

Overcoming Autopsy Barriers in Pediatric Cancer Research

Jennifer L. Alabran, MSc,^{1,2} Jody E. Hooper, MD,³ Melissa Hill,⁴ Sandra E. Smith,⁵ Kimberlee K. Spady,⁵ Lara E. Davis, MD,^{1,2,6} Lauren S. Peterson, BS,^{1,2} Suman Malempati, MD,^{2,6} Christopher W. Ryan, MD,^{7,8} Rae Acosta, RN,^{2,6} Sheri L. Spunt, MD,⁹ and Charles Keller, MD^{1,2*}

Background. More than 13,000 children annually in the United States and Canada under the age of 20 will be diagnosed with cancer at a mortality approaching 20% [1,2]. Tumor samples obtained by autopsy provide an innovative way to study tumor progression, potentially aiding in the discovery of new treatments and increased survival rates. The purpose of this study was to identify barriers to autopsies and develop guidelines for requesting autopsies for research purposes. **Procedure.** Families of children treated for childhood cancer were referred by patient advocacy groups and surveyed about attitudes and experiences with research autopsies. From 60 interviews, barriers to autopsy and tumor banking were identified. An additional 14 interviews were conducted with medical and scientific experts. **Results.** Ninety-three percent of parents of deceased children did or would have consented to a

research autopsy if presented with the option; however, only half of these families were given the opportunity to donate autopsy tissue for research. The most significant barriers were the physicians' reluctance to ask a grieving family and lack of awareness about research opportunities. **Conclusions.** The value of donating tumor samples to research via an autopsy should be promoted to all groups managing pediatric cancer patients. Not only does autopsy tumor banking offer a potentially important medical and scientific impact, but the opportunity to contribute this Legacy Gift of autopsy tumor tissue also creates a positive outlet for the grieving family. Taking these findings into account, our multidisciplinary team has developed a curriculum addressing key barriers. *Pediatr Blood Cancer* © 2012 Wiley Periodicals, Inc.

Key words: autopsy; cancer; childhood; end-of-life care; research

INTRODUCTION

Although survival rates have greatly increased over the past decades for some pediatric cancers, certain subtypes including high-risk sarcomas and diffuse intrinsic pontine gliomas (DIPG), have an unimproved or near-zero survival rate despite novel therapies [3,4]. This observation highlights the need for improved treatments and new research approaches for rare pediatric tumors. One way to advance knowledge of rare cancers is to study the disease at all stages including the point when treatment has failed and the child has succumbed to the disease. Obtaining quality tumor samples that may be donated directly to a research laboratory or frozen in a biorepository for future research has several important benefits. Autopsy samples allow researchers to collect the most biologically aggressive component of the tumor which has not been eradicated by any treatment administered, to sample multiple sites of disease, and to collect larger specimens than might be possible in a living patient [5]. Fresh samples may provide highly valuable tissue for researchers to study because living cell tumor cultures can sometimes be established; nevertheless, frozen or even paraffin-embedded samples have already proven to be of great value and numerous examples can be cited to show how such autopsy samples have revealed fundamental mechanisms of tumor progression [5–12].

Despite these significant advances in the understanding of pediatric cancers facilitated by autopsy tissue for research, the number of tumor donations from autopsies remains small. To some extent this reflects a general decline in the frequency of autopsies over the decades in the United States where an autopsy is only performed in 5% of all hospital deaths [13]. This decline has been attributed to physicians' minimal knowledge regarding the procedure, physicians' unwillingness to ask for consent, the assumption that families will not consent, uncertainty of how to approach the family, and the rationale that improved imaging and clinical laboratory tests already shed light on the cause of death [13–15]. However, some studies suggest that autopsy continues to identify unrecognized medical problems even in patients dying of cancer [16,17].

Many physicians currently have not had adequate training in the autopsy procedure [18] and as a result may be insufficiently aware of the benefits. Not only do tumor samples from an autopsy for research offer a potentially important scientific impact, but the opportunity to contribute a Legacy Gift (i.e., the donation of autopsy tumor tissue to science) may also create a small positive aspect for an otherwise devastating event for the grieving family. The goal of this study was to identify barriers to performing pediatric autopsies for research purposes and to develop guidelines that institutions may use to encourage physicians to address tumor donation with families.

Additional Supporting Information may be found in the online version of this article.

¹Pediatric Cancer Biology Program, Papé Family Pediatric Research Institute, Oregon Health & Science University, Portland, Oregon; ²Department of Pediatrics, Oregon Health & Science University, Portland, Oregon; ³Department of Pathology, Oregon Health & Science University, Portland, Oregon; ⁴Northwest Sarcoma Foundation, Portland, Oregon; ⁵Parent Advocates; ⁶Division of Pediatric Hematology/Oncology, Oregon Health & Science University, Portland, Oregon; ⁷Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon; ⁸Division of Hematology/Oncology, Department of Medicine, Oregon Health & Science University, Portland, Oregon; ⁹Department of Oncology, St. Jude Children's Research Hospital and Department of Pediatrics, University of Tennessee Health Science Center, Memphis, Tennessee

Grant sponsor: NCI; Grant number: NCI R01 CA 133229-04S2.

C.K. and C.W.R. are members of the Board of Directors of the Northwest Sarcoma Foundation, a co-recipient of NCI R01 CA 133229-04S2.

*Correspondence to: Charles Keller, MD, Pediatric Cancer Biology Program, Papé Family Pediatrics Research Institute, Department of Pediatrics, Oregon Health & Science University, 3181 S.W. Sam Jackson Park Road, MC-L321, Portland, OR 97239-3098.
E-mail: keller@ohsu.edu

Received 30 May 2012; Accepted 16 August 2012

METHODS

This study was performed under approval of the Oregon Health & Science University institutional review board. Parents were informed of this study by the Northwest Sarcoma Foundation (as this study originally focused on pediatric sarcomas) or by other pediatric cancer patient advocacy groups, particularly the pediatric brain tumor community who participated in unexpected large proportion. Parents who were interested in participating in this study self-identified and contacted the investigators. After a verbal or written consent, interviews were conducted by a single, Master level interviewer who has 5 years of experience working with cancer patients and their families, and interview results were transcribed for analysis. Interviews were conducted from September 2010 through August 2011 in which barriers to autopsy consents for research purposes were identified by parents. Children of the parents interviewed were newly diagnosed, in remission, recently relapsed, in hospice care, or deceased. Emphasis for families who were interviewed was placed on pediatric tumors, such as metastatic rhabdomyosarcoma or diffuse intrinsic pontine glioma, for which outcomes have remained dismal for >40 years [4,19]. Questions asked in the survey are given in Table I. Medical professionals were identified by parent-community advocates as professionals with first-hand experience in research autopsies and were also interviewed to identify barriers from the medical perspective. Scientists who have been highly involved in accepting tumor donations were also interviewed to identify barriers from the research side. In addition, medical staff and scientists who had little or no experience in tumor donation

were interviewed to identify perceived barriers. Upon completion of the interviews, a multidisciplinary team integrated findings to design a course for medical professionals on how to approach autopsy discussions with parents.

RESULTS

Eighty-four families were self-referred to this study after an initial parent advocate contact, as detailed in the Methods Section. Twenty-three families did not follow up to an email or phone call to schedule an interview, and one family later declined to be interviewed. The other 60 parents, 45 mothers and 15 fathers, were interviewed representing 54 children and more than 40 different hospitals across the United States, Canada, and Australia (Table II). At the time of the interview, 70% of the children were deceased while the remaining 30% were alive, among whom one-fourth were on active treatment for relapsed disease. Forty percent of the parents were not aware of tumor donation but would have considered an autopsy for the purpose of research samples in the event of the child's death. All of the families whose child was alive at the time of the interview would consider an autopsy if their child were to die. Sixty-one percent of the families whose child was alive at the time of the interview donated tumor tissue at the time of diagnosis (biopsy) or from surgery.

The attitudes of parents of deceased children in this cohort regarding autopsies for the purpose of research samples were very positive. If the opportunity to donate tumor tissue to research had been presented, 93% of parents state they did or would have

TABLE I. Questions Used During Phone Survey to Assess Views on Autopsies and Tumor Banking

For family interviews:

Did your child's medical team present the option to donate samples to research to you?

If so, did you and your child ever donate tumor samples? When?

If not, how did you find out about donating to research?

In the event that your child's health fails, would you consider an autopsy for research purposes?

What barriers may exist in obtaining consent for an autopsy for research purposes?

Did you and your child decide to leave a Legacy Gift when he or she passed away?

If an autopsy was performed, was it suggested by the doctor or requested by you?

If you approached the medical staff about donating, were they receptive to your request?

When and how would you like to be approached about the Legacy Gift opportunity?

Who would you like to speak to you first about tumor donation?

Would your child be part of the decision making process?

Would your religion or cultural beliefs play a role in deciding to donate?

Why would you consider a Legacy Gift?

What would be the best way to educate families about tumor donation?

Would you want to know what research was being done with your child's Legacy Gift?

If so, what would be the best way to communicate this information to you?

For rhabdomyosarcoma families: Are you aware of COG's D9902 protocol?

For medical professional interviews:

In your training, were you exposed to autopsies?

How often do you request an autopsy?

Do you consider autopsies for research purposes?

What are the current challenges of tumor donation?

How do you think these issues could be addressed?

Would you consider tumor banking if existing protocols were established at your institution?

When would you approach the family/patient to discuss this option? When is the best time?

For an adolescent patient, who would you approach first, the patient, family or both?

What have been some of the outcomes from having an autopsy discussion?

Do you think religion/culture plays a role in asking a family or the decision the family may make?

What tools would be helpful for you to have when you approached a family about autopsies?

TABLE II. Demographics of Interviewees

Patients/families			
Age of child at diagnosis	Median: 6 years; range: 3 weeks to 15 years old	n = 51	85%
Age of adolescent or young adult at diagnosis	Median: 20 years; range: 16–40 years old	n = 9	15%
Time from diagnosis to interview	Median: 39 months; range: 9–208 months	n = 60	100%
Time from death to interview	Median: 19 months; range: 1–70 months	n = 42	70%
Country of origin			
	United States	n = 57	95%
	Canada	n = 2	3%
	Australia	n = 1	2%
Diagnosis			
Brain tumors			
	Diffuse intrinsic pontine glioma	n = 20	33%
	Medulloblastoma	n = 8	13%
	Glioblastoma multiforme	n = 1	2%
Leukemia/lymphomas			
	Hodgkins lymphoma	n = 3	5%
	Acute lymphoblastic leukemia	n = 1	2%
Solid tumors			
	Rhabdomyosarcoma	n = 19	32%
	Osteosarcoma	n = 3	5%
	Ewings sarcoma	n = 1	2%
	Intimal sarcoma	n = 1	2%
	Undifferentiated sarcoma	n = 1	2%
	Mesenchymalchondrosarcoma	n = 1	2%
	Teratoma	n = 1	2%
Religion			
	Christian/Catholic	n = 20	33%
	Jewish	n = 5	8%
	Mormon	n = 1	2%
	Spiritual (unspecified)	n = 2	3%
	No religious belief	n = 20	33%
	Not identified	n = 12	20%
Medical professionals			
	Physicians ^a	n = 8	57%
	Scientists ^a	n = 2	14%
	Pediatric nurses	n = 2	14%
	Social workers	n = 3	21%
	Other	n = 1	7%

^an = 2 (14%) interviewees were both physicians and scientists.

consented to a research autopsy and donated tumor tissue to science (7% would not have, whether families were aware of the option or not); however, only half of the families of deceased children who would consider an autopsy were presented with the opportunity to donate autopsy tissue for research. The remaining half of the families of deceased children who would consider a Legacy Gift were not made aware of the option until after the child died or were told there was no benefit to an autopsy and that tumor samples were not needed. In three instances for which a family had made the decision to donate, parents were told tumor tissue was not needed. In four other instances, the medical staff was unable to arrange an autopsy requested by the families, thereby adding to the reported grief of the family. Seven percent of the families were aware of tumor donation through other parents but chose not to have an autopsy performed for the purpose of research samples. Informative case histories are provided online which describe what may happen due to poor communication among all parties involved in an autopsy and tumor donation (Supplemental Text I).

Although physicians may routinely ask families about autopsy for the purpose of research samples, none of the families interviewed were approached by a physician requesting an autopsy; however, parent-driven request for autopsy was frequent in our cohort because of the enriched inclusion of DIPG patients and families. The Children’s Oncology Group (COG) D9902 Biology Protocol has for a decade permitted tissue, particularly

rhabdomyosarcoma, to be donated to a tumor bank at all stages of disease including post-mortem. In our study, parents of children with rhabdomyosarcoma were asked if participation in D9902 was presented as an option to the family. All 19 children were being treated at a COG affiliated hospital where D9902 was open. Only 2 out of 19 families whose child had rhabdomyosarcoma knew of the protocol and understood when donations could be made to the tumor bank, whereas 8 out of 19 knew of the protocol but thought the protocol was for tumor samples from diagnosis only and did not contribute at a later time point. The remaining 9 out of 19 families reported that the protocol was not presented in any form to the family.

Family-related and medical professional-related barriers were identified and frequency of each barrier was recorded (Table III). Parents most frequently cited the physicians’ reluctance to ask (52%) and the lack of educational information available for families (47%) as major barriers. Medical professionals cited logistics (71%) as the major barrier, and similar to the family-reported barriers, also cited the physicians’ reluctance to ask due to the prospect of having an uncomfortable conversation with a family (50%). Additional barriers identified were the lack of awareness of tumor donation and the value of tumor samples to research, the uncertainty as to when to discuss tumor donation with a family, the absence of a motivation to ask (e.g., a current COG or institutional protocol), the lack of an immediate reward or recognition for the physician, the uncertainty about protocols and hospital

TABLE III. Frequencies of Identified Barriers to Autopsies for Research Purposes

Family identified:
Physicians' reluctance to ask
Lack of educational information for parents
Medical staff unaware of tumor donation option and/or value
Uncertain when is an appropriate time to discuss tumor donation
Logistics (e.g., coordination, location of death, transportation, cost, etc.)
No motivation or immediate reward for the physician
Medical staff identified:
Logistics (e.g., coordination, location of death, transportation, cost, etc.)
Physicians' reluctance to ask
Medical staff unaware of tumor donation option and/or value
Uncertain when is an appropriate time to discuss tumor donation
Lack of educational information for parents
Coordination with research scientists
Lack of protocols
No motivation or immediate reward for the physician

tissue collection procedures, and the coordination with the research institution who would obtain the samples.

Interviewed parents were asked which member of the medical team should approach families about tumor donation and when the best time would be to discuss the possibility of donating tissue to research via an autopsy. In most cases (90%), parents preferred that the primary physician initiate the discussion but felt that subsequent questions could be answered by anyone on the medical team. The remaining 10% of families suggested a nurse, a hospice care provider, or anyone who showed compassion and understanding of the situation.

Acknowledging that the time may be different for each family, parents identified two times as the most appropriate and conducive to gaining consent. Although the majority of parents felt that the time of a child's initial diagnosis can be overwhelming, 43% felt that exposing parents to the general concepts of tumor donation and research at diagnosis is valuable (Supplemental Fig. 1). Second, 73% of parents suggested that the subject of an autopsy for tissue donation might be usefully broached after the discussion changes from curative treatment options to palliative care options. Uniformly, parents felt that after death was the least desirable time to initially discuss a research-related autopsy.

Families also articulated what they considered to be the most appropriate forms of follow-up once a donation has been made to science. Although families vary in the amount of details they wish to receive, parents felt that information provided by the researcher when the family was ready to receive this information would be valuable and would honor the child. In particular, learning of medical advances made through research from the tissue donated would be a positive experience and validate the child's Legacy Gift. Fifty-eight percent of parents reported that even if the donation does not result in the establishment of a cell line [10], emphasis should be placed on the positive contributions of how a donation that resulted in frozen or fixed tissue still contributed to the knowledge of science and that particular type of cancer [7,11].

Religious beliefs identified by the families are shown in Table II. For our interviewees, religion would not have forbidden an autopsy for the purpose of research samples for any family.

Many families (72%) stated that tumor donation was seen as a positive way to give back to another's life and was felt to be supported by the family's religious and spiritual beliefs.

DISCUSSION

While we acknowledge that our study has an inherent bias due to the method in which families were non-randomly self-referred to us to be interviewed, with a large representation of pediatric sarcoma and brain tumor families, much can be learned from these interviews. The current study sheds light on a paradigm of particular interest: while a national protocol is in place for tissue donation for rhabdomyosarcoma, eligible families were not aware of the option to donate resulting in low autopsy rates. In contrast, the community of parents with children diagnosed with DIPG is peer-educated about the need for tissue for research because tumor tissue is not otherwise routinely biopsied or resected at any point during the standard treatment in the United States. Families in this DIPG community thus advocate for donation individually despite the lack of a formal protocol, thereby leading to a high autopsy rate. In our study, the autopsy frequency was ten-fold higher than other reported contemporary rates [13], which we attribute to the presence of families of patients with DIPG among our interviewees.

Medical teams often believe grieving parents are reluctant to consent to an autopsy but the real barrier may be that parents are not given the opportunity to consent. The literature reports that many physicians will not ask for an autopsy because the physician believes that the family is already emotionally distraught, the cause of death is known [20] and that asking will only upset the family more [21]. Nevertheless, an autopsy for the purpose of research samples may offer great benefits to the bereaved family [22,23]. This altruistic act can give the family a sense of empowerment and control over the child's death and provide the family with hope that something good might come from their devastating experience [6,24]. In addition to the benefits to families, an increase in autopsies might also increase the range of tumor samples available and lead to a new understanding of pediatric cancers or even new therapies.

Although some institutional and national tissue banking protocols to collect autopsy tumor tissue exist, the literature reflects that very few autopsies have been performed for research purposes [5]. Currently only two COG protocols exist that includes postmortem samples to be donated to a biorepository. In order to increase tissue donation and sample availability, additional COG autopsy protocols will likely need to be written and physician awareness increased. Contributing to a centralized tissue bank, such as the COG Biorepository that has a scientific oversight committee, could be one approach to establishing a national tumor tissue bank of autopsy samples.

One of the barriers identified by both the family and medical staff was the medical professionals' lack of awareness of tumor donation options and the potential value of an autopsy. Education on the practical aspects of autopsy and the communication skills required to obtain autopsies can begin in medical or nursing school and continue throughout a medical professional's career so that the value is understood and the approach to obtaining autopsy consent is not forgotten [13,15]. Emphasizing the value of tumor tissue to science from the beginning of the child's diagnosis and throughout the course of disease is an important

step in educating a family about research opportunities. Families who have contributed tumor tissue during the child’s biopsy or resection may be better prepared to have a Legacy Gift discussion.

In our study, the lack of educational information for families about tumor banking and research opportunities was identified as a barrier. Parents whose child had undergone autopsy for research had learned about tumor donation through online avenues including listservs, blogs and foundation websites. To address the lack of information available for families and provide guidelines for medical professionals, we have designed handouts for physicians, including pathologists, and the families (www.ccurefast.org). Providing guidelines for a researcher is challenging as each scientist will have different needs for tissue acquisition and shipping. Similarly, providing guidelines for funeral homes is also beyond the scope of this report as such guidelines will depend on individual state laws.

One of the major barriers identified was physician reluctance to ask. The physician might begin by assessing the family’s understanding and engagement in the child’s treatment, and whether or not to include the patient in the conversation. The religious or cultural beliefs of a family are important issues to be considered even though the majority of religions allow autopsies to be performed as an individual choice or under special circumstances that benefit the living [25] (Table IV). Parents may ask how quickly the autopsy needs to happen after the child expires. Logistically the time limitations for burial (e.g., within 24 hours for Judaism) are consistent with the most successful timeframe for collecting the most valuable tissue (i.e., less than 6 hours [8,26] after death) although valuable tissue has been obtained at 14 hours postmortem [10].

A family may request as little as a postmortem biopsy or may permit a partial or full autopsy to be performed that would benefit both the medical and scientific communities. In an even less invasive approach, circulating tumor cells collected from a post-mortem blood draw within 3–6 hours can also be used to establish a viable cell line [12] for research. Although offering such limited autopsies is appropriate and may result in higher consent rates, the physician should emphasize the potential value of a full autopsy and the additional investigational and educational benefits an autopsy offers [5,14].

Some flexibility may exist in deciding which medical professional is the best person to discuss tumor donation and an autopsy with the family (e.g., if available, a palliative care team member or social worker could be present with the physician during the discussion to help answer questions a family may have about the

process). In order to elicit the family’s wishes, one may ask questions about what is important to the family about remembering and honoring the child. Conversations may be most productive when the medical professional can convey the benefits to the family, future families, and medical science, and if families are given examples of how tissue donated by other families has contributed to a better understanding of pediatric cancers. Families noted that when the physician informs parents that curative options have been exhausted, a family may be in denial about the child’s prognosis and may not wish any further procedures to the child before or after death, resulting in lower consent rates. Nevertheless, parents preferred that the option be presented well prior to the child’s death, allowing them to discuss the idea and make proper arrangements in advance. Empathy and a willingness to address the questions a family may have about the autopsy procedure are important, although answers need not be especially graphic.

Once a family has decided to donate the child’s tumor to research the medical professionals should arrange for the donation to happen in a seamless manner. Communication between each specialty involved will be the key to a successful donation. Identifying one member of the team who will be the single point of contact and who will ensure that the family’s wishes are met regardless of the obstacles was reported as an important aspect of relieving the family of logistical responsibilities and improving the quality of the end of life experience. For example, when a child’s death is imminent, the pathologist could work with the Decedent Affairs office (if available) to coordinate the logistics of the autopsy, as well as contact the researcher to inform them of the current status of the patient and ensure that the samples are obtained correctly.

Whether a child who dies in hospice or outside of hospital care can be transported to the autopsy facility will be institution specific and ideally should be explored with the help of the pathologist well before the time of death. Upon the child’s death, it should be possible for the family to be provided with complete assurance that the donation has been seamlessly prearranged so as to relieve any additional stress to the family. Information from the autopsy becomes part of the child’s medical record and is available to the family whenever they are able and willing to receive the information. Finally, if a family chooses to donate to a specific laboratory and request an ongoing dialogue, the researcher should communicate with the family that the tumor samples have been received. Later, if the family requests, the research findings derived from the donated samples might be shared. However, this dialogue requires consideration of the Health Insurance Portability and Accountability Act privacy regulations as well as state and local ordinances. If the Legacy Gift is donated to COG, tracing the results is not possible.

In conclusion, while acknowledging that any conversation about an autopsy is emotionally challenging, physicians should recognize that many families wish to be presented with the option of postmortem donation. Research autopsies are indeed possible in many cases and are often valuable to not only the pediatric cancer research field but the families as well.

ACKNOWLEDGMENT

We are grateful to the families who participated in this study and provided their insight. Funding was provided by the NCI via

TABLE IV. Autopsy Perspectives in Major World Religions

Religion	Strictest view or doctrine regarding autopsy
Buddhism	Body should be undisturbed for 3 days following death to allow soul to continue on to the next life
Christianity	No official doctrines prohibiting autopsy, except in Christian science
Hinduism	Autopsy may upset the immortal soul
Islam	Burial should occur immediately and autopsies are generally not allowed
Judaism	Burial should occur as soon as possible and with the body in its entirety

the Caroline Pryce Walker Conquer Childhood Cancer Act of 2008 (NCI R01 CA 133229-04S2). We thank Linda Stork, Oren Becher, and Alexandra Swanson for their critical revision of the manuscript and for important intellectual contribution. We also thank Nancy Goodman for her inspiration and support, Maria Costello for graphic design assistance, Caroline Macuiba for Legacy Gift workshop design, and Heidi Peck (OHSU Decedent Affairs) for her provision of study materials.

REFERENCES

- National Institutes of Health. Cancer Incidence and Survival Among Children and Adolescents: United States Seer Program 1975–1995. Surveillance Research Program. <http://seer.cancer.gov>. Published 1999. Accessed January 25, 2011.
- 2011 November 2, 2011 Canadian Cancer Society. <http://www.cancer.ca> Published 2011. Accessed November 2, 2011. <http://www.cancer.ca/Canada-wide> Accessed November 2, 2011.
- Group AaYAOPR. U. S. Department of Health and Human Services. National Institutes of Health. Closing the gap: research and care imperatives for adolescents and young adults with cancer. Adolescents and Young Adults Oncology Progress Review Group. Published 2006. Accessed November 2011.
- Donaldson SS, Laningham F, Fisher PG. Advances toward an understanding of brainstem gliomas. *J Clin Oncol* 2006;24:1266–1272.
- Spunt SL, Vargas SO, Coffin CM, et al. The clinical, research, and social value of autopsy after any cancer death: A perspective from the Children's Oncology Group Soft Tissue Sarcoma Committee. *Cancer* 2012;118:3002–3009.
- Angelini P, Hawkins C, Laperriere N, et al. Post mortem examinations in diffuse intrinsic pontine glioma: Challenges and chances. *J Neurooncol* 2011;101:75–81.
- Zarghooni M, Bartels U, Lee E, et al. Whole-genome profiling of pediatric diffuse intrinsic pontine gliomas highlights platelet-derived growth factor receptor alpha and poly (ADP-ribose) polymerase as potential therapeutic targets. *J Clin Oncol* 2010;28:1337–1344.
- Broniscer A, Baker JN, Baker SJ, et al. Prospective collection of tissue samples at autopsy in children with diffuse intrinsic pontine glioma. *Cancer* 2010;116:4632–4637.
- Wu G, Broniscer A, McEachron TA, et al. Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. *Nat Genet* 2012;44:251–253.
- Monje M, Mitra SS, Freret ME, et al. Hedgehog-responsive candidate cell of origin for diffuse intrinsic pontine glioma. *Proc Natl Acad Sci USA* 2011;108:4453–4458.
- Paugh BS, Broniscer A, Qe C, et al. Genome-wide analyses identify recurrent amplifications of receptor tyrosine kinases and cell-cycle regulatory genes in diffuse intrinsic pontine glioma. *J Clin Oncol* 2011;29:3999–4006.
- Burton KW. Pioneers: A lasting gift. *Science* 2007;315:23. *Science* 2007; 23.
- Hooper JE, Geller SA. Relevance of the autopsy as a medical tool: A large database of physician attitudes. *Arch Pathol Lab Med* 2007;131:268–274.
- Burton JL, Underwood J. Clinical, educational, and epidemiological value of autopsy. *Lancet* 2007; 369:1471–1480.
- Charlton R. Autopsy and medical education: A review. *J R Soc Med* 1994;87:232–236.
- Pastores SM, Dulu A, Voigt L, et al. Premortem clinical diagnoses and postmortem autopsy findings: Discrepancies in critically ill cancer patients. *Crit Care* 2007;11:R48.
- Shojania KG, Burton EC, McDonald KM, et al. Changes in rates of autopsy-detected diagnostic errors over time: A systematic review. *JAMA* 2003;289:2849–2856.
- Rosenbaum GE, Burns J, Johnson J, et al. Autopsy consent practice at US teaching hospitals: Results of a national survey. *Arch Intern Med* 2000;160:374–380.
- Oberlin O, Rey A, Lyden E, et al. Prognostic factors in metastatic rhabdomyosarcomas: Results of a pooled analysis from United States and European cooperative groups. *J Clin Oncol* 2008;26:2384–2389.
- Stolman CJ, Castello F, Yorio M, et al. Attitudes of pediatricians and pediatric residents toward obtaining permission for autopsy. *Arch Pediatr Adolesc Med* 1994;148:843–847.
- Grunberg SM, Sherrod A, Muellenbach R, et al. Analysis of physician attitudes concerning requests for autopsy. *Cancer Invest* 1994;12:463–468.
- Sullivan J, Monagle P. Bereaved parents' perceptions of the autopsy examination of their child. *Pediatrics* 2011;127:e1013–e1020.
- Oppewal F, Meyboom-de Jong B. Family members' experiences of autopsy. *Fam Pract* 2001;18:304–308.
- Millar T, Lerpiniere C, Walker R, et al. Postmortem tissue donation for research: A positive opportunity? *Br J Nurs* 2008;17:644–649.
- Burton EC, Gurevitz, Stacy A. Religions and autopsy. 2010; <http://emedicine.medscape.com/article/1705993-overview>.
- Embuscado EE, Laheru D, Ricci F, et al. Immortalizing the complexity of cancer metastasis: Genetic features of lethal metastatic pancreatic cancer obtained from rapid autopsy. *Cancer Biol Ther* 2005; 4:548–554.

Supplemental Material

Although each child's case history for this project offered invaluable information, we have chosen select ones here that address major issues with current autopsy tumor banking procedures. We also provide one vignette demonstrating how tumor donation can change the outlook of pediatric cancer research. After each case history, solutions are offered that may circumvent specific pitfalls.

Case History #1. The Importance of a Legacy Gift to a Family

A three year old girl was diagnosed with diffuse intrinsic pontine glioma. When the family realized that the tumor was growing and was very aggressive, the patient's mother organized the paperwork for tumor donation. This included very specific instructions for half of the donation to be kept locally while the other half was to be sent to a designated research institution. The patient's physicians met with the pathology team and a representative from the tumor bank to ensure that the donation would go smoothly and a detailed letter was sent to the family explaining what would happen upon the child's death.

Six months later the patient was admitted to the hospital. The family was asked at that time if the advanced directives and tumor donation paperwork from the previous hospital stay still applied and they affirmed this. Weeks later, the patient died. Four hours after her death, the patient's parents told the nursing staff that they were ready for the tumor to be removed from their daughter's brain. The family's wishes were respected and the body was taken to the morgue where the pathology team was on standby and ready to perform the autopsy.

The next day the family returned to the hospital with other family members who wished to view the body. Upon the patient's father asking the social worker about the size of the tumor, the parents were advised by the pathologist that the tumor had not been entirely removed. The parents were told that slides had been prepared for pathology and that there were photos available if they wanted to see them. The parents insisted that they wanted their daughter to be 'rid' of the tumor, and they wanted the entire tumor to be donated for research. Making the initial decision to have an autopsy had been difficult, especially because of the graphic, detailed letter that explained what would happen. Given the situation, the family had to make a decision to request for a second time that the tumor be removed. Although the patient's tumor was removed at that time, 24 hours had now passed and the tumor could have been donated to research within five hours. Half of the tumor was eventually sent to the research institution but the family has not been able to obtain any further information on how the sample was used.

This scenario not only shows the importance of clear communication to all involved about the purpose of the autopsy and the wishes of the patient and family, it also shows that different communication methods may be used with varying effectiveness. Although this family chose to read the graphic, detailed report explaining the autopsy procedure, many families could be made distraught by such information. Approaches should be individualized. Additionally, had the family not inquired about the tumor, the child's tumor never would have been removed making the autopsy seem as though it was done in vain. Recognition of the value of the tumor samples and follow-up communication between the researcher, the family, the clinician and the pathologist when specimens are received might help to avoid such a situation. Follow up from the researcher with the family when new findings have been discovered is important. Although the family was upset about the circumstances, the family finds peace in knowing their daughter's tumor was donated to research. They believe that the tumor holds key answers to finding better treatments and a cure.

Case History #2. The Value of Communication and Teamwork.

A fourteen year old girl was diagnosed with diffuse intrinsic pontine glioma upon biopsy, and the patient was treated with radiation and chemotherapy. While the patient was in hospice care, the family approached the medical team to express the patient's desire to help others with the same type of brain cancer by donating her tumor to research.

The patient died just under twenty months from diagnosis. In the hours following her death, the patient's parents were devastated to realize that though tumor tissue donation had been discussed in the medical team, the logistics

had not been arranged. The research institution was unable to coordinate the collection of the tissue at that point because of the rural location of the patient at the time of death.

The following day, a Saturday, a representative of the state eye bank offered to send someone directly to the funeral home to recover the tumor tissue. With help, the family was able to reach a scientist who believed that the tissue donation would still be very useful despite the fact that the body had been embalmed. The scientist worked with the family to obtain the necessary consent forms, while the eye bank representative drove through a winter storm to recover the tumor tissue within 24 hours of the patient's death.

The family was grateful to all who went the extra mile to see that the patient's wish was fulfilled. They hope that their daughter's gift will help researchers find better treatment options for children with diffuse intrinsic pontine glioma.

This scenario might be avoided in future situations by fully understanding the family's wishes upon the death of the child. Advance planning with all participants is key to ensure that all possible arrangements are in place prior to the child's death, especially if the child dies at home. Active communication is important not just with the primary physician and the family but also with the researcher, pathologist, and possibly the funeral director. Often funeral directors will play a large role in ensuring the transportation of the child. Given the time to discuss the logistics, it may be possible that either transport or an autopsy service provider close to the family's home can be arranged.

Case History #3. A Legacy Gift Sheds Light on a Deadly Disease.

A five year old boy was diagnosed with a large diffuse intrinsic pontine glioma. Understanding the grim prognosis, the family approached a physician to ask if donating the child's brain tissue could possibly help other children after his death, and did decide to donate tissue to research when that time came in hopes that his death would not be in vain. The child began the standard six weeks of radiation therapy but due to the patient's deteriorating condition, the family chose to stop treatment after just a few days.

The patient died less than two months after diagnosis. Following a limited autopsy and tissue collection shortly after death, researchers were able to culture what would become the world's first reported DIPG cell line and to develop the first reported DIPG xenograft mouse model. This work has resulted in a publication in a high-impact scientific journal¹³. Researchers on many continents are using the cells to conduct drug testing, and the animal model continues to be used in pre-clinical studies.

This vignette is an example of how both science and medicine can be impacted by tumor donation. The family finds great comfort and strength in knowing that the patient's legacy lives on because of their selfless gift to science and the priceless tumor samples donated to research provide an innovative way to study pediatric cancers and offer hope to all involved that new treatments will be discovered.

Case History #4. A Sub-optimally Planned Legacy Gift

A thirty-one year old woman was diagnosed with a pontine glioblastoma multiforme and treated with radiation and chemotherapy. Fifteen months later when her cancer had progressed, the family decided they would donate her tumor to science with hope that her gift might lead to a cure or better treatment options. When the mother contacted a researcher to discuss tumor donation, the researcher responded with great enthusiasm. Later on, the researcher realized that because the patient was not seen at the researcher's institution, an autopsy could not be performed at that institution. The researcher recommended that the patient's mother contact a local hospital to ask if a limited autopsy could be done there.

A few weeks later, the researcher advised the family that a colleague was able to arrange for the autopsy at a nearby institution. The third party contacted the family to discuss the logistics and requested that the paperwork be signed by the end of the week so they could meet with the pathologist and discuss the donation. Although the family tried to contact the institution throughout the week, they did not receive the paperwork or speak with the pathologist before the week ended.

The patient died early the following week and was transported to the funeral home. The family, realizing that the consent forms were not signed, contacted the researcher who immediately sent the forms, and the paperwork was completed. The funeral home was advised to transport the body immediately to the hospital. Upon arrival, the driver was advised that the death certificate was not sufficient documentation, but that a “transit permit” was required. Two and a half hours later, the pathologist refused to handle the donation without the proper paperwork.

The family was now the *de facto* primary responsible party for the tissue donation, and despite their grief sought to ensure success of the tissue donation. Unfortunately, it would be morning before the proper paperwork could be obtained. Jewish burial customs include arranging the burial as soon as possible after death, typically in the first 24 hours. Given this timeline, the tumor donation could not be accommodated and the family was forced to forego the donation that had meant so much to them.

This scenario might be avoided in future situations by identifying a single point of contact for the family who can coordinate all aspects of the process. The family should not be the responsible party for coordinating the autopsy. Researchers should also be aware that while consents for research can be completed by the patient, in many states an autopsy consent cannot be completed by the patient before death but must be signed by a family member after the demise. Furthermore, the awareness of local and state ordinances should also be considered as the permit in this scenario was needed for transit between two counties within the state and was required by the institution. All parties involved in a donation should know who is responsible and how to proceed.