Review article

The Benefits of a Specialized Transplant Histopathology Laboratory

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Histopathology is invaluable to clinicians as it provides concrete evidence which supports other diagnostic methods during patient care. In the United States, the Organ Procurement and Transplantation Network was established by the National Organ Transplant Act of 1984 to improve the organ donation and transplantation process. The histopathology laboratory is critical to the organ allocation and allograft monitoring phases of transplant due to the significant impact histopathology diagnostic testing has on patient health outcomes. Although the general histopathology laboratory is commonly utilized, the transplant specialized laboratory is proposed as a solution meant to consolidate fragmentation evident in general laboratories. Fast turnaround time (TAT), supported by a comprehensive test menu, advanced instrumentation, and around-the-clock service provided by competent histotechnologists and specialty pathologists result in timely and reproducible histopathology reports with reduced diagnostic errors. Managers seeking to establish a transplant specialized histopathology laboratory must consider various aspects prior to opening a new laboratory such as startup and operation costs, initial and subsequent test menu offerings, geographic location, and clientele. Although follow-up studies must be conducted to gauge the specialized histopathology laboratory's impact, improved laboratory efficiency and TAT results in improved patient care and outcomes.

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Introduction

Histology has a long history which eventually developed into the medical discipline known as histopathology. The histopathology laboratory is staffed by professionals which prepare tissue specimens and diagnose disease based on visualized histologic abnormalities. In the United States, the histopathology laboratory plays a significant role in the organ donation and transplantation system. Histopathology services are necessary to gauge the condition of donated organs and follow-up on organ transplanted patients.

Despite the histopathology laboratory's importance in the organ donation and transplantation process, there are weaknesses which stem from the overwhelming use of general histopathology laboratories. The transplant specialized histopathology laboratory mitigates the weaknesses posed by the general histopathology laboratory. Use of the specialized laboratory poses many benefits to the organ allocation and transplantation process. By implementing a histology laboratory specialized in transplant pathology, patient outcomes would improve due to decreased turnaround time and enhanced laboratory efficiency.

Background

Histology is defined as the microscopic study of anatomy. As such, histology is also known by the term microanatomy. Unlike anatomy, the science that studies the body's organ systems, histology focuses on the tissues which compose the individual organs. Tissue is composed of morphologically similar cells that as a unit perform specific functions. In modern day medical education, histology is a foundational science which clinicians in training must study to gain an intimate understanding of the human body.[1]

Histology, and the use in medicine, has a long history. Marcello Malpig, also known as the father of modern physiopathology and pathology, was a seventeenth Italian physician who first incorporated microscopic observation in autopsies of various organisms.[2] Malpig published many works describing the microscopic structures of various organ systems, including the nervous, cardiovascular, renal, and respiratory systems. It was not until Marie-Francois Xavier Bichat, an eighteenth-century French physiologist and anatomist, that the concept of tissue came to be.[3,4] Bichat proposed that organs were a collection of tissues, and that tissue was the foundation for which human anatomy was based. Like Malpig, Bichat was a strong proponent for the correlation between data gathered from autopsies and the clinical study of patients. As such, both men believed that abnormal changes to organs were related to the development of disease.[2,3]

Despite Malpig's and Bichat's groundbreaking work, it took several centuries for histology's official recognition as a medical discipline. This was due to Santiago Ramon y Cajal's and Camillo Golgi's work in neurohistology, which resulted in the Physiology Nobel Prize in 1906.[5] Today, the study and diagnosis of disease in tissue is known as histopathology.

Tissue visualization in contemporary histopathology is possible due to advancements made in microscopy. The technological advancements made to optical lens in the nineteenth century paved the way for the development of modern light microscopes and other lens dependent image detection systems.[5] Some examples of current image detection systems include the transmission electron microscope, the fluorescent microscope, and digital microscope scanning systems. Although advancements made in imaging technologies improved microscopic observation, it was the study and development of improved tissue preparatory techniques which enhanced microscopic tissue visualization and identification.

Tissue preparatory techniques seek to promote tissue fixation, ease tissue sectioning, and improve tissue component differentiation through chemical staining.[5] Although there are many tissue fixatives to choose from, 10% neutral buffered formalin (NBF) is the fixative

of choice for routine paraffin infiltration processing and sectioning.[6] On the other hand, if urgency requires rapid results, NBF fixation and routine processing is forgone for rapid frozen sectioning of freshly dissected tissue. Tissue staining techniques include chemical, immunohistochemical, and molecular staining detection methods (among other techniques) which specimen preparers may apply to formalin-fixed paraffin embedded (FFPE) tissue or frozen tissue sections.[7,8] In modern histopathology, there are many histotechnology techniques and image detection systems available for diagnostic use.

Histopathology is the gold standard for the diagnosis of disease because it allows for the direct visualization of tissue abnormalities.[9] It is an invaluable diagnostic tool that reinforces other diagnostic methods, such as medical imaging techniques, blood tests, and physical examinations. When histopathology is leveraged in conjunction with other diagnostic methods, the patient benefits from a thorough microscopic analysis of the disease state resulting in a definitive diagnosis. With an established diagnosis, the proper therapeutic intervention is used to improve patient outcome. As such, the histopathology laboratory is an integral part of patient care.

The histopathology laboratory is staffed by a variety of personnel who work together to convert tissue specimens into high quality images and supply diagnostic evaluation.[10] At the core of the histopathology laboratory are the histotechnologist and histopathologist. Histotechnologists are professionals trained in the art of histotechnology, the science of tissue preparation into the stained microscope slide. The histopathologist evaluates the prepared microscope slides and provides diagnostic interpretations. Optional staff which promote laboratory efficiency include laboratory assistants and pathologists' assistants. Their employment depends on the histopathology laboratory's case volume and specimen types received. The culminating efforts of the histology laboratory personnel result in increased patient care quality and improved outcomes, particularly in organ donation and transplantation.

Organ donation and transplantation is the surgical process of removing an organ from a donor's body to place it into the body of a recipient. This is a medical intervention performed when the organ of a recipient is failing, and a replacement is necessary to sustain life. Organ transplantation can extend the recipient's life by several years. However, an organ donation shortage exists within the United States which complicates the process.

The United States Congress passed the National Organ Transplant Act (NOTA) in 1984 to address the need for increased organ donation.[11] NOTA's goal is to improve patient access to transplantation, clarify who has authority on patient organ donation decisions, and protect the patient's choice to donate. This act established altruism as the sole motive for organ donation and banned the sale of organs. Most importantly, NOTA streamlined and eased the organ donation, matching, and placement process through the establishment of the Organ Procurement and Transplantation Network (OPTN).[11,12]

The OPTN's purpose is to maintain a science-based national organ matching registry to promote equitable and fair organ allocation and access, and a maximized organ supply.[13] As per NOTA, a private, not-for-profit organization under federal contract must operate the OPTN.[11] The United Network for Organ Sharing (UNOS) manages the OPTN. All organizations involved in the organ donation and transplantation process must be members of the OPTN and abide by the policies.[14]

Key OPTN member organizations include transplant centers, organ procurement organizations (OPO), and histocompatibility laboratories.[15] Transplant centers are hospitals that offer transplantation services. There are 248 active transplant centers in the United States. There are 56 active organ procurement organizations (OPO). These organizations engage in deceased donor organ recovery. There are also 139 histocompatibility laboratories that per-

form diagnostic testing for donors and recipeents during the organ procurement and transplantation process. Surveillance testing post-transplantation is a major function of the histocompatibility laboratory which transplant patients need to monitor their health status. Despite the extensive network of organizations dedicated to maximizing opportunities for organ donation and transplants, an organ shortage still exists which burdens patients awaiting transplantation.

As of January 31, 2024, there are 103,408 patients on an active waiting list for an organ.[16] While the waitlists for each of these organs varies, kidneys have the longest waitlist at 88,809 followed by livers at 9,869.[16] Despite the long waitlist, only 46,630 transplants took place in 2023.[16] Cadaveric donors made possible 85% of transplants, while living donors accounted for 15%.[16] Organ donors are vetted extensively by the key OPTN members to determine eligibility for organ donation.

Traditionally, organ eligibility for donation stems from donor history. However, in the case of donors with extended donor criteria, history is insufficient.[17] In 2002, UNOS established the extended criteria donor to decrease organ recipient waiting times.[17] The extended criteria donor is defined as an individual over the age of 60 years, or over the age of 50 with comorbidities.[17,18] These comorbidities include death due to stroke, a history of hypertension, and serum creatinine level greater than or equal to 1.5 mg/dL.[Aragni-18] For a 50-year-old cadaveric donor to be considered an extended criteria donor, at least two comorbidities must be present.[18]

Due to the less-than-ideal characteristics of expanded criteria donor organs, transplantation outcomes are comparably shorter than organs from ideal donor candidates. As such, OPOs and transplant centers must decide whether the benefits of transplanting an extended criteria donor organ outweigh the risks. The histopathology laboratory plays a significant role in extended criteria donor organ utilization decisions and is necessary to monitor the health status of donor allografts post-transplantation.

Histology in Organ Allocation and Transplantation

The histopathology laboratory processes and evaluates biopsies taken during the organ allocation and transplant monitoring stages. The OPO or receiving transplant center may request biopsies from deceased extended criteria donors.[19,20] After transplantation, recipients are biopsied for organ rejection surveillance. Without histopathology diagnostic services, patient outcomes would decrease due to deficiencies in quality of care.

Procurement biopsies on extended criteria donors determine transplantation utility. Transplantation utility is dependent upon the extent of histological injury seen in the biopsy. Typically, donor kidneys are biopsied to judge the degree of interstitial fibrosis, tubular atrophy, glomerulosclerosis, arteriolosclerosis, and arteriosclerosis.[17] Histopathology evaluation requirement of donor liver biopsies depends on inconclusive visual assessment of the organ during surgery, and laboratory and clinical preoperative assessment of the patient.[19] In these cases, histopathology results would contribute to the final decision.

Due to donor factors and practice pattern variability in transplant programs and OPOs, 23% to 78% of cadaveric donors are biopsied.[17,21] Surgically discovered lesions require additional biopsy for histopathology evaluation to rule out suspicion of malignancy, chronic disease, or other transplantation contraindications.[19] Cadaveric donor organs are discarded if biopsies reveal transplantation contraindications.[17-19,21] Accepted extended criteria donor allografts increase patient outcomes and are more likely to survive transplantation.

Post-transplantation, the allograft recipeent is biopsied to monitor signs and progression of organ rejection and graft dysfunction. Allograft protocol biopsies is a beneficial surveillance method in high risk transplanted kidney patients.[22,23] Before the kidney allograft

is transplanted and reperfused with blood, a time zero-hour biopsy is taken to establish baseline conditions for future histological comparisons.[23] One hour after allograft transplantation, a biopsy is taken to assess conditions after reperfusion.[23] Later biopsies are taken at three to six months to assess for subclinical allograft rejection.[24] There is prognostic value in long-term graft survival for six- to twelve-month biopsies.[23,24] Histological evaluation at the one-year mark assesses the presence of chronic interstitial inflammation, glomerulonephritis, BK-virus nephropathy, and calcineurin inhibitor neurotoxicity.[23] Three-, five-, seven-, and ten-year biopsies verify immunosuppression and malignancy development in late period post-transplantation.[23] Allograft rejection treated patients may also be biopsied for follow-up evaluations of histological improvement.[24] Allograft surveillance reduces graft failure and increases long-term survival due to earlier medical interventions.[23]

After biopsy procurement, the specimen is sent to the histopathology laboratory for evaluation. Upon receipt of the specimen, it is accessioned, or registered, by laboratory staff using the patient information provided in the associated requisition form. The type of requested testing is ascertained from the requestion form to determine the protocol laboratory personnel must follow during preparation. The biopsy specimen then undergoes several steps during processing to prepare the sample for histopathology examination.

A histotechnologist, or other trained personnel, grosses the specimen. Grossing consists of describing the specimen's color, measurement, shape, and (if applicable) weight. Grossing personnel must also note the fixative state of the specimen to determine eligibility for requested diagnostic testing.

A diagnostic test that clients may request is the rapid hematoxylin and eosin (H&E) stain. The OPO or transplant center requests this test, when necessary, during intraoperative organ allocation procedures.[25] Rapid H&E stains are performed on frozen sections. To obtain frozen sections, the histotechnologist embeds an unfixed specimen in optimum cutting temperature (OCT) compound, or other cryotomy embedding compounds. The specimen is rapidly frozen at a temperature between -15°C and -30°C depending on the lipid content of the tissue.[26] The histotechnologist sections the frozen tissue and mounts the sample on a slide. Sectioned slides are stained with a shortened H&E protocol validated for frozen sections. The histopathologist evaluates the frozen H&E slides and creates a preliminary histopathology report for distribution to the requesting OPO or transplant center.

Requests for routine processing prompts specimen fixation in 10% NBF prior to processing in a cassette. Tissue processing consists of graded alcohol dehydration, xylene clearing, and paraffin wax infiltration.[27] The histotechnologist embeds the processed specimen in paraffin wax for conversion into a block.[28]

The histotechnologist sections the paraffin-embedded tissue block. During tissue block sectioning, ribbons of paraffin tissue sections are formed.[29] The ribbons are floated on a heated water bath where the paraffin tissue sections are mounted on slides and prepared for H&E staining validated for routinely processed FFPE tissue.

The histotechnologist stains and coverslips the routine H&E slides. The H&E-stained slides are given to the histopathologist for preliminary examination. The histopathologist then prepares the report for submission to the requesting client.

A follow-up histopathology report is sent to the client with diagnostic results of additional diagnostic testing. Aside from routine H&E staining, other tests may be ordered. This depends on the specimen's fixative state, the laboratory's routine staining protocols, preliminary diagnosis, and client requests. Routine tests may include histochemical special staining techniques. Other tests include immunohistochemistry (IHC), immunefluorescence (IF), and *in situ* hybridization

(ISH). Electron microscopy (EM) imaging may also be requested. Regardless of testing processes, the histopathology laboratory must engage in quality control (QC) and quality assurance (QA) practices throughout specimen preparation and evaluation to minimize artifacts and factors that negatively impact diagnosis.

QC and QA are important in the histopathology laboratory because the diagnostic evaluations supplied to requesting providers determine donor organ acceptability and patient treatment plans. Poor QC and QA practices in the histopathology laboratory lead to an increase in unnecessary extended criteria donor organ discards. This results in extended wait list times for donor organ availability, which negatively affects patient outcomes. Poor QC and QA practices also lead to delayed or improper treatment plan execution, which negatively affects patient outcomes and graft survival. A histopathology laboratory with good QC and QA practices positively contributes to the pre- and post-transplantation aspects of patient care.

Although histopathology processing and evaluation is a key component in transplantation, it is often a fragmented process that requires the involvement of multiple laboratories. Various aspects of specimen processing can be performed by different histopathology laboratories. Not all histopathology laboratories are fully equipped with the instrumentation or testing necessary for transplant diagnostics. For example, a histopathology laboratory may have the staff and equipment to perform special stains, but not IHC testing. These laboratories would need an external IHC facility to complete this procedure. Also, some healthcare systems may have multiple histopathology laboratories, but specialist histopathologists may be centralized in one location for consultation. This highlights the need for process consolidation to improve transplanted patient outcomes.

Specialized Histology Laboratory

The transplant specialized histopathology laboratory is a full-service laboratory which consolidates all transplant histopathology services into one facility. This specialized laboratory focuses solely on rendering diagnostic testing and evaluation to organ donors and transplanted patients. As such, it is an instrumental asset to organ allocation and allograft follow-up surveillance. This type of laboratory is staffed by specially trained and experienced personnel that prepare and evaluate specimens with the equipment and tools necessary for quality transplant pathology diagnostic accuracy.

Given the critical nature of the transplantation process, the specialized histopathology laboratory adheres to fast turnaround time (TAT) constraints. TAT is a critical component of quality reporting indication in histopathology due to its importance in patients' treatment plan development, safety, and health outcome.[30,31] In the histopathology laboratory, the TAT begins from the time of specimen receipt to preliminary H&E result availability.[32] According to the College of American Pathologists (CAP), the recommended preliminary reporting TAT for 90% of surgical cases is up to 4 days from the date of receipt.[33] A specialized histopathology laboratory focused only on the transplant population produces quality results in a significantly shorter timeframe than recommended by CAP.

The transplant laboratory processes time sensitive specimens which require results within a few hours. A transplant specialized laboratory follows strict preliminary reporting TATs for all specimen types received. Frozen sectioned H&E slides and routinely processed specimens sent by an OPO have a reporting TAT of 1 to 4 hours, respectively.[34] For all other routinely processed specimens, the TAT is 6 to 8 hours depending on the specimen's fixative state when received.[34] Routinely processed explanted allografts are reported in less than 36 hours from the time of receipt.[34] Other processes and diagnostic tests are performed the same day upon receipt of the biopsy sample and submitted for final reporting the following day. If the tests are particularly

urgent, they are reported within hours of the initial report's completion. The specialized histopathology laboratory is optimized for fast TAT capability.

Some defining characteristics of a transplant specialized histopathology laboratory are the hours of operation and staff availability. This type of laboratory operates 24 hours a day, seven days a week, all year round. Laboratory personnel supply services during regular working hours and remain on-call after hours to support continuity of service. Highly trained and experienced histotechnologists and transplant pathology specialized histopathologists staff the specialized laboratory.

Experienced transplant specialized histopathologists bring critical expertise and authority to the laboratory and organ allocation and transplantation processes. The expertise and experience of a specialized histopathologist is invaluable to high-stakes diagnostic and treatment decisions.[35] All diagnostic testing performed by the histopathology laboratory is assessed by specialized histopathologists with knowledge of transplant pathology specific conditions. Generalist histopathologists would not have the experience necessary to consistently recognize transplant specific histological changes.

Specialized histopathologist expertise increases the diagnostic accuracy and reproducibility of histopathology reports as compared to generalist histopathologists.[36] This is of particular importance during the procurement of cadaveric donor kidneys with extended donor criteria. A generalist histopathologist is more likely to overscore donor kidney histological parameters compared to a specialist histopathologist, which contributes to an increased procured organ discard rate.[17,36-38] Interpretation agreements are also more likely amongst specialist histopathologists as compared to generalist histopathologists.[37] Due to generalist histopathologist interpretation risk, second opinion from a specialized histopathologists is necessary.[37,39]

The reproducibility and error reduction of histopathology diagnostic interpretation is a significant benefit of the specialized histopathologist. Diagnosis originating from a specialized histopathologist decreases organ discard and waitlist times. Transplant patient outcomes also improve due to increased safety, quality of care, and allograft survival resulting from prompt treatment decisions. Specialist histopathology interpretations result in decreased diagnostic errors and unnecessary treatments. Diagnostic errors are debilitating, potentially fatal, and result in increased healthcare expenditure.[40] In a transplant specialized histopathology laboratory, the specialist histopathologist utilizes complex methodologies to accurately diagnose patients.

The specialized histopathology laboratory has a comprehensive test menu developed specifically for transplant pathology. Pathologist and histotechnologist expertise are leveraged to create custom protocols and novel test methods by application of evidence-based practice (EBP) and evidence-based medicine (EBM). According to a transplant histopathology laboratory (C. Hersh, oral communication, January 2024) the SMPDL-B3 and B7 immunohistochemical stains were developed for the detection of focal segmental glomerular sclerosis (FSGS) in kidney transplant patients.[41] The development of the SMPDL-B3 and B7 IHC stains provides clinicians with critical evidence necessary to better tailor treatment plans and improve patient care. Staffed histotechnologists are fully competent in applying validated testing methodologies during specimen preparation. The in-house availability of a limited yet comprehensive test menu denotes the efficient use of resources and maintenance of staff competencies.

The in-house availability of testing methodologies allows for time-efficient reporting of results. Testing procedures are completed and submitted for pathology interpretation faster as compared to other laboratories. Given the range of testing necessary for transplant pathology, general laboratories often send out specimens to external laboratories due to test

menu unavailability. Limitations to a laboratory's test menu are due to a combination of factors, including lack of testing personnel expertise and competency, fiscal reasons, and lack of necessary instrumentation.

A specialized laboratory has state-of-the-art instrumentation which allows for the prompt and quality completion of diagnostic testing methodologies. Automation of key instruments in the specialized histopathology laboratory positively affects specimen processing TAT. Automation also contributes to staining consistency and reproducibility by limiting human variability and error in specimen processing. Automated instruments include the specimen processor, autostainer, and immunohistochemical stainer. These instruments handle tissue processing, chemical slide staining, and antibody slide staining, respectively. Another key instrument is the whole slide imaging (WSI) system.

The WSI system allows the transplant specialized histopathology laboratory to leverage telepathology for diagnostic purposees. Telepathology, or digital pathology, is the use of telecommunication technology to render remote diagnosis on stained slides.[42] WSI systems are scanners that digitize microscope slides for remote image viewing and diagnostic interpretation.[43] The validation and use of WSI systems requires comparison to light microscopy (LM) slides, and other stain-specific microscopy slide types (such as IF stained slides) to ensure concordance and diagnostic accuracy.[43-45]

In the specialized histopathology laboratory, WSI systems capable of digitizing LM and IF slides are an advantage to rapid TATs. Digital pathology induces rapid TATs by facilitating specialized histopathologist availability for routine and rush diagnostic services during working hours and after hours.[39] The specialized laboratory's use of digital pathology promotes continuity of care throughout all hours of the day.

Discussion

The histopathology laboratory is an integral part of patient care. It is the gold standard for diagnosis and supplies critical information to the field of transplant medicine. In the United States, general histopathology laboratories engage in much of the organ procurement and transplant testing. The transplant specialized histopathology laboratory provides benefits such as short TAT, specialized and experienced histopathologists, competent personnel, specialized testing, and modern equipment. These benefits legitimize the need for a transplant specialized histopathology laboratory.

The transplant specialized histopathology laboratory is not the only specialty histopathology laboratory. There are many operating laboratories that specialize in other subfields, such as dermatologic, gastroenterologic, neurologic, and ophthalmic pathology. Published guidelines for the set-up of cancer and neuromuscular specialized histopathology laboratories are also available.[46,47] The existence of these laboratories and guides indicates that a specialized laboratory is feasible and is a useful contribution to histopathology diagnostics.

There are some considerations to bear in mind prior to creating a specialized histopathology laboratory. A newly established laboratory initially relies on sister laboratories for financial support due to high start-up costs. The initial test menu consists of basic diagnostic testing, such as preliminary rapid H&E and routine H&E staining. As the laboratory grows financially independent, the testing menu is expanded to include other diagnostic methods. The primary clientele initially consists of local OPOs. With time, transplant centers and other medical centers with transplant patients are gained as clients. The more clients the laboratory acquires, the greater the volume of cases received for processing and laboratory expansion.

The clients available to new laboratories depend on geographic location. As such, the volume of cases received is dependent on the laboratory's local vicinity. Initial specimen receipt sporadicity is expected. To accommodate the initial low specimen volume, testing personnel must be scheduled on call as

needed. It is imperative that laboratory management determine if the geographical region poses a transplant pathology need that is sufficient to justify, sustain, and grow a new facility. Laboratory management must carefully consider the laboratory's financial matters to acquire testing materials, cover overhead costs, and retain testing personnel.

Further investigation into the benefits of the transplant specialized histopathology laboratory is necessary to solidify the impact and need in the field of transplantation medicine. A guide on how to set up a full-service transplant laboratory specialized in histopathology is a supplement that would benefit interested laboratory managers. Follow-up studies on the outcomes of procured organs, allograft survival, and overall patient health resulting from diagnostic reporting from a transplant specialized histopathology laboratory should be performed to solidify veracity and utility.

Conclusion

Understanding the limitations of general histology laboratories in the organ procurement and transplantation processes prompts investigation for improvements and solutions. The transplant histopathology laboratory is a solution to these limitations. The goal of this specialized histopathology laboratory is to improve transplant patient outcomes though optimization of a key quality indicator, TAT. Pathologist expertise, coupled with competent personnel, availability of specialized testing, and utilization of state-of-the-art instrumentation all play a key role in the improvement of patient care and safety. Although there are crucial factors to consider prior to the establishment of a specialized laboratory, the benefits gained from a facility are invaluable. The consolidation of transplant histopathology diagnostic testing is an asset to patient care due to reductions in TAT, a reduction in discarded procured organs, and allograft rejection.

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