Rapid Autopsy Programs and Research Support: The Pre– and Post–COVID-19 Environments

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Abstract: Each rapid autopsy is a powerful opportunity to supply multiple researchers with many valuable tissue specimens at the same time. Since the beginning of the development of rapid autopsy, the overriding organizing principle for all rapid autopsy programs has been that the samples or organs must be removed and processed as rapidly as possible. To accomplish this, some rapid autopsy programs are focused on only 1 tumor type, whereas others accept patients demonstrating all tumor types and sometimes other diseases as well. Rapid autopsy programs are logistically complicated and labor-intensive structures; therefore, the key to their success is program flexibility and maintaining a multidisciplinary focus. The necessary collaborations in the complex relationships between clinicians and researchers can be broken down into a series of thought and action steps that must be understood, accepted, and practiced by all participants. A crucial part of the preface steps (prior to death) for a rapid autopsy is the study consenting process. It is extremely important that this individualized consent is obtained for postmortem specimens and that it is written in terms general enough to be used for patients with all types of diseases and for an appropriate range of future research uses. The advent of SARS-CoV-2/COVID-19 (severe acute respiratory syndrome coronavirus 2/ coronavirus disease 2019) has presented new challenges and opportunities to the field of autopsy pathology. Guidelines and practice had to be created and adapted to protect physicians and staff while maximizing diagnostic yield. However, any autopsy performed on a patient dying of or with COVID-19 represents a unique opportunity to contribute to understanding the disease mechanisms and to improve death certification, thus assisting in both clinical care and the development of health public policy.

Key Words: autopsy, cancer research, COVID-19, postmortem, rapid autopsy

A rapid autopsy has been shown to be a powerful tool for advancing research at essentially no risk and with no distress to the contributing patient. As such, rapid autopsy has contributed substantially to the understanding of metastatic spread since its earliest days. Rapid autopsies are postmortem examinations performed on an urgent basis (measured in hours) after the death of the patient, and sampling tissues using a rapid autopsy from patients with advanced malignancies provides unique research opportunities. First, tumor tissues can be procured in large quantities from multiple separate body sites. Second, neoplastic tissues can be sampled in short time intervals after the death of the patient means that rapid research projects can be collected during a single case. Collection in short time intervals after the death of the patient means that rapid autopsy tissue quality can, in many instances, be considered comparable to fresh surgical biopsy tissue.1

Examples of RAP Contributions to Cancer Research

Tissues harvested during rapid autopsies have successfully been utilized for DNA sequencing, RNA expression analysis (including in situ hybridization), proteomic approaches, and immunohistochemical studies in the field of prostate,3,4 pancreas,5 breast cancer,6 and brain tumors.7 In addition, these tissues have provided the opportunity to develop patient-derived animal models recapitulating the end stage of metastatic disease and to utilize molecular studies that have become milestones in understanding intratumor heterogeneity.8,9

A selective overview of major scientific contributions enabled by rapid autopsies includes activity by 3 of the longest-running RAPs in the United States (ie, University of Michigan, Ann Arbor; University of Washington, Seattle; and The Johns Hopkins University, Baltimore) and offers some helpful insight into the research advances achieved so far. In 1996, the University of Michigan developed a RAP specifically for prostate cancer.10 By 2003, the
program had performed 30 rapid autopsies on patients with hormone-refractory prostate cancer. Researchers combined tissue microarray immunohistochemical analyses with hierarchical clustering of the cDNA expression pattern on many different metastases, including multiple bony sites for each patient. From this, they were able to show that metastatic hormone-refractory prostate cancer is characterized by heterogeneous morphology, immunophenotype, and genotype, reinforcing the concept that metastatic prostate cancer is a group of diseases even within the same patient and that obtaining metastatic tissue is of crucial importance to understanding the biology of cancer.\(^3\) Later, the same group performed a groundbreaking study, revealing a quantitative molecular clock based on mutations; for example, the model revealed an approximately 15-year time span between creation of the initial founder cell and the development of metastases. This result has major implications for development of screening for early prostate cancer, increasing the likelihood of successful treatment in this highly lethal disease.\(^4\)

From initially being the preserve of a few academic institutions, RAPs have recently been spreading throughout the United States, Canada, Australia, and very recently in Europe as well. Some of these programs are focused on only 1 tumor type, whereas others accept patients demonstrating all tumor types and sometimes other diseases as well.

**A Sample Rapid Autopsy From Consent to Conclusion**

A review of the sequence of events and sampling procedures for an example rapid autopsy case is helpful to illustrate factors...
affecting case logistics, the importance of clear communication with research teams, and the unparalleled sampling opportunities afforded by autopsy. The limiting variable to research sampling at autopsy is not the amount of tissue available as has often been the case in other approaches to tissue sampling, but rather only the time and expertise of a skilled autopsy team. Prioritization of locations and types of specimens is key, as is an ability to customize sampling in real time during the autopsy as discoveries are made of treatment effects and new metastatic sites.

Background

The patient was a 71-year-old man with an 11-year history of prostate cancer. He was initially diagnosed when he was found to have an elevated prostate-specific antigen level and underwent a prostate biopsy that showed Gleason grade 4 + 5 = 9 prostatic adenocarcinoma. He then underwent a radical prostatectomy, which confirmed the Gleason grade, with a stage T3b N0 and negative surgical margins. Because of a rise in his prostate-specific antigen following surgery, he was treated with hormonal therapy and radiation therapy. He subsequently developed resistance to hormonal therapy and underwent multiple additional lines of treatment, including TAK-700, sipuleucel-T, enzalutamide, abiraterone with prednisone, and radium-223. He was then found to have bone metastases involving his ribs, vertebrae, and pelvis. Treatment was started with nivolumab, docetaxel, and cabazitaxel. Despite the treatment, metastases progressed involving the liver and skull base, and the patient began to experience significant neurological symptoms attributed to his skull metastases. A rapid research autopsy was consented by the patient's legal next of kin, and less than a month after consenting, he died while in hospice care. After confirmation of the consent, the patient was transported to the hospital, and the autopsy was begun 5 hours after death. The rapid autopsy was attended by the lead pathologist, an autopsy assistant (diener), a specimen coordinator, a pathology postdoctoral fellow, 3 research associates from the prostate cancer research team, and a dedicated pathology photographer.

Tissue Sampling Procedure

The lead pathologist sampled all readily accessible metastatic sites with sterile scalpel and forceps, using fresh instruments for each site. Normal tissue controls were sampled in situ by the same method. Samples were placed on the dedicated cart covered by a sterile surgical drape and dissected by the postdoctoral fellow. Tissue sampling avoided macroscopically evident necrotic areas. Metastatic tissues were distributed to the prostate cancer research associates. Fresh samples for cell culture were taken first with corresponding specimens snap frozen in liquid nitrogen and fixed in 10% neutral-buffered formalin for routine histopathologic processing. The specimen coordinator recorded all sample locations, dates and times of collection on specimen tubes, and a specimen manifest. All of the organs were subsequently removed from the body en bloc, weighed, and sectioned at every 1 to 2 cm. A hollow point drill was used to sample bone cores from vertebrae, including T10 to T12 and L1 through L5, as well as bilateral iliac crests. The adipose tissue adjacent to the greater curvature of the stomach had nodular areas, tan-white on cut surface. There were adhesions between the serosal surface of the duodenum and the surrounding soft tissue. The liver parenchyma had multiple firm tan-white nodules at the hilum and throughout the parenchyma, ranging from 0.2 to 3.5 cm in greatest dimension. The extrahepatic biliary system and portal vein were surrounded by adhesions and white-tan nodules. The pancreas had a nodular surface with a firm parenchyma. A firm tan-white nodule was found in the left adrenal gland. The left fourth and fifth ribs showed tan firm nodules on the interior surface, ranging from 0.1 to 0.2 cm in greatest dimension. Finally, there were firm tan-white nodules on the anterior surface of the thoracic and lumbar vertebrae, measuring up to 0.9 cm in greatest dimension. All the other organs, including brain and spinal cord were unremarkable.

Summary of an Example Rapid Autopsy Case

In summary, 27 metastatic sites (liver, pancreas, right and left adrenal, prostate bed, paraaortic, perigastric, periaortic and mesenteric lymph nodes, sternum, right posterior chest wall, left fifth rib, T10–T12, L1, L3–L5, right and left Iliac crest) and 9 normal tissues (skin, skeletal muscle, heart, lung, pancreas tail, thyroid, kidney, liver, spleen) were sampled both with frozen tissue and formalin-fixed and paraffin-embedded tissue. A total of 76 specimens were harvested, including 4 fresh, 35 frozen, and 37 formalin-fixed. The prostate cancer team research associates also collected more than 100 specimens.

Postcase Activities

Postcase activities usually include the review of all histologic sections of metastatic samples and normal control tissues and recording the percentage of neoplastic tissue, viable tumor, and other cells. For specific cases, PowerPoint slides are prepared that summarized the clinical history of the patient, the rapid autopsy findings with photomicrographs, the analysis of tissue viability and the timing of tissue sampling. This material can then be circulated among the members of both the autopsy and research teams. One month after the autopsy, a joint meeting is held by the 2 teams to review rapid autopsy findings, make clinical-pathologic correlations, and discuss planning for follow-up genetic and other studies utilizing the samples, as well as goals for the upcoming cases.

Summary on RAPs as a Partner in Research

In the era of personalized medicine and as understanding of intercancer and intratumoral heterogeneity grows, rapid autopsies have been shown to be a powerful tool for advancing research at essentially no risk and with no distress to the contributing patient. Indeed, families of donors have very often testified that their experience in this type of postmortem donation is a rewarding way for them to contribute to science. Academic and health centers with a substantial investment in cancer research should consider developing and using this emerging research support tool and evaluate to what extent these programs can contribute to their cancer research mission. As rapid autopsy becomes more widely accepted and utilized, it will be essential for those involved in these programs to communicate and share techniques and resources. It is hoped that over time this new research-oriented 21st-century purpose for the ancient field of autopsy will increasingly contribute to leading edge research in cancer and generally support research throughout the United States and internationally.

RAPID AUTOPSY PROGRAM ORGANIZATION AND LOGISTICS

Rapid autopsy programs are logistically complicated and labor-intensive structures; therefore, the key to success is program flexibility and maintaining a multidisciplinary focus. Flexibility is important to creating the appropriate team for a specific program environment and set of research goals. Many programs are on-call 24/7 often with at least 2 rotating teams that cover 1 or multiple week shifts. However, successful programs may also be run by only 1 team that is on-call for a restricted number of hours every day. These programs are usually led either by pathologists or oncologists, although integrated work between the 2 subspecialties...
and specifically between clinicians and researchers is always crucial for the programs to thrive in the long term.16

**Active Steps for Implementing a RAP**

Successful collaborations in the complex relationships between clinicians and researchers can be broken down into a series of action steps given in Figure 1. The concept of utilizing postmortem tissue and the potentially available quantities of tissue is sufficiently new to some researchers that some careful a priori thought is required about how the RAP will fit into existing projects or create new avenues for investigation (CONSIDER). The patient population and sample types must be determined. Postmortem intervals (PMIs) can markedly affect how tissue may be successfully utilized, and parameters for different case scenarios should be delineated (DEFINE, MEET). The RAP must then be reviewed with potential participants and families (DISCUSS), and proper legal documents acquired (CONSENT). Pathologists and researchers and/or other scientists who perform the rapid autopsy must work closely prior to and at the time of collection (COOPERATE) and during evaluation and subsequent research (COLLABORATE). Lastly, rapid autopsy pathologists should create a communication loop about research results, family experiences, and evolving case needs (FEEDBACK).

**The Study Consent**

A crucial part of the precase activities (prior to death) is the study consenting process, in which the patient or his/her legal next of kin signs and gives his/her consent to collect and use his/her tissues for future research. The study consenting process may include explicit permission for a wide spectrum of possible future uses (such as genetic sequencing, generation of cell lines, tissue banking, sharing of tissue with researchers at different institutions, taking images of cases, retrieval of slides and blocks from prior biopsies and resection specimens, and the collection of premortem blood specimens). Of course, the patient can decide to restrict his/her consent as they may prefer.

It is extremely important that this individualized consent is obtained for postmortem specimens and that it is written in terms general enough to be used for patients with all types of diseases. It appears likely that such individualized consent will soon be required for genetic testing and cell lines, even in deceased patients, as regulatory agencies become aware of the expanding potential of postmortem tissue. In addition to the necessary study consent, rapid autopsies require a consent for the autopsy procedure itself, in the same way as regular diagnostic autopsies.

**Sampling Goals and Approaches**

Each rapid autopsy is a powerful opportunity to supply multiple researchers with many valuable specimens at the same time. For example, a single rapid autopsy case can provide tumor tissue to in-house researchers, tissue to 3 other out-of-state institutions (including National Institutes of Health), and banked tissue for the program itself, as well as normal controls of brain, eye, pituitary, heart, pancreatic duct, and skeletal muscle for other research.

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**FIGURE 1. Planning and action steps by RAP director and researcher for a successful rapid autopsy collaboration.**

This Figure was adapted by permission from Springer Nature: Performance of Rapid Research Autopsy, Hooper JE, Duregon E in Autopsy in the 21st Century, by Hooper JE, Williamson AK, Eds., 2019.
groups. To accomplish this, it is imperative to have prearranged sampling protocols that specify types of tissue and processing necessary for this type of multifaceted action during a case. Each research group has a designated representative, and these people are contacted as a group as soon as the patient's death is known. Research teams provide supplemental personnel to help in the autopsy, with the extent and composition of these teams varying by the number of specimens sought and the extent of immediate on-site processing required. It can also be highly useful to sample each lesion/normal tissue in parallel by allocating part of the same area to be collected fresh in media such as RPMI, part flash frozen in liquid nitrogen or gradually frozen in OCT, and part formalin fixed. Corresponding studies utilizing cell lines or xenografts, sequencing, and immunohistochemical staining can create synergy, helping to delineate the "life cycle" of a cancer cell. It is important to have at least 1 team member dedicated exclusively to specimen labeling and tracking to facilitate this important parallel sampling.

Timing and Processing of Samples

Since the beginning of the development of rapid autopsy, the overriding organizing principle for all the RAPs has been that the samples or organs must be removed and processed as rapidly as possible. With this press for "high-quality" tissue comes the need to determine the critical markers of quality for human postmortem tissue. The PMI is defined as the time elapsing between the time of death and the time the tissue has been placed in the preservative (either medium for fresh samples, snap freezing in liquid nitrogen, or fixation in formalin). Depending on the center and the particular aspects of the case involved, typical PMI can range between 0.5 and 23 hours. Postmortem tissue quality can be affected by PMI, premortem (agonal) conditions, and postmortem (preanalytical) factors. Traditionally, a low PMI has been the hallmark of high tissue quality.

Although the effect of PMI on sampling can be highly individualized by type of cancer or disease and patient body habitus, some general PMI guidelines for successful sampling can be gleaned from the literature on the subject. As depicted in Figure 2, fresh samples with living cells are best gathered within 6 to 8 hours of death. Specimens for RNA and DNA sequencing may be frozen or placed in a media with stabilizing reagent and are generally best collected within 12 hours of the death at most. Histology and immunohistochemistry will still produce good results after 12 hours of PMI. However, the author has had the experience of cell lines growing from a sample taken after 12 hours when the setting (within an area of hemorrhage) was propitious. Rapid autopsy pathologists and researchers should discuss together what collections will be done if circumstances (family concerns, weather, traffic, or any of many other circumstances) might extend the PMI longer than had been planned.

Examples of Successful RAP Organizations

The varied approaches to creating and implementing the complex logistics of a RAP team will be highlighted in the 4 examples discussed below.

At the University of Nebraska Medical Center, a rotating research team is available 24 hours, 7 days a week, consisting of 2 full-time technicians, with participation of 3 on-call technicians and pathology assistants. The RAP of the University of Michigan at Ann Arbor consists of 2 teams, an autopsy team and a tissue procurement team, which are alerted and work together during each case, and all are available 24/7. The autopsy team consists of a staff genitourinary pathologist, genitourinary pathology fellow, pathology resident, and a pathology assistant. The tissue

**Suggested Post Mortem Interval Guidelines for Effective RAP Tissue Sample Utilization**

This Figure was reprinted by permission from Springer Nature: Performance of Rapid Research Autopsy, Hooper JE, Daregon E in Autopsy in the 21st Century by Hooper JE, Williamson AK, Eds., 2019.

**FIGURE 2.** Suggested PMI guidelines for effective RAP tissue sample utilization.
The advent of SARS-CoV-2/COVID-19 (severe acute respiratory syndrome coronavirus 2/coronavirus disease 2019) has presented new challenges and opportunities to the field of autopsy pathology. Guidelines and practice had to be created and adapted to protect physicians and staff while maximizing diagnostic yield. At the same time, delineating a new disease has illuminated the unique power of multiorgan sampling that autopsy brings.

**COVID-19 Autopsy Procedures**

In March 2020, the US Occupational Health and Safety Administration issued guidelines that recommended against autopsies of COVID-positive patients. Unfortunately, related to these guidelines, the contingencies of Decedent Affairs office, and personal protective equipment shortages, multiple autopsy services including many at major institutions chose not to perform COVID autopsies. In some cases, performance of autopsies was shut down altogether. The US Occupational Health and Safety Administration guidelines were subsequently revoked, and the Centers for Disease Control and Prevention published recommendations for COVID autopsy performance. In a survey conducted by Dr Alex Williamson on an autopsy Listserv that began in May 2020, approximately 50% of surveyed participants were at institutions performing COVID-positive autopsies (A. K. Williamson, email, March 24, 2020). Most were performing autopsies that were modified in some way from the standard autopsy procedure.

Current Centers for Disease Control and Prevention recommendations and international guidelines suggest the addition of airborne precautions to standard and contact precautions including the use of an Airborne Infection Isolation Room with negative pressure and at least 6 changes of air per hour, or the best protective environment available. Personal protective equipment should include at least an N95 mask or an equivalent personal respirator. The use of an oscillating saw is not suggested, although a vacuum shroud could be used to protect against aerosols. At our institution, we modified the autopsy procedure substantially. Our guidelines were arrived at in active discussion with our complete autopsy staff and trainees, taking into account not only their safety but also their emotional comfort levels with the procedure. COVID autopsies were performed in a separate negative-pressure suite, and all surfaces were thoroughly cleaned and bleach prior to removal of the patient in the closed body bag. Pre-COVID, we typically used a modified Letulle or en masse technique, removing all organs in 1 block and then dissecting. For COVID cases, however, we remove the chest organs for evaluation but perform in situ sampling or individual organ removal for abdominal and pelvic organs unless other specific investigation is warranted by questions in the clinical history. An oscillating saw is not used. All organs and tissues are fixed for 48 hours prior to sectioning.

Initially, no brains were removed from COVID autopsies, while a vacuum shroud for the oscillating saw was on order. However, an alternative method for brain removal arose as a result of a research project. Dr Matthew Stewart, an otolaryngology–head and neck surgeon, had attended COVID cases to sample mastoid and middle ear tissue, a project that ultimately demonstrated the

### TABLE 2. Ongoing COVID-19 Autopsy Research at The Johns Hopkins University

| Subject Area | Specialty | Organ(s) | Type of Sample | Status of Project |
|--------------|-----------|----------|----------------|-------------------|
| Presence of SARS-CoV-2 in middle ear | Otolaryngology—head and neck surgery | Mastoid, middle ear | Fresh for polymerase chain reaction | Published JAMA Otolaryngology, ongoing |
| Demographic, disease, pathologic features | Pathology | All sampled | Autopsy report data, fixed for histologic evaluation | Published, Arch Pathol Lab Med |
| Serum markers, complement cascade | Rheumatology | Lung, heart, kidney | Blood/serum, fixed for IHC | Submitted, under revision |
| Immune cells in response to infection, mechanisms of damage | Immunology/pathology | Heart, lung, kidney, liver | Frozen for flow cytometry, fixed for IHC | In progress |
| Endothelial damage | Cardiology | Heart, lung, kidney, liver, skin | Fixed for IHC | In progress |
| Development of IHC, in situ | Pathology | Heart, lung, kidney, liver | Fixed for IHC | In progress |
| Lung pathology | Pulmonology | Lung, bronchi | Fixed, other testing | In progress |
| Histology and ultrastructure | Pathology | Lung | Fixed for histology and EM | In progress |
| Presence and spread of virus | Neurology | Vagus nerve, skeletal muscle | Fixed for IHC | In progress |
| Effects on brain | Neurology, neuropathology | Brain | Fixed in methanol and formalin | In progress |
| Effects of SARS-CoV-2 infection | Otolaryngology | Trachea | Fixed | In progress |

EM, electron microscopy; IHC, immunohistochemistry.
presence of viral DNA in these spaces. In the process of this activity, he realized that the calvarium could also be removed using a similar technique with hand tools, and subsequently, brains have been removed in 10 cases to date, with portions of brain tissue sampled in 2 additional cases.

The Johns Hopkins Hospital autopsy service follows a COVID testing policy that mirrors that of the Department of Surgery for the most invasive and high-risk procedures. This includes a history screening with questions about symptoms, travel, and possible exposures. Outside patients with histories suggestive of COVID are not brought in for autopsy. Inpatients from within the hospital system must have had polymerase chain reaction testing with result within 5 days of the autopsy, and decedents coming from outside the hospital must have had testing within 2 days. If testing has not been performed within these time parameters, stat testing from nasopharyngeal swabs is performed, and the combined history and these test results dictate what autopsy procedure will be followed.

COVID-19 Research at The Johns Hopkins University

The RAP at The Johns Hopkins Hospital was suspended from March to October 2020, because of the necessity for personal protective equipment conservation and the requirement to develop a testing protocol for decedents being brought in from outside the Hopkins hospital. During that time, resources and techniques utilized for the RAP were redirected to COVID research. The same generalized research autopsy study consent was approved for COVID cases and signed by the next of kin at the time of consenting for autopsy. Researchers collaborated with the autopsy director to design projects. Fresh, slow-frozen, and formalin-fixed specimens, as well as samples in glutaraldehyde for electron microscopy, were collected for researchers in parallel with samples for clinical diagnosis. Flash freezing was not used because of the risks of aerosolization. Ongoing research investigations from these COVID cases are outlined in Table 2. It is important to note that postmortem specimens may be utilized in combination with blood and tissue samples that were taken during life, as is currently being done in studies of serum markers and the complement cascade. Multiple immunohistochemical studies, development of an in situ hybridization assay, and flow cytometry are all now being performed to evaluate the character of responding inflammatory cells. Autopsy samples are also being used as controls in the development of clinically used immunohistochemical stains as well.

However, COVID autopsies at Johns Hopkins have not been performed on extended hours, and work with fixed tissue would not necessarily require the type of individualized consent used for ethically sensitive work such as cell lines or genetic sequencing. This means that any medical center currently performing COVID-positive autopsies could participate in these types of research collections. Fixed samples could even be shipped to other centers, if requested.

In addition to the collection of specimens specifically for research, any autopsy performed on a patient dying of or with COVID-19 represents a unique opportunity to contribute to understanding of disease mechanisms and to improve death certification, thus assisting in both clinical care and the development of health public policy. Pathologists with the willingness and skill to perform these procedures, supported by the administration of their medical centers, will be able to demonstrate the true value of autopsy in the modern era.

INTO THE FUTURE

Rapid autopsy is a thoroughly modern application and contribution for an otherwise foundational medical technique and a chance for the practitioner of autopsy to demonstrate extraordinary value in a fresh new way. While rapid autopsy can supply tissue for developing new genomic and proteomic studies, it can and should also fulfill the worthy purposes that all autopsies can fulfill: diagnostic accuracy, education, training, and information and closure for family members and colleagues.

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