Cover Story

The need for integrated research autopsies in the era of precision oral medicine

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ABSTRACT

Background. Autopsy has benefited the practice of medicine for centuries; however, its use to advance the practice of oral health care is relatively limited. In the era of precision oral medicine, the research autopsy is poised to play an important role in understanding oral–systemic health, including infectious disease, autoimmunity, craniofacial genetics, and cancer.

Types of Studies Reviewed. The authors reviewed relevant articles that used medical and dental research autopsies to summarize the advantages of minimally invasive autopsies of dental, oral, and craniofacial tissues and to outline practices for supporting research autopsies of the oral and craniofacial complex.

Results. The authors provide a historical summary of research autopsy in dentistry and provide a perspective on the value of autopsies for high-resolution multiomic studies to benefit precision oral medicine. As the promise of high-resolution multiomics is being realized, there is a need to integrate the oral and craniofacial complex into the practice of autopsy in medicine. Furthermore, the collaboration of autopsy centers with researchers will accelerate the understanding of dental, oral, and craniofacial tissues as part of the whole body.

Conclusions. Autopsies must integrate oral and craniofacial tissues as part of biobanking procedures. As new technologies allow for high-resolution, multimodal phenotyping of human samples, using optimized sampling procedures will allow for unprecedented understanding of common and rare dental, oral, and craniofacial diseases in the future.

Practical Implications. The COVID-19 pandemic highlighted the oral cavity as a site for viral infection and transmission potential; this was only discovered via clinical autopsies. The realization of the integrated autopsy's value in full body health initiatives will benefit patients across the globe.

Key Words. Autopsy; virtopsy; dental; oral; craniofacial; biorepository; multiomics; precision medicine.

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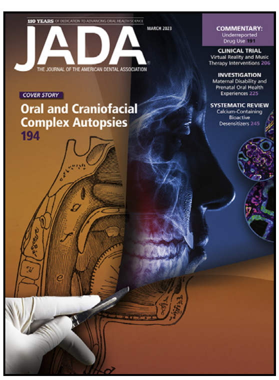


REFRAMING A ROLE FOR RESEARCH AUTOPSIES IN MODERN MEDICINE

As the mouth is the window to the body, autopsy is the window opening to understand the relationship between health and disease states. Although autopsy has benefited the practice of medicine for centuries, its use to advance the practice of oral health care is relatively limited. Most conventional autopsy procedures use surgical methods for forensic, clinical, or academic purposes[1]; outside of forensics (that is, forensic odontology), autopsies involving oral and craniofacial tissues are uncommon.[2] However, even in medicine, conventional autopsies are widely known to have been on the decline over the past 50 years, especially in hospital settings.[3,4] For example, in the United States, since the 1970s, conventional autopsies have decreased from 50% of all hospital deaths to less than 5%[5,6]; this is comparable globally.[7,8] The reasons for the decrease in autopsies include cultural or religious objections, high costs for time and limited personnel, and growing opinions about the lack of an autopsy's usefulness compared with other diagnostic techniques.[9,10]

Despite these beliefs, conventional autopsies still have enormous value for guiding treatment decisions, understanding trends as to the cause of death, and providing context for health care policy prioritization and research.[11] For example, the conventional autopsy used for research purposes, sometimes called the "research autopsy,"[12] has proven useful for understanding cardiovascular diseases,[13] stroke,[14] multiple sclerosis,[15] cancer biology and chemotherapeutic failures,[12,16] and viral pandemics, such as influenza A virus subtype H1N1[17] and COVID-19,[18,19] and epidemics caused by Zika virus.[20] Despite this utility, autopsies have been used limitedly in research of the oral and craniofacial complex, and few of the most widely productive autopsy centers in the world include tissues and fluids of the oral and craniofacial complex as part of their inspection, sampling, and biobanking procedures (Figure 1). There remains a need to apply new techniques and promote the wider recognition of dental, oral, and craniofacial tissue relevance for global initiatives that aim to promote precision medicine as well as oral and overall health.[21-24]

As the research and clinical communities begin to realize the promise of high-throughput and high-resolution, multiomic assays, so-called deep phenotyping, using genomic, epigenomic, transcriptomic, proteomic, and metabolomic sequencing to usher in the era of precision medicine for oral and overall health,[25] there is a need to integrate the oral and craniofacial complex into the practice of autopsy in medicine (Figure 2). Consider efforts to understand the bidirectional relationship of the oral cavity in the context of extraoral diseases, such as cardiovascular disease,[26] type 1 and type 2 diabetes,[27,28] and inflammatory bowel diseases,[29] among many others,[30] which could benefit from integrated research autopsy, biobanking, and downstream multiomic assays.[31,32]

The oral cavity is contiguous with the skin and a part of the aerodigestive tissues at the axis of breathing and digestion. Several rare diseases affect these shared epithelial barriers, such as epidermolysis bullosa,[33] Job syndrome (hyperimmunoglobulinemia E syndrome),[34] acanthosis nigricans,[35] and recurrent respiratory papillomatosis,[36] as well as systemic diseases of the liver, kidneys, and hematopoietic, immune, and endocrine systems that can include lesions in the oral cavity.[29,37] To address these concepts and argue for increased collaboration, we provide a historical overview of the research autopsy in dentistry, describe the advantages of minimally invasive autopsies in the oral and craniofacial complex, and provide a perspective on the value of autopsies for high-resolution multiomic studies to benefit the era of precision medicine.

A BRIEF HISTORY OF AUTOPSIES IN MEDICINE AND DENTISTRY

An overview of autopsy in medicine

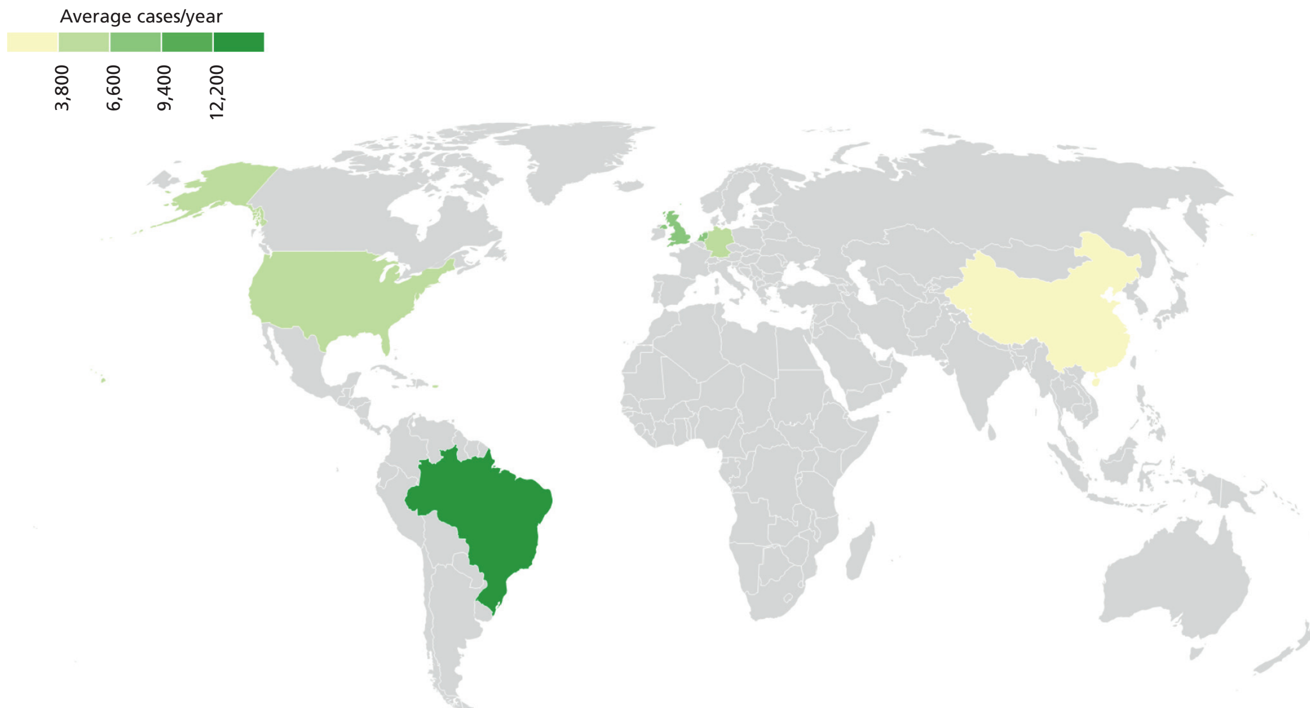
In the 20th century, autopsy was able to clarify, elucidate, or outright reveal disease etiology for an estimated 75 medical conditions, and growing.[38] Some medical disciplines have been quick to use autopsy to understand relevant diseases in their field; one of the greatest impacts of autopsy has been for cardiovascular diseases, including congenital heart disease, atherosclerotic diseases, coronary artery disease, and myocardial infarction.[39-42] For example, the embolus triggered by the rupture of a coronary plaque was first elucidated in postmortem examinations and histopathologic studies of heart vessels in patients who died from cardiovascular diseases.[43,44] This deeper, nuanced understanding of atherosclerotic disease enabled scientific discoveries that resulted in advances in cardiovascular disease treatment. Furthermore, the evolution of histologic and biomolecular methodology using autopsy samples elucidated the cell and molecular immune response of cardiovascular diseases, changing the use of medications to prevent the formation of new plaques.[45,46] Other conditions that have benefited from autopsy include tuberculosis[47] and HIV,[48] as well as cytomegaloviruses and herpesviruses.[49] These and many other findings that have been facilitated by means of conventional autopsies are well-reviewed elsewhere, as mentioned.

The research autopsy in oral health research

A literature search of dental or oral autopsy primarily revealed the role of oral and craniofacial biology in forensic applications.[2,50-53] Simply put, autopsy in dental, oral, and craniofacial research has been limited historically to outside of oral pathology training or to support the work of forensic odontologists (Table). Although this may have been a missed opportunity, there is still an opportunity to break down artificial barriers between oral health care and medicine by means of routinely including oral tissues as part of research supported, even in part, by autopsies. There are still high-volume autopsy centers in North America (United States), South America (Brazil), Europe (United Kingdom, Germany, the Netherlands), and Asia (China) (Figure 1); this is not to overlook many other autopsy centers or hospitals with their own active autopsy services.[54] Even

ABBREVIATION KEY

AD: Alzheimer disease.
CT: Computed tomography.
IHC: Immunohistochemistry.
ISH: In situ hybridization.
MIA: Minimally invasive autopsy.
MRI: Magnetic resonance imaging.
scATAC seq: Single-cell sequencing assay for transposase-accessible chromatin.
scRNA seq: Single-cell RNA sequencing.



Autopsy Center	City	Focus	Estimated Mean No. of Cases/y	Mandatory Oral/ Craniofacial Sampling?	Dental Professionals Included on Autopsy Team?
Brazil	São Paulo	Pathology	15,000	Yes, tongue and salivary glands	Yes
Netherlands	General	Pathology	7,000	No, monoblock	No
United Kingdom	General	Academic, forensic, pathology	7,000	Yes, tongue	No
Germany	Hamburg, Eppendorf	Forensic, pathology	6,000	No, monoblock	No
United States	New York	Forensic, pathology, antropology	5,000	No, monoblock	-
China	Shangai, Dhenzen	Pathology, academic	1,000	No	-

Figure 1. Opportunities to collaborate with high-volume autopsy centers. Although the number of conventional autopsies performed has decreased across the globe, there are still major autopsy centers in North America (United States), South America (Brazil), Europe (United Kingdom, Germany, the Netherlands), and Asia (China). Because there remains a need for studies that incorporate autopsy as a valuable tool for understanding human disease, there is an opportunity to collaborate with these and other sites that perform autopsies to advance initiatives in precision oral medicine. For example, there are collaborations between the University of São Paulo and local and international partners. Considering this is a highly productive autopsy center (≈ 15,000 cases per year), collaborations for dental, oral, and craniofacial research are possible here because this center includes oral tissues as part of autopsy procedures and invites dental professionals to participate as part of the autopsy team. -: Not available.

among these high-volume centers, there is little coordination between medical and oral health researchers (Figure 1).

Because there remains a need for studies that incorporate dental, oral, and craniofacial tissues, there is also a need to establish networks and secure funding for these studies. If possible, the usefulness of the integrated autopsy could benefit both oral and overall health. For example, an integrated biopsy design could include removing entire structures from multiple sites, like whole alveolar processes, mandibles, temporomandibular joint, tonsils and the tissues comprising Waldeyer ring, and tongue samples that include neurovascular complexes. There is a need to collect samples from healthy people both young and old for the possibility of designing research studies that can age-, sex-, and ancestry-match samples whenever possible. To achieve this will take various investigative teams to coordinate and share samples as part of a global biobanking network.

Although there are numerous examples of autopsy benefiting various dental, oral, and craniofacial projects throughout the 20th century (Table), it remains unknown which challenges are the most impactful to address to increase its utility. Conventional autopsies typically use invasive surgical tools to completely remove organs and tissues, but when planning for including dental, oral,

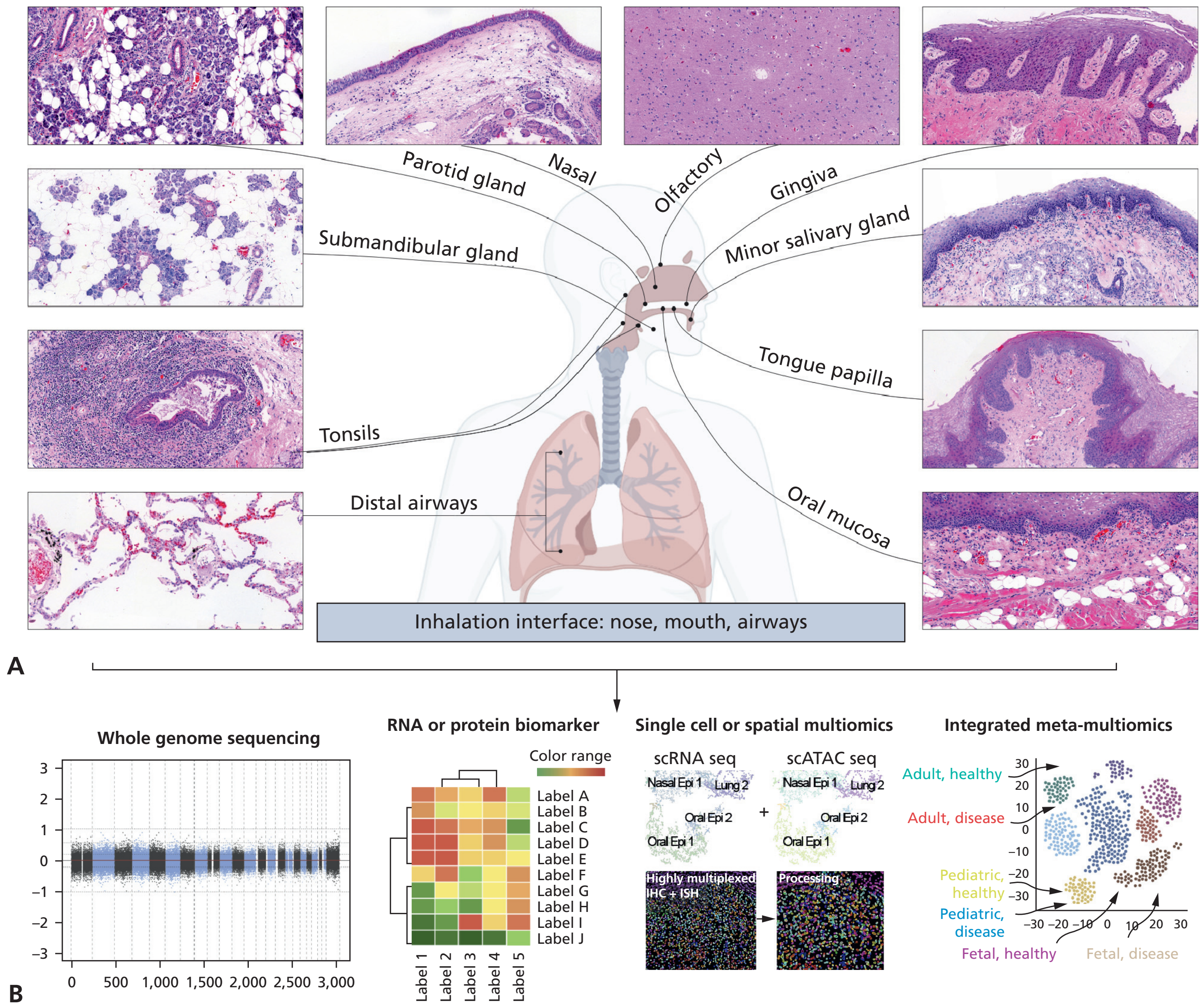


Figure 2. Sampling the integrated anatomy of the aerodigestive tract through autopsy. **A.** The oral cavity is the beginning of both the airways and digestive tract. There are several common—and especially rare—diseases that affect the oral cavity in addition to more internal niches of these tracts. New advanced sequencing and imaging technologies, which are foundational for the new single-cell and spatial biology, are laying the foundation for new ways to conceptualize the tissue niches considering cellular and molecular spatial organization, cellular neighborhoods, and structural motifs—the so-called rules or core components that construct a niche. These concepts may provide important and novel biological readouts for precision medicine. For example, considering integrated oral, nasal, and airway barrier niches—the so-called inhalation interface, which displays unique niches from external to internal sites, may be a potential accelerator for these efforts. **B.** This integrated sampling approach could be leveraged for curated biobanking, single-cell and spatial multiomic studies combined with genomic sequencing, and noninvasive sampling of RNA and proteins for disease biomarker discovery. IHC: Immunohistochemistry. ISH: In situ hybridization. scATAC seq: Single-cell sequencing assay for transposase-accessible chromatin. scRNA seq: Single-cell RNA sequencing.

and craniofacial tissues, some specifically tailored protocols need to be created and followed. Furthermore, for ethical or legal reasons, it is not possible to remove all tissues in every case, as some deceased bodies will be prepared for burial at the family's discretion.

Due to the gross sampling strategies discussed, 1 objection to autopsies including dental, oral, and craniofacial tissues, is the disfigurement that can occur when recovering these tissues in conventional en masse sampling methods.[99] The development of minimally invasive autopsies using magnetic resonance imaging (MRI) and computed tomography (CT) to guide sample acquisition could mitigate that (Figure 3).[100-102] If sustainable partnerships can form across academic hospitals, public and private research institutions, and industry, it would be expected that autopsies including dental, oral, and craniofacial tissues would increase to support discoveries across disciplines. To highlight these opportunities, we focused our review on the use of autopsy in periodontal disease and salivary gland disease research, although other

Table. A historical summary of autopsy in oral health research*

STUDY	SAMPLE TYPE	SAMPLES, NO.	DISCIPLINE	LOCATION
Wright and Fenwick, 1981[55]	Tongue	46	Pathology or oral medicine	United Kingdom
Van der Wal and Van der Waal, 1986[56]	Tongue	100	Pathology or oral medicine	The Netherlands
Hashimoto and Colleagues, 1987[57]	Mandible	62	Pathology or oral medicine	Japan
Takeda and Yamamoto, 1989[58]	Minor salivary glands	195	Pathology or oral medicine	Japan
Whittaker and Colleagues, 1989[59]	Maxilla	1	Periodontal or oral surgery	United States
Tanimoto and Colleagues, 1990[60]	Temporomandibular joint	15	Radiology	Sweden
Landini, 1991[61]	Alveolar bone	25	Radiology	Japan
Moskow and Polson, 1991[62]	Mandible or maxilla, gingiva	350	Periodontal or oral surgery	United States
Pedersen and Colleagues, 1991[63]	Mandible	3	Orthodontics	Denmark
Donath, 1992[64]	Alveolar bone	1	Periodontal or oral surgery	German
Moskow, 1992[65]	Mandible or maxilla	20	Periodontal or oral surgery	United States
Nyström and Colleagues, 1993[66]	Maxilla	1	Periodontal or oral surgery	Sweden
Vacek and Colleagues, 1994[67]	Mandible or maxilla, gingiva	10	Periodontal or oral surgery	United States
Widmalm and Colleagues, 1994[68]	Temporomandibular joint	224	Pathology or oral medicine	United States
Wehrbein and Colleagues, 1995[69]	Maxilla	1	Orthodontics	German
Wehrbein and Colleagues, 1995[70]	Maxilla	1	Orthodontics	German
Lindh and Colleagues, 1996[71]	Mandible	7	Radiology	Sweden
Rautemaa and Meri, 1996[72]	Gingiva	2	Periodontal or oral surgery	Finland
Wehrbein and Colleagues, 1996[73]	Mandible	1	Orthodontics	German
Uden and Colleagues, 1998[74]	Periodontium	13	Periodontal or oral surgery	United States
Kuramitsu and Colleagues, 2001[75]	Fibrous cap	381	Periodontal or oral surgery	United States
Riviere and Colleagues, 2002[76]	Brain	34	Periodontal or oral surgery	United States
Rocha and Colleagues, 2008[77]	Salivary glands	36	Pathology or oral medicine	Brazil
Ohyama and Colleagues, 2009[78]	Biliary tract, portal vein, and hepatic artery	1	Periodontal or oral surgery	Japan
da Silva and Colleagues, 2011[79]	Salivary glands	45	Pathology or oral medicine	Brazil
Otani and Colleagues, 2011[80]	Stomach	1,531	Pathology or oral medicine	Japan
Pyysalo and Colleagues, 2013[81]	Brain	7	Pathology or oral medicine	Finland
Gondak and Colleagues, 2014[82]	Tongue	53	Pathology or oral medicine	Brazil
Louhelainen and Colleagues, 2014[83]	Pericardial fluid	22	Pathology or oral medicine	Finland
Fonseca and Colleagues, 2015[84]	Tongue	1	Pathology or oral medicine	Brazil
de Paula and Colleagues, 2017[85]	Salivary glands	20	Pathology or oral medicine	Brazil
Kim and Colleagues, 2018[86]	Alveolar bone	1	Periodontal or oral surgery	China
Bertoldo and Colleagues, 2019[87]	Tongue	27	Pathology or oral medicine	Brazil
de Mello Gomes and Colleagues, 2019[88]	Tongue, salivary glands	50	Pathology or oral medicine	Brazil
Matuck and Colleagues, 2020[89]	Gingiva	8	Pathology or oral medicine	Brazil
Bandou and Colleagues, 2021[90]	Not applicable	403	Epidemiology	Japan
Gameiro and Colleagues, 2021[91]	Maxilla	1	Orthodontics	Denmark
Huang and Colleagues, 2021[92]	Minor salivary glands, tongue, gingiva, mucosa	18	Pathology or oral medicine	United States
Matuck and Colleagues, 2021[93]	Major and minor salivary glands	25	Pathology or oral medicine	Brazil

* Dental or oral autopsies may often be thought of in the context of forensics; however, there is also a limited history of using autopsy in dental, oral, and craniofacial research. This list, although not comprehensive, includes research projects from the past 4 decades that have used autopsy to support their findings and includes projects that have helped define the oral axis of infection with severe acute respiratory syndrome coronavirus 2 in the early days of this COVID-19 pandemic.

Table. Continued

STUDY	SAMPLE TYPE	SAMPLES, NO.	DISCIPLINE	LOCATION
Sakashita and Colleagues, 2021[94]	Submandibular salivary gland	64	Pathology or oral medicine	Japan
Sørensen and Colleagues, 2021[95]	Dental calculus	10	Forensics	Denmark
Sowmya and Colleagues, 2021[96]	Tongue, buccal mucosa	10	Pathology or oral medicine	India
Wong and Colleagues, 2021[97]	Salivary glands	8	Pathology or oral medicine	German
Zarpellon and Colleagues, 2022[98]	Tongue, gingiva, mucosa	30	Pathology or oral medicine	Brazil

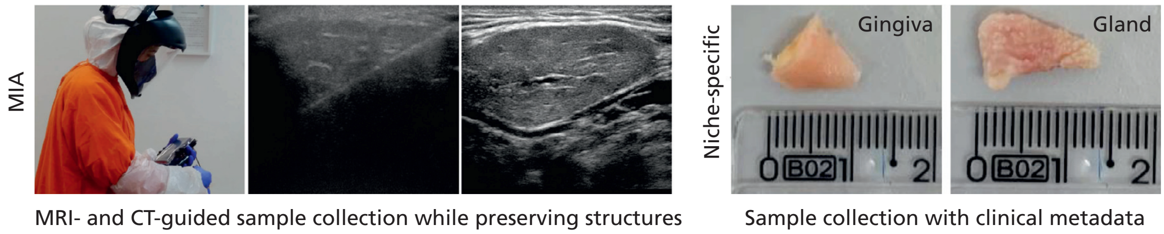


Figure 3. Using new autopsy techniques to increase use in oral health research. An objection to autopsy is the disfigurement that can occur when recovering tissues from the oral and craniofacial complex. The development of minimally invasive autopsies (MIAs) using magnetic resonance imaging (MRI) and computed tomography (CT) to target tissue sample recovery may be a way to overcome this objection to increase dental, oral, and craniofacial sample acquisition. If sustainable partnerships can form across academic hospitals, public and private research institutions, and industry, the number of autopsies including dental, oral, and craniofacial tissues would increase to support discoveries across disciplines.

head and neck cancers[103] and temporomandibular joint disorder have also benefited[68,104,105] (Table).

An overview of autopsy in periodontal medicine

Historically, periodontal disease researchers have used autopsy more often to make discoveries about local and systemic disease mechanisms, dating back to the early 19th century, as the disease was still being defined. As redefined, periodontitis was studied widely in the 20th century. What has been clear for many decades is that periodontitis is caused by dysbiosis that elicits a destructive immune response of the alveolar bone in susceptible people[106]; however, for some people, periodontal lesions can be the result of diseases that either originate in other parts of the body or are systemic in their involvement.[107] Many questions remain about the etiology and pathophysiology of periodontal diseases in the oral cavity, and the relationships between the mucosal immunology of the overlying gingiva, osteoimmunology of the local alveolar bone, and systemic conditions remain mostly unresolved. This is because systemic conditions can modify the periodontal status and sometimes periodontal pathogens can contribute to the establishment of systemic disease,[108] as well as numerous well-known host-modifying factors, such as genetics, smoking, diabetes, and obesity.[109]

In classic studies to understand the pathophysiology of periodontitis, there is considerable evidence of autopsy's role in clarifying disease mechanisms and outcomes. For example, at the turn of the 20th century, periodontal tissues were examined at the time of autopsy, which informed further research into the classification of periodontal disease.[110] Many examinations of periodontal tissues in healthy and diseased sites were examined over the next 50 years, as the classification and definitions of periodontal diseases continued to be refined.[111] At the same time, although not technically an autopsy study, Waerhaug[112] added his take on the concept of traumatic occlusion using skulls to study occlusal relationships and site-specific bone loss. Furthermore, in 1961, Gargiulo and colleagues[113] reported on an important study of the dentogingival junction in health using integrated measurements of autopsy blocks from this and past studies.[114] The researchers established that there are some common measurements of this structure that are still referenced to this day.[115]

The classic physiopathology of periodontitis was further explored in parallel. For example, in the 1970s, Waerhaug[112] supported the hypothesis in the field that subgingival plaque could contribute to attachment loss in an observational study of 6 autopsied patients. In this study, a correlation was drawn using the biofilm thickness related to site-specific bone loss. In a classic study from the 1990s, researchers also observed periodontitis progression using pediatric tissues and complemented with spleen and lymph node tissue from deceased bodies, to better understand the extent of host inflammatory infiltration.[116] However, the challenge with these studies is often a lack of well-annotated medical histories that would substantiate these claims.

Through these types of studies over a 120-year history, hypotheses were supported or challenged using what we would now call "research autopsies." Although they can be rare, conventional autopsies have also been used in some case reports to create a link between fatal diseases and periodontal findings. There are few of these articles, likely due to the limited number of dentists and oral pathologists working in autopsies centers around the world.[83,117] These findings have reported periopathogens in distant body sites, such as infected pharyngeal[118] and liver[78] tissues, supporting the long history of the oral-systemic link. The bidirectional phenomenon of disease-disease (polyimmune) associations has been discussed in the literature as periodontal medicine[30]; this idea has been termed a rediscovery, as it has existed for more than a century after Hunter[119] published his work on oral microbes and their role in systemic diseases. This early work was only possible via building off of oral-systemic work from Miller[120] at least a decade before Hunter.[119] Despite these early efforts, the true mechanisms of causation, as opposed to simply association, remain another opportunity for integrated research autopsies, as some important questions, such as how periodontal diseases differ, and those disease subtypes can influence inflammatory signatures in body fluids (saliva, urine, blood) and at distant organs, such as the kidneys and heart.[121]

Although there is much to be understood about the oral-systemic links for the more than 60 systemic diseases associated with periodontitis, 1 such link with Alzheimer disease (AD) would have been difficult without using research autopsy as a tool. Building off a seminal report that found evidence for periopathogen virulence factor lipopolysaccharide in brains with AD,[122] 1 such periopathogen, *Porphyromonas gingivalis*, was found in the brains of patients with AD.[123] Researchers using autopsy samples also found *P gingivalis* in amyloid plaque formation in patients with AD. This discovery used brain specimens obtained during autopsy procedures, but not from gingival tissues from the same patients.[123] The idea to test the AD-periodontal disease link was justified after several observational and association studies.[124-129] In other studies published previously, researchers suggested that gingipain inhibitors or periodontal treatment could mitigate the appearance of β-amyloid in the brain tissues of patients with AD.[130,131] Another possible oral-brain axis is aneurysms, as researchers performing an autopsy study found endodontic and periopathogen DNA in aneurysm clipping and autopsy material.[81] Although this is an emerging field and the literature is sparse, the collaboration between oral health researchers and neurobiologists will continue to be critical for the next advances.

An overview of autopsy in salivary gland diseases

Among the barrier niches, salivary glands are one of the most distinct tissues in the craniofacial complex; however, they also share features with other exocrine glands across the body.[132] There is now an emerging rule set for related tissue structures across the body,[133] and the formation of these oral glandular secretory structures depends on diverse cell migration from the neural cord to the ectomesenchyme, as epithelial-mesenchymal interactions are necessary for maturation and secretion of saliva.[134] This maturation process is essential during human facial development, as well as aging, when they play an important role in dental, oral, and craniofacial homeostasis through the regulated flow of saliva secretions.[135,136]

Although the morphology and maturation of salivary glands were determined in ex vivo culture,[137] these fundamental processes of salivary gland biology were confirmed using research autopsy.[88] Furthermore, the branching morphogenesis necessary for salivary gland development was first described in animal models and then validated in autopsy samples acquired at different gestational ages.[138] The evolutionary conservation of some salivary gland development is also shared between other exocrine glands, such as submucosal glands of the nasal cavity and lower airways, and the relationship between salivary glands and systemic health has been discussed with growing frequency due to their roles in infectious diseases, such as COVID-19[92] and their polyautoimmune involvement in diseases such as rheumatoid arthritis,[139] multiple sclerosis,[140] and Sjögren disease.[141] The use of salivary gland tissues obtained by means of research autopsy procedures not only has illuminated human embryology[142] and physiology[143] related to glandular biology but has also provided a fundamental understanding of viral interactomics, as the glands are known hot spots of infection.[144,145] This understanding has led to research on salivary viromes and saliva as a viral transmission medium,[92,146,147] as well as salivary tests for diseases such as COVID-19.[148]

It can now be argued that the research autopsy became a foundational tool in the understanding of the oral infection axis in COVID-19. For example, viral invasion in epithelial cells is a common mechanism of pathogenicity, but it was unknown whether oral epithelial barrier cells expressed the requisite membrane molecules to encourage host-viral interactions to permit productive infection. As Huang and colleagues[92] and Matuck and colleagues[93] described, severe acute respiratory syndrome coronavirus 2 was one of the first viruses found using in situ approaches to invade and replicate inside acinar and duct cells of the salivary glands. This was discovered using research autopsy material in collaboration with autopsy groups at the National Institutes of Health and the University of São Paulo, respectively, and led to advanced spatial biology methods being applied to research autopsy samples of major and minor salivary glands obtained from patients who died of COVID-19–related complications. Due to the historic divide between oral health care and medicine, this kind of sample collection is challenging to curate, as major salivary gland tissues have limited sampling access using extraoral approaches common in conventional autopsies; however, integrating sample collections across the body is an important endeavor for pandemic preparedness measures for future viral pandemics.[149]

THE VALUE OF INTEGRATED AUTOPSIES IN THE ERA OF MULTIOMICS

New methods to benefit integrated research autopsies

Although the number of conventional autopsies has generally decreased in medicine, the advent of virtual autopsies (virtopsies), which use MRI and CT only, are on the rise,[100] especially in combination with advanced diagnostic tools assisted by artificial intelligence and machine learning.[150,151] Furthermore, minimally invasive autopsy, which combines MRI and CT with targeted microsurgery, has become a new technique for even more directed postmortem studies of human disease.[102] Researchers are also beginning to combine clinical metadata (that is, sex, age, and ancestry) with artificial intelligence– and machine learning–assisted analysis of virtopsy and classical histology assays as a modern way to advance disease-oriented research from transdisciplinary teams.[152]

Minimally invasive autopsies can contribute to solving the problem of removing samples from head and neck tissues without creating damage to facial recognition or ethical problems. The focused use of advanced imaging tools, such as ultrasonography, tomography, and nasofibroscopy tubes that can be attached to a monitor or even a smartphone make it more possible to reach internal body niches for sampling specific tissues from the respiratory tract and adjacent tissues at the same time as dental, oral, craniofacial, and oral and nasal cavity tissues (Figures 2 and 3). Refined approaches like this will allow for more collaborative projects to understand the cell types that are shared and unique among related sites, especially considering the emerging concept of the inhalation interface of the oral and nasal cavities, pharyngeal tissues, and lower airways (Figure 2), in addition to the oral-gut and oral-brain axes referenced in this article.[29]

Although rapid autopsy or warm autopsy programs, which collect targeted tissues within hours after confirmed death, continue to be popular in academic medical centers,[54,153] there is a need to include oral and craniofacial specialists, such as oral pathologists, oral surgeons, oral medicine, periodontists, radiologists, and geneticists, as well as basic science research teams focused on oral-systemic disease research, to advance whole body health initiatives. For example, because larger amounts of tissue can be preserved and processed from multiple sites, in rapid autopsy studies, researchers have acquired new knowledge on tumor evolution within the same patient.[154,155] The ideal team of the future would include patients and their families who are educated about the value of an integrated, minimally invasive, and rapid autopsy procedure well before the need to consent, collect, and process tissues.

Biorepositories for multiomics assays

In an ideal world, high-volume and dedicated autopsy sites would be funded to build out comprehensive biorepositories in which deidentified, well-annotated, and bar-coded patient samples are logged in searchable databases for research teams. This is especially important for the approximately 7,000 defined rare diseases for which any samples are challenging to obtain. As there is the ability to sample and subdivide tissues, downstream analysis-optimized biobanks would be able to make the same sample available to multiple researcher teams or different samples available to multiple groups for multiple assays, such as host single-cell and spatial multiomics (that is, combined genomics, epigenomics, transcriptomics, proteomics, and metabolomics in parallel with bulk and emerging single-cell microbiomics techniques).[12,156,157] The field of host-microbe interactions (that is, interactomics) is nascent, but could benefit directly from these approaches.[158]

The presence of oral health care professionals in the rapid autopsy team could contribute to a deeper understanding of these diseases via integrated biobanking of oral tissues with whole-body samples. This inclusion will be important because the rapidity of the collection can ensure that rapid autopsy materials are of the highest quality and even comparable with freshly collected surgical biopsies, as has been reported.[159] Considering all of these factors in the context of a branched, international autopsy network in which sample data are shareable and searchable could facilitate future studies on severe chronic diseases with oral manifestations and may advance the field of craniofacial genetics in ways not possible previously.

FUTURE DIRECTIONS

The partnership of oral health research centers, dental schools, academic hospitals, and associated autopsy centers is important for the future of oral and overall health initiatives. Among all members of these new transdisciplinary teams, it will be important to normalize a research culture in which autopsies are a useful tool for the rapid understanding of disease pathophysiology. As samples grow within these partner networks, more equitable inclusion of samples considering age, sex, and ancestry will be possible with appropriate statistical power to shorten the distance between preclinical and clinical research. In addition, considering the COVID-19 pandemic, emerging viral diseases are predicted to be encountered continually and are likely a burden that humanity will continue to endure. In the past 2 decades, pandemics have become more common.[160] Evidence now indicates that the oral cavity plays a more important role in viral diseases than may have been appreciated previously, and the described establishment of new autopsies centers, participants, and practice must be a goal for global pandemic preparedness and biosecurity of the future. ■

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