸ These same services also give families the ability to write to the transplant recipient as a further comforting measure while they are going through such a difficult period. This opportunity enables the family of the patient and recipient to form a relationship which furthers the families healing process as they are able to witness firsthand what significant effect their child's donation has made on another individual.

Resources for Clinicians

The Gift from a Child website provides an array of resources that can aid clinicians and other health professionals in being able to have difficult conversations with parents as well as patients in regards to the donation process. In regards to how clinicians should initiate these difficult conversations, it is imperative that these discussions don't come off as being rushed and there is a substantial time for both the family to process what is going on with their child and have an opportunity to fully comprehend all the information prior to making a definite decision. In general, this process should be personalized to the values of the child and the family. It is vital that the child has a strong say in this decision and has bought-in as it will help to take some of the pressure off of the family and provide the child with a feeling that some good is able to come from their unfortunate circumstance. Some parents shut down the idea without considering it because they do not take their child's opinion into consideration. By allowing the child to direct the conversation about their own life, their values can be better respected and they can feel a deeper sense of purpose from their lives. While approaching a child with this opportunity, it is vital that they have clear and open communication with

the family as well to create a dialogue where the child's voice is heard and valued.

Overall, “discussions about organ donation can greatly benefit patients’ families...[as] advance planning helps surrogates, relieving them of the burden of making such difficult decisions under stress” and during this time of grief.¹⁵ Following clinicians' explanation about the donation process, there is a group of individuals known as tissue navigators whose sole purpose is to help families understand where and how to go about donating. Within the Gift from a Child program, these tissue navigators work in ensuring that there is clear and open communication between the families and those retrieving the donated tissue so that everything goes about in a timely manner while still maintaining dignity and respect for the deceased child and the grieving family. By utilizing Swifty’s resources along with the outline that the authors of this paper will provide, physicians will be better equipped and educated on how to carry out this process.

ETHICAL ANALYSIS: RESPONSIBILITY OF CLINICIANS

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 benefited from the same progress. Pediatric high-grade glioma patients, like those with astrocytoma or glioblastoma multiforme, 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 years¹⁶.

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, national research programs, and philanthropic groups like the Swifty Foundation 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. For this to happen we need tissue samples from these patients to perform the appropriate research. Pediatricians need to be better educated on how to approach patients and their families about the importance of tissue donation. This is not an easy task, especially when the child is nearing death. However, as part of informed consent, pediatricians have the ethical responsibility to present tissue donation as a viable option in all these situations. 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 autonomy¹⁷. 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 in the future. 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 recommendations 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. This research is available through various educational resources listed above. Pediatricians need to be better educated about these resources, this should start in medical school and medical residency. Training our physicians early and educating them about these valuable resources is not only good for pediatric medicine but it will possibly save lives in the future.

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 deceived¹⁸. 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 an 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 friends¹⁹. Children may be vulnerable individuals but they have the ethical right to know and understand their diagnosis, prognosis, treatments and care plans. There are also programs that educate these children on how their tissue will be used in various research projects. Can their tissue grow tumors on mice? Could the children even name their mice? These educational tools help to educate patients and families about the need for tissue donation. 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."²⁰ 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. In 2022 it is estimated that 10,470 children (birth to 14 years) and 5,480 adolescents (aged 15-19 years) will be diagnosed with cancer. Globally, there are more than 300,000 children diagnosed with cancer each year. The overall incidence of cancer in the United States is on the increase averaging 0.8% increase per year since 1975. About 1 in 285 children will develop cancer before the age of 20. In 2018, 4,317 children were diagnosed with cancer in the United States, which is 47 children per day. Cancer is the number one cause of death by disease among children. Cancer alone represents nearly half of the top seven causes of death by disease in children aged 0-19 years.²¹ 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 healthcare 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 February 2, 2022, President Biden reignited the Cancer Moonshot Program to end cancer as we know it. The goals are to reduce the death rate from cancer by at least 50% over the next 25 years and improve the experience of people and their families living with and surviving cancer. As part of this program, President Biden has proposed a new vision for biomedical and health research in the Advanced Research Projects Agency for Health (ARPA-H) with the goal to improve the U.S. government's capabilities to speed research that can improve human health and to improve our ability to prevent, detect and treat a range of diseases including cancer. This will include accelerating clinical trials without compromising safety and effectiveness. He wants to turn our cancer care system into a learning system. When asked, most people with cancer are glad to make their data available for research to help future patients, if it can be done easily while respecting their privacy.²² Putting a face to cancer, as Michael Gustafson and his family 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.

CONCLUSION

If modern medicine is going to one day push pediatric brain cancer to a point where there are effective methods of treatment, then having focused research now is vital. To recap, patients and families want some good to come in the future from their circumstances but oftentimes, clinicians are not initiating these conversations to forgo the process. In order to circumvent these barriers to pediatric post-mortem tissue donation, clinicians should utilize the resources set before them by the Swifty foundation's Gift From a Child program. Once these clinicians are better educated on how this process works, what they are expected to do, and how and when to carry out these conversations, an adequate amount of research can happen and outcomes of childhood brain cancer can begin to become increasingly positive.

Further, hospitals establishing clear and effective protocols for carrying out this process would take pressure off of the clinician and would lead to more donations occurring.

On the side of the patient and family, it is imperative that they are fully informed and understand how they can help to push the development of future treatment for the conditions that they or their loved ones suffer from. In order to make this process as comfortable and easy for the family as possible, clinicians should make them aware of resources like family companions, the 1-800-support number, contact information to those who have benefitted from such generous gifts, and family stories of how this process transformed the way that they viewed their unfortunate circumstances. As the youth are the successors of the world, it is vital that everything in the power of modern medicine is done to work towards eliminating the diseases that are keeping them from reaching their full potential. We have seen that an increase in tissue donation would push science to further analyze the unanswered questions of how these mysterious cancers work. Therefore, it is our humble opinion that healthcare today has a responsibility to do everything in its power to educate those who are in a position to increase the frequency of pediatric post-mortem brain cancer tissue donation to ultimately decrease the amount of innocent lives that are taken each year.

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