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SURVEY

3D Reconstruction of Light Microscopic Images and Its Significance for Better Clinical Decisions: A Systematic Review Emphasizing Gastric Histopathology

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ABSTRACT Histopathological findings depend on the distinction between normal and subtle changes in mucosal tissues. These distinctions are made based on the nature of the cell lining, nuclear hyperchromasia and cyto-architecture of glands. Diagnosis is mostly based on the experience of the pathologists, which is a subjective procedure. This research focuses on automating the process through 3D reconstruction of gastric histopathology images enhancing quantitative diagnosis. It emphasizes the advantages of 3D reconstruction from light microscopic serial section gastric images over whole slide imaging for clinical decision-making. Comparative analysis shows that processing and analyzing WSI scans are more expensive than light microscopy. While 2D imaging with light microscopy faces challenges due to limited focal depth, especially for thin sections, the objective of this research is to highlight the importance of transforming 2D gastric images into 3D by layering sequential sections. It will offer insights into glandular texture and volume, aiding in distinguishing between malignant glands and benign mimickers. The paper presents a summary and comparative examination of the registration techniques necessary for reconstructing 3D histopathology images. Additionally, it discusses future directions in the field of 3D histopathology reconstruction and acknowledges its potential benefits for research scholars. This will hold potential interest for pathologists when grading gastric carcinoma.

INDEX TERMS Histopathology, gastric gland, serial section, registration, 3D reconstruction.

I. INTRODUCTION

Histopathology is a laboratory investigative method required for the diagnosis and prognostic staging of a disease by visualizing microscopic sections taken from diseased tissues and examining them under a light microscope [1], [2]. Pathologists are responsible for making tissue diagnoses and helping clinicians manage a patient [3], [4]. The tissues in histopathology are obtained from clinical medicine or surgery departments, where it typically involves the removal of tissue called biopsy [5]. In endoscopic gastric biopsy, one pinched out small fragment from the inner lining of the stomach of a patient is visualized under a microscope after being cut into thin slices and staining [2], [6]. This paper concentrates on advantages of 3D reconstruction and visualization of 3D tissue structure for quantitative diagnosis. The paper emphasized gastric histopathology biopsy images for their complexity and heterogeneous characteristics. Gastric cancer is very common in places where smoked meat is consumed, and Sikkim is one of them [7], [8] because of certain types

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of food intake [9]. Gastric glands are distinguished by their tubular architecture and are found in the inner lining of the stomach. The cells present in the inner lining are prone to malignant transformation, and 95% of the overall number of malignancies is gastric adenocarcinoma [10]. Early detection of gastric carcinoma is very important as it not only influences the treatment but also prognosticates. One of the main symptoms of adenocarcinoma is the presence of tumors with central ulceration region in the gastric gland. Pathologists in routine practice visually navigate and inspect the tissue sections on glass slides through light microscopy to identify the cyto-architectural changes of the gastric gland with infiltration in the underlying stroma. Cytological changes essentially include nuclear changes in the form of an increased NC (Nucleomegaly Cytomegaly) ratio, nuclear hyperchromasia, nuclear membrane irregularity, and a typical mitotic figure [10].

Traditional light microscopic images are produced in the form of two dimensional (2D) images. Diagnoses by the pathologists are based on some well-defined criteria given in standard texts [11] and guidelines, along with some intuitive criteria to get a 3D idea about the tissues. The whole procedure is prone to a high degree of individual interpretive variation. This has also been seen sometimes that Kappa statistical interpretation varies between two or more pathologist examining the same slide simultaneously under a double headed microscope [11]. In the recent past, histopathological image 3D reconstruction has gained enormous importance [12], [13]. The software available with the Whole Slide Scanner (WSI) is able to produce a 3D view for histopathology images [14], [15]. WSI has a wide range of applicability for producing high resolution histopathology images [16], [17]. The limiting factor in the WSI scanner is its high cost & time consuming for its hardware and thus they are yet not widely employed in regular clinical workflow of pathology [18]. WSI scanner is still not capable to produce 3D structure for any specific cell [16], [19].

3D view of gastric glands will help to see the distinct features of irregularities in cell clusters and branching of tubules [20], [21]. 3D reconstruction of gastric carcinomatous glands along with their lumina in serial histological sections will contribute to establishing a strict morphological association between the adenocarcinoma and its related lesions [22].

The delicate nature of stomach tissue makes it difficult to get several sections from the same sample. Studies reveal that the average width of stomach glands is between 0.03 and 0.05 millimeters [23], but this can vary largely. Serial sections are mostly cut with a thickness ranging from 3 to 4 microns using a microtome. To visualize a 3D volume of a gastric histopathology gland with a width of 0.03 to 0.05 millimeters, there is a requirement of approximately 10 to 16 sections with a thickness of 3μm. However, in the case of gastric histopathology, it is sometimes difficult to get these many sections. Once the serial sections have been obtained, the next phase is the role of the registration algorithm. Registration algorithm will create a coherent 3D structure by overlaying the 2D sections. The registration algorithms are computational processes designed to align and map the coordinates of each serial section accurately.

According to the works described above, there are several review articles on histopathological image analysis that list the different types of cancers that are treated in the medical community. But very few of them pay particular attention to histological analysis of gastric glands and the importance of having volumetric view of gastric gland. A total of 110 papers were initially downloaded related to histopathology image analysis and then 20 papers which were not found to be relevant to our work were rejected. 14 papers were comprehensively reviewed concerning image registration, along with 12 papers focusing on 3D visualization of medical images. Additionally, 64 relevant papers were examined to enhance the overall understanding within this area of study.

The objective of this review was not to evaluate technical aspects or select the optimal model for 3D reconstruction. Instead, its focus was on emphasizing the importance and significance of 3D reconstruction from light microscopic images, which is used as a gold standard by pathologists in their subject assessment.

The following are the author's major contributions to this work.

1. Survey of various recent review papers written by different authors based on a variety of factors, including the topic, the number of articles examined, dataset, results, limitations, future direction etc. in this field of study.
2. Review on registration techniques applied on medical images: A number of studies in the last few years are analyzed and a summary of their key information, including detailed dataset information, parameters considered, implementation details, findings are provided.
3. Review on various 3D reconstruction techniques and tools used by different authors are highlighted in this work.
4. Future direction identified by various authors are identified and highlighted.

There are total six sections in this paper and the organization of the various sections of the paper is depicted in Fig. 1.

II. HOW WILL 3D REPRESENTATION OF LIGHT MICROSCOPIC IMAGES HELP IN DISEASE DIAGNOSIS?

A. CONVENTIONAL MICROSCOPY VERSUS WHOLE SLIDE IMAGING IN PATHOLOGY

Light microscopy is the gold standard for histopathology, but its 3D view limitation can be surpassed with Whole Slide Imaging (WSI) for a better understanding of gastric histopathology. Though whole slide imaging instruments have been commercially available for some time, their technological potential has not been completely harnessed [18]. Mostly, it is used for the transmission of images of slides for consultation or for use in educational settings. One possible technological advancement, the authors believe, is the conversion of the 2D visualization of single sections under

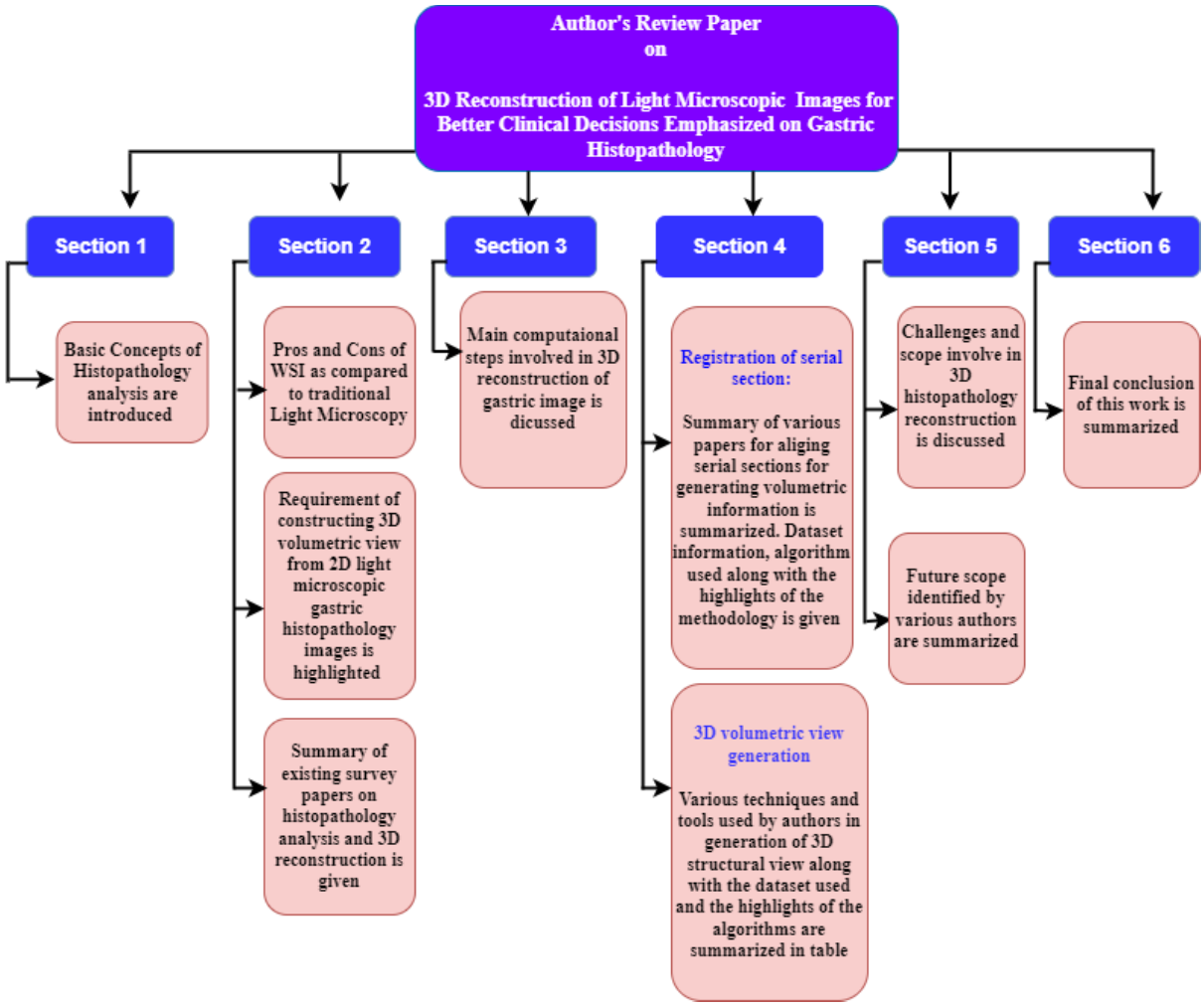

FIGURE 1. Organization of the paper.

a light microscope to a 3D reconstructed digital image. WSI adoption in routine digital pathology workflows has been hindered by technology limitations, image quality concerns, high-workload management challenges, and storage costs [17].

Despite technological progress, WSI's clinical histopathology utility is limited and could be a financial burden without significant benefits for trained pathologists [14], [26]. The use of WSI incurs high computational complexity as compared to a light microscope due to the huge size of the data set that it uses during processing. Thus, the conversion of 2D images captured through light microscopy (traditionally the most commonly used technique in most hospitals globally) to 3D images would be beneficial only if some mathematical algorithm was developed that can produce a 3D representation of a 2D histopathological specimen.

B. IMPORTANCE OF 3D RECONSTRUCTION FROM LIGHT MICROSCOPIC IMAGE

Pathologists analyze the morphology of lesions and relationships in the gastric wall through light microscopy. 2D imaging of light microscopy has the limitation of a small focal depth, even for thin sections, and so it cannot distinguish subtle changes in the specimen at hand with high precision. Differentiating the malignant glands from their benign mimickers like regenerative atypia, is a qualitative assessment by experienced pathologists. It is also very important for the pathologists to understand the association between atypical regeneration, dysplasia, and Helicobacter infection in gastric specimens. Sometimes, it is difficult to predict the strict morphologic criteria of adenocarcinoma and related lesions. Therefore, it would be novel to have a better computational model that can illuminate those minute details of the sample specimen and provide a precise and clear view of the cancer precursor lesions. In imaging technologies, 3D reconstruction has played a role of paramount importance in CT, USG as well as in MRI. However, the 3D representation of gastric histopathology images is complex. In [27], Yamada et al. explored benefits of 3D visualization of gastric gland tissues through the imageJ tool from endoscopic images. This reconstruction helps in locating the tumor cells, which were found in the lower part of the gastric mucosa. Identifying the ablation line from a gastric endoscopy is very limited. Yamada et al. [27] found that this can be overcome significantly through

TABLE 1. Summary of existing survey papers on reconstruction of medical images.

Reference	Topic/ Abstract	Number of papers reviewed in detail	Results/ Output of previous work given	Existing Methods discussed	Performance Evaluation of previous work	Proper Data Set Description of existing work	Limitations of existing techniques identified	Future scope specified
This paper	Survey on Reconstruction of Light Microscopic Images emphasized on gastric histopathology	110	Yes	Yes	Yes	Yes	Yes	Yes
Mriganka Sarmah (2023) [31]	Survey of methods and principles in three-dimensional reconstruction from two-dimensional medical images	Not Specified	Yes	Yes	Yes	Yes	Yes	Yes
Shiliang Ai (2021) [32]	Review for Gastric Histopathology Image Analysis Approaches	130	Yes	Yes	Yes	Yes	Yes	Yes
Chen Li (2020) [33]	Review on cervical histopathology image analysis	60	Yes	Yes	Yes	Yes	No	Yes
Zhichao Liu (2021) [34]	Survey deep learning in microscopy image analysis	Not Specified	yes	Yes	Yes	Yes	Yes	Yes
Satya P. Singh (2020) [35]	Review on 3D deep learning techniques on Medical Images	133	No	Yes	Yes	Yes	Yes	Yes
Anny Yuniarti (2019) [36]	Deep Learning Techniques for 3D Reconstruction	55	No	Yes	Yes	Yes	Yes	Not clearly specified
Jonas Pichat (2018) [37]	A Survey of Methods for 3D Histology Reconstruction	Not exactly specified	No	Yes	No	No	Yes	Yes
Geert Litjens (2017) [39]	A survey on deep learning in medical image analysis	300	No	Yes	No	Not properly specified	Yes	Yes

3D imaging. Miyamoto et al. [28] generated 3D structure of gastric veins from MDCT (Multiple Detector Computed Tomography) images which could reveal the presence of tumors in the walls of gastric gland along with their vascular arrangement. Vascular endothelial growth factor in gastric mucosa with intestinal metaplasia or dysplasia, Helicobacter Pylori, atrophic gastritis is some of the major reasons leading to intestinal as well as diffuses gastric carcinogenesis [29], [30]. 3D view of gastric glands will help in localizing H pylori in stomach tissues. Structural detailing for the gastric tissue images can be highlighted through 3D reconstruction from multiple sequential 2D histopathology sections. Spatial association that exists between various features of the gastric gland tissue can be exemplified through 3D reconstruction and it will provide a comprehensive view of molecular anatomy of abnormal growth region.

Several survey papers in this field are reviewed in depth and details like number of papers reviewed, methodologies used, data set description, evaluation metrics, limitations and future directions are summarized in table 1.

III. BASIC STEPS OF 3D HISTOLOGY RECONSTRUCTION

Individual histological samples need to be deeply analyzed to draw a conclusion on a specific disease. 3D virtual image generated from successive histological sections of different stain specimen (e. g Hematoxylin and Eosin) enables the visualization of the structural and spatial relationship of tissue parts. The basic computational steps to be carried out for representing gastric gland in 3D structure are described in Fig. 2. The traditional process followed by pathologists include the major steps of tissue sample preparation, staining, producing serial sections and digitization using light microscope. Tissue samples are commonly obtained through biopsy or surgical resection. During the process of tissue sample preparation, the tissue sample is fixed using an appropriate fixative solution, such as formalin. Fixation helps maintain tissue shape and guard against deterioration. The fixed tissue is then dehydrated by removing water from it by treating it with a series of alcoholic solutions [37]. Then thin sections are cut using a microtome and mounted onto glass slides. These sections are typically around 4-6 micrometers thick [40], [41]. To improve tissue visualization, staining methods like H&E staining are used which imparts color to nuclei (blue) and cytoplasm (pink), respectively [37]. Under a light microscope, these produced and stained serial sections can be examined, allowing for the analysis of tissue morphology and pathological alterations.

Computational process involved in 3D reconstruction mainly involves extraction of region of interest, alignment of serial sections and viewing the 3D volumetric view using a visualization tool. Ability to detect the morphology of tissues in gastric gland wall is of main interest for the pathologists. So, extraction of the tissue gland region and its 3D visualization will provide quantitative information regarding tissue perfusion. Extraction of tissue gland region is very challenging because individual tissue morphology is different in nature and unique in gastric tumors. Main advantage of this extraction is that it will make the approach more efficient in terms of computational time. Through Whole Slide Imaging (WSI) technology, it is evident that 3D view of histopathology images can be generated by overlaying thin slices of same sample sections one after another. Proper serial section alignment will help to gather in-depth information about the inner textures of the tissue sample at hand. Section to section alignment based on matching features is crucial as any kind of distortion or misalignment will recur information loss leading to a poor resolution view. Light microscope remains an irreplaceable tool for the pathologists due to its low maintenance cost and user-friendly handling. The image processing software available with light microscope are able to produce high resolution 2D images of putative areas instead of redundant whole slide images. Extensive research is being carried out to produce 3D view of various tissue structures. Among which 3D reconstruction using thin serial sections are commonly discussed. Thin serial sections of a given specimen are non-linearly deformed during its preparation. So, image registration algorithms play a vital role for 3D histology image reconstruction.

IV. CURRENT STATE OF THE ART TECHNIQUES FOR RECONSTRUCTION OF HISTOPATHOLOGY IMAGES

A. IMAGE REGISTRATION (ALIGNMENT OF HISTOLOGICAL SECTIONS)

The main purpose for gastric biopsy is to diagnose the adenocarcinoma and to visualize various morbid state including dysplasia and metaplasia in gland polyps. Histology slides are prepared in thin slices from same sample. Pathologists usually view these thin sections in different planes through light microscope and analyze the morphology of 3D organs. These thin slices can be cut from the same sample specimen using microtome within the thickness 3 micrometer to 5 micrometers. Computationally a 3D texture can be built by aligning these ultra-thin sections one after another and this 3D texture can be used for quantification. Chances of misalignment and local deformations between serial tissue sections get introduced during sample preparation process. Capturing the morphological deformation of these gland textures with a stain variation is challenging. Computationally, overlaying the thin histological slices involves registering (aligning) the slices into correct coordinate. The correct coordinate system will then be referenced with the template image. Reconstruction is homogeneous when the slices are stacked individually one after another but always there be a slight drift in their aperture. That is; rotation and translation variance should be insignificant during the registration.

In order to find pertinent contributions, we searched PubMed for articles using search term (Registration [Title/Abstract]) AND (Histopathology [Title/Abstract]) and found 330 results when accessed on 15th June,2023. Year wise statistics of paper publication is clearly shown in Figure 8. When the search key was made more specific to

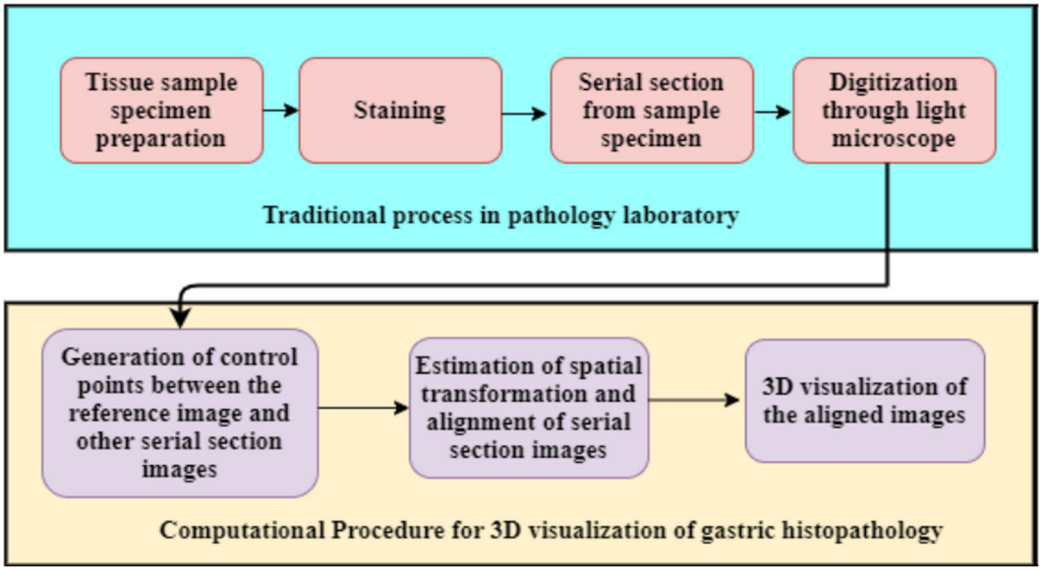

FIGURE 2. General workflow of Histopathology 3D reconstruction.

"Gastric + Histopathology + Registration", only 8 results were shown. However, when using the same search method with other histopathological samples, such as lung, kidney, prostate, liver, and breast, more papers are discovered to have been published in the past ten years. This signifies that much work is not done in the domain of gastric histopathology registration. To supplement our understanding of registration approaches, we have looked at several works from Google Scholar in addition to PubMed.

1) CLASSIFICATION OF IMAGE REGISTRATION TECHNIQUES

The selection of registration methodology is influenced by the unique properties of the histopathological pictures, such as the presence of deformations, the degree of local changes, and the required level of accuracy. To get the best alignment results for histopathology pictures, a combination of registration techniques may be used in practice. The classification of frequently used image registration methods for histopathological images is summarized as follows:

a: BASED ON NATURE OF TRANSFORMATION

In the presence of outliers and other artefacts in the input pictures, the nature of the transformation-based image registration approaches ensures accuracy and resilience. The most basic type of image registration is rigid registration since it only considers translation, rotation, and scaling as possible picture transformations. When the images being aligned contain comparable anatomical components and just differ in position and orientation, it works well [42]. Non-rigid registration methods enable more intricate spatial transformations that take anatomical variances and deformations into account. These techniques are particularly useful for aligning images of soft tissues that undergo non-linear shape changes due to factors such as organ motion, growth, or disease progression [43], [44]. Histopathology image registration frequently employs affine registration. It supports transformations including translation, rotation, scaling, shearing, and reflection. While small deformations are not captured by affine registration, it can align pictures with global geometric discrepancies.

b: BASED ON TRANSFORMATION DOMAIN

Global registration aims to align entire histopathology images or large regions of interest (ROIs) without explicitly considering local deformations. Global registration techniques work well when the pictures have comparable global structures and undergo simple transformations [42]. This method is frequently applied when aligning whole slides images or when the regions of interest span a considerable area with little local distortion. On the other hand, the goal of local registration is to accurately record local changes and deformations in histopathological pictures. It aims to align specific structures or regions of interest that exhibit significant morphological differences. Local registration methods are particularly useful when the images involve complex deformations, tissue distortions, or when aligning specific anatomical features [42], [44].

c: BASED ON DIMENSIONALITY

Histopathology image registration techniques can be classified based on the dimensionality of the images being registered. In histopathology, the most common scenario involves aligning two-dimensional (2D) histopathology images, typically represented as digital whole-slide images or individual tissue sections. 2D-2D registrations are commonly used when aligning consecutive sections from the same tissue sample or when aligning different tissue samples for comparison. 2D-3D registration techniques involve mapping the 2D

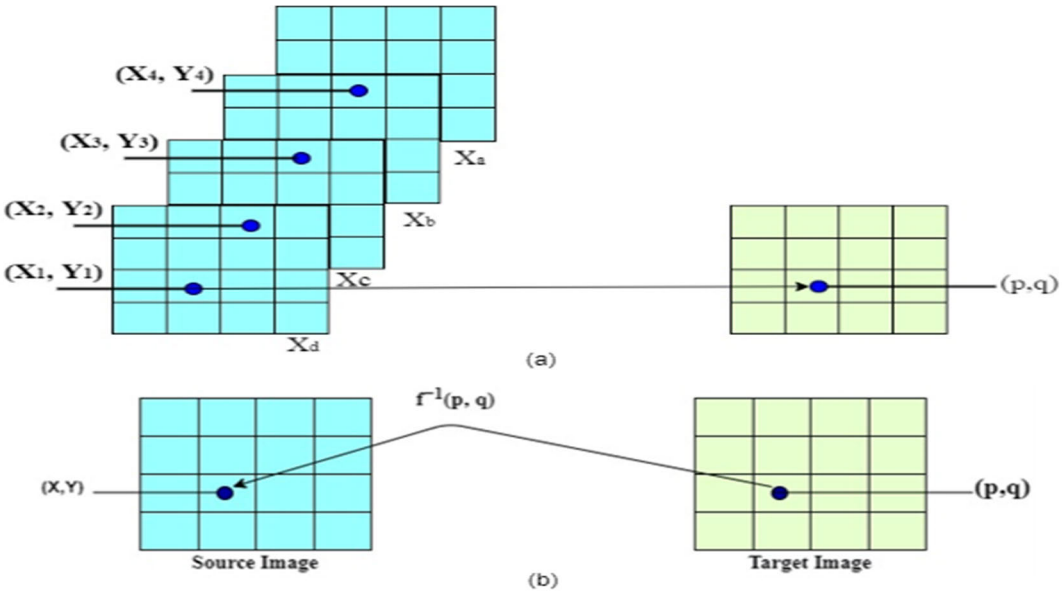

FIGURE 3. a) Forward registration b) Backward registration for section alignment.

histopathology image onto the corresponding location within volumetric image, such as a computed tomography (CT) or magnetic resonance imaging (MRI) scan. 3D-3D registration can be applied to align multiple 3D histopathology volumes acquired from the same or different samples. This type of registration enables the analysis of volumetric changes or fusion of multiple histopathology volumes [42].

In most of the previous literature, section to section alignment is done by performing forward registration [40], [45]. In forward registration serial section images are over-stacked onto a template image based on matching features or characteristics. The goal is to find the transformation parameters that minimize the difference between corresponding pixels or features in the two images. If X_1 to X_n are the serial section of input histology images and X_r is the template image, then the registration function R (S, T) is a mapping from X_1, X_2, X_n onto X_r where S represents the thin slices of histology images and T represents the resultant overlaid mapped image [46].

Fig. 3 (a) shows how the section images will be stacked in forward direction with respect to the template image. Here X_a, X_b, X_c and X_d represent the serial section images. Initially (X_1, Y_1) coordinate of X_a will be mapped with (p, q) coordinate of X_r and then (X_2, Y_2) of X_b will be mapped with (X_1, Y_1) of X_a and so on.

Since registration is performed with the goal of bringing common features of two or more images into coincidence. Any kind of distortion or misalignment during registration phase will not provide clear z- axis information. The major concern is to consider the complex deformation that occurs when the gastric tissues are removed from the body and subsequently sectioned for histology evaluation. Thus, for better performance and accurate alignment of serial sections, instead of only forward registration, both forward and backward (reverse) registration may be performed. Reverse transformation along with forward transformation might contribute positively to estimate the correspondence between images and avoid misalignment or gaps between two serial sections. In Zhang et al. and Zheng and Chellappa used the technique of bidirectional image registration where for reverse transformation, the destination pixel coordinate is calculated by an inverse function and then the corresponding coordinate points of the source image is determined [47], [48]. Figure 3 (b) depicts the backward registration technique where the destination image pixel coordinate (p, q) is mapped to the coordinates (x, y) of the source image using the inverse function $f^{-1}(p, q)$. In any gap that persists between the points of mapping, it can be eradicated by introducing new pixels, where the new pixel values are determined by interpolation of several neighboring points around it.

Table 2 summarizes various registration algorithms being applied on various samples over the years along with their nature of transformation. However, limited research is found on automated image registration process that is applied on gastric histopathology. The pictorial representation of the 3D view of gastric histology is depicted in Fig. 4.

B. VARIOUS 3D RECONSTRUCTIONS TOOLS AND TECHNIQUES

3D morphological information of histological tissue structures helps in quantitative monitoring of disease growth as well as its early detection, providing an in-depth insight to gastric surgeons about the cellular and anatomical structural mechanisms of the tissues. It provides a vital role in the clinical therapy of gastric carcinoma. Sometimes a CT scan or MRI test is carried out for further examination to identify

TABLE 2. Registration algorithms developed for 3D histopathology image reconstruction.

Year	Reference	Nature of transformation	Registration Technique	Sample	Highlights
2010	Arganda-Carreras et al. [49]	Rigid	Shape based rigid registration	H and E-stained Gland tissue of mouse of thickness 5 micrometer and size ranging from 3,000x3,000 to 5,000x5,000 pixels.	Phase correlation method used in local group registration can be applied on samples having minimum distortions
2013	Song et al. [41]	Rigid/ Nonrigid	Unsupervised content classification algorithm based on 2D multi-stain registration	80 sections of two liver surgical specimen stained with Hematoxylin and Eosin (H and E), Sirius Red, and Cytokeratin (CK) with average image size 1.4 G (Specimen A) and with average image size 18.5 G (specimen B)	This algorithm can be used when multiple stains are used to highlight different problematic region
2015	Wang et al. [40]	Rigid/ Affine	Data normalization is done using sparse approximation technique for image registration	Two datasets of 30TEM sections (512x512 pixels and 50nm thickness) and 20 ssTEM serial sections (1024x1024 pixels and 40-50nmthickness) drosophila brain neural tissues	Data normalization technique can be applied to reduce the variations between the tissue structures
2017	Obando et al. [50]	Non rigid	B spline multistained registration	8 pairs WSI Lung tissue images (8 images containing cancerous cells and 8 containing T cells) stained with Cytokeratin and CD3	This method is suitable to control the deformation level while scaling the deformation on large images. It performed well in terms of average error and standard deviation.
2018	Kugler et al. [51]	Non rigid	Geometric (landmark) based registration	2600 multi stained (H and E, AntigenKI-67, Cytokeratin-19)	The proposed algorithm can be used to construct

TABLE 2. *(Continued.)* **Registration algorithms developed for 3D histopathology image reconstruction.**

				images of pancreatic cancer tumor of mouse having serial section thickness of 4 micrometer	smooth trajectories to determine the deformations in the image dataset
2019	Lotz et al. [52]	Rigid	Parametric and Nonlinear registration	ANHIR (Automatic Nonrigid Histological Image Registration) data set which includes 8 different tissues including lung, gastric, colon tissues etc. stained with different dyes of thickness 2 to 5 micrometer	The algorithm performed robustly in 99.6 % of the training cases by reducing the landmark registration error significantly.
2019	Kajihara et al. [46]	Nonrigid	Nonrigid registration Using blending rigid transforms	Human embryo histological sections from image dataset of Kyoto collection	Problem of tissue discontinuation and deformation is addressed significantly by the proposed method. It is robust to different stained samples.
2020	Keikhosravi et al. [53]	Affine	Image intensity-based registration	206 images containing Pancreas and Breast tissues of size 1024x 1024	The proposed method is capable of performing automatic registration of the second-harmonic generation (SHG) and bright-field (BF) images of histology slides with excellent performance.
2020	Nan et al. [54]	Affine	DRMIME: Differentiable Mutual Information and Matrix Exponential for Multi-Resolution Image Registration	ANHIR (Automatic Non-rigid Histological Image Registration) data set having variety of multi stained WSI tissue images (lung lobes, colon, mammary glands etc.) of size 100k x 200k pixels each	This method can be applied to both mono-modal and multi- modal registration using mutual information neural estimation

TABLE 2. *(Continued.)* **Registration algorithms developed for 3D histopathology image reconstruction.**

					(MINE) as a metric for accurate registration.
2021	Chen et al. [55]	Rigid/ Affine/ Elastic	Hierarchical and Multi-View Registration (HMVReg) is used which includes global rigid registration and multi-view affine transformation	Private data set including 6 patients with 30 stomach images, 6 patients with 30 lung images, and 8 patients with 56 liver images.	This method can be used for solving the problem of translational and rotational differences, globally isotropic deformation, and locally anisotropic distortion.
2022	Strenge et al. [56]	Non rigid	Non rigid registration based on topological information	1630 histological images along with corresponding Optical Coherence Tomography images	It can be used for multimodal registration. Accuracy of registration: 200 ± 120 µm
2022	Ge et al. [57]	Non rigid	Unsupervised structural feature guided convolutional neural network (SFG).	ANHIR (Automatic Non-rigid Histological Image Registration) data set having variety of multi stained WSI tissue images	This technique can be used to overcome repetitive texture and section missing
2023	Awan et al. [58]	Non rigid	Deep feature-based registration (DFBR)	COMET dataset and an additional multi-IHC histology dataset	This technique used data-driven descriptors to estimate the global transformation which outperforms hand crafted feature- based approach

the exact irregular area in the gastric gland and determine the progression of the disease [59], [60], [61], [62], [63]. However, there is a significant financial burden associated with this whole process. A literature review reveals that 3D reconstruction of light microscopic gastric histopathology images is not yet extensively explored.

The size of the gastric gland tissue might differ based on the location within the stomach, an individual's variability, and health problems. On average, the width of a typical gastric gland varies between 0.03 to 0.05 millimeters [23].

Therefore, a thorough 3D visualization of the gland's interior structure may be acquired by using roughly 10 to 16 successive gastric serial section with a thickness of 3 to 5 microns and adopting an appropriate computational approach for 3D reconstruction. During our advanced search in PubMed with the keyword "3D+ Reconstruction+ Histopathology" in the search area [Title/ Abstract], 56 results were seen in the period 2013 to 2023 when accessed on 30th June 2023. However, on modifying the search key to "3D+ Gastric + Histopathology + Reconstruction" no results were found.

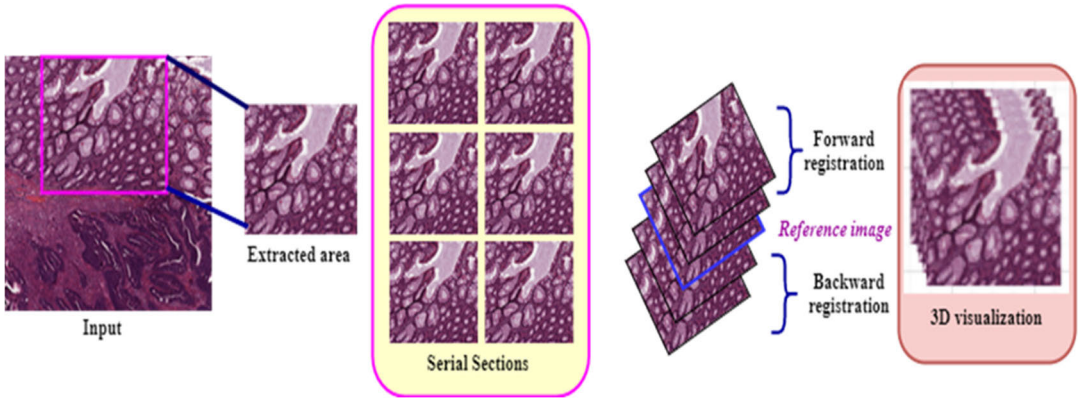

FIGURE 4. 3D View of gastric histopathology.

Light microscope, which is readily available and used in all hospitals is limited to 2D gastric histopathology imaging. It has a limiting factor of providing depth information of the tissue structures and therefore does not have the capability to provide 3D information about the gastric tissue samples. To create 3D views from various other 2D histopathology samples, a variety of approaches have been used recently. Some of these techniques include:

i) ***Serial sectioning and alignment:*** To produce a 3D representation, serial histopathological sections are obtained, aligned, and stacked. For precise alignment and reconstruction, alignment techniques like feature-based matching or registration algorithms are used [40], [64].

ii) Depth estimation: To infer the 3D structure of the tissue, depth information is obtained from 2D histopathological images. To determine depth and produce a 3D picture, methods like stereo matching, depth from focus, or depth from motion are used [63].

iii) Multi-plane imaging: A 3D representation is produced by combining several histopathological pictures that were taken at different focus planes. To combine focus areas from different planes and create a 3D picture, methods like focus stacking or extended depth of field algorithms are used [53].

iv) Image-based modelling: From 2D images of the tissue's histology, mathematical models or algorithms are used to rebuild the tissue's 3D structure. A 3D representation is made using approaches such as structure from motion, shape-from-shading, or contour-based methods [63].

v) Volumetric reconstruction: Algorithms are employed to reconstruct a 3D volume from a stack of 2D histopathology images. Techniques such as tomographic reconstruction, voxel-based methods, or surface-based methods are utilized to generate a 3D view [59], [65], [66].

vi) Surface Reconstruction: Surfaces can be reconstructed to create a 3D model by segmenting objects of interest, such as tissue borders or cell nuclei, in each 2D section. The surfaces are extracted, and a 3D representation is produced using methods like marching cubes or level set methods [59].

Different researchers have tried different techniques to develop 3D views from multiple histopathology samples to help the medical fraternity in better disease diagnosis. Some of their results achieved is highlighted in fig. 5.

Robert et al. [64] in their work used three datasets: dataset A having 70 sections from a human liver stained with H&E and showed a deposit of metastatic colorectal cancer next to a blood vessel, dataset B which contained 100 sections from a cirrhotic human liver stained with picrosirius red and dataset C which consisted of 111 sections from an 18-day old mouse embryo stained with H&E. It employs an innovative technique for slice-to-slice image registration, employing automatic registration algorithms specifically created for histopathology pictures and virtual slides. The results achieved by the authors is shown in Figure 5 (a), (b) and (c). Jansen et al. [67] worked on the transurethral bladder where specimens were cut into 4 μm sections and stained with hematoxylin and eosin (H&E). Digital images were obtained using a scanner and aligned through rigid and affine image alignment. To construct 3D segmentations of the tumor and muscularis propria (MP), manual delineation was done. On a 3D workstation, the Vesalius3D interactive visualization tool was used to visualize the data, and the output is shown in Figure 5(d). Figure 5(e) shows the result obtained by the authors using 100 to 200 serial sections of lung tissues with a thickness 4-6 micron. To create 3D models, commercially available or custom software is then used to process these serial digital images [26]. The author's research employed 3D histopathology datasets with more than 100 sections [68]. Each slide is created in accordance with the standard 2D workflow. The Leica Aperio AT2 scanner was used to scan the WSI pictures, which are then combined into a slide stack. A slide stack with 50 images from a colorectal cancer was scanned at 20x and the final result obtained can be seen in Figure 5(f) [68].

Through our extensive literature survey, we could not find any work done to create 3D view of light microscopic gastric histopathology gland images. However, there are few works where the authors have explored image analysis on gastric

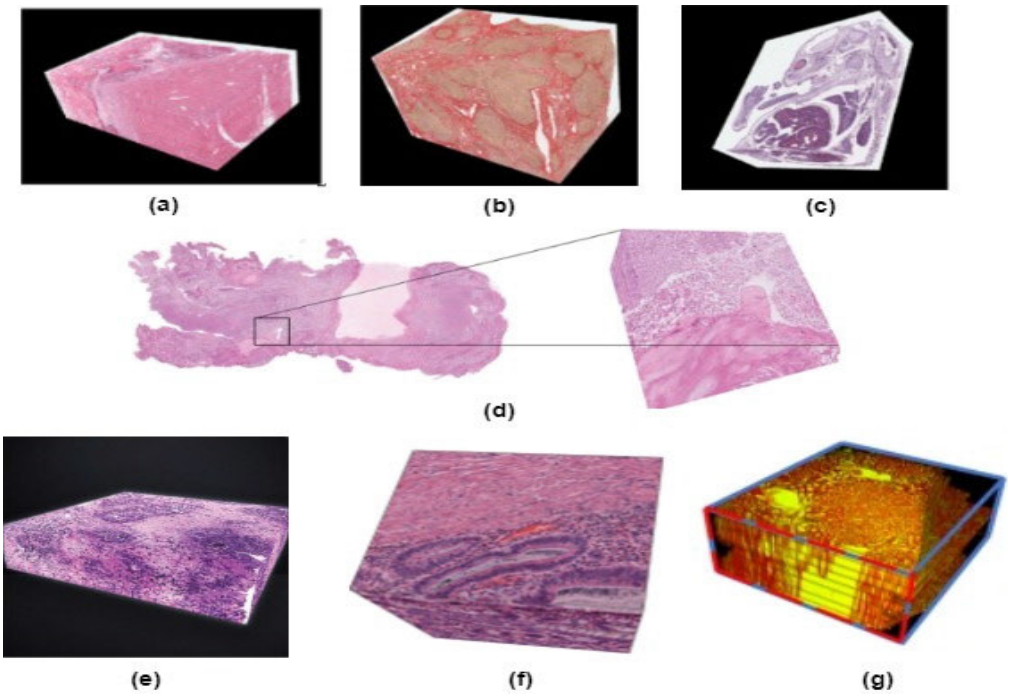

FIGURE 5. (a) 3D volume from 70 sections from a human liver containing a deposit of metastatic colorectal carcinoma adjacent to a blood vessel [64] (b) 3D view from 100 sections from a cirrhotic human liver infected with hepatitis C (stained with picrosirius red) [64] (c)111 sections of an 18-day post-fertilization mouse embryo (stained with H&E) [64] (d) 3D view of bladder tumors [67] (e) 3d view of lung tissues using 100-200 sections [26] (f) Slide stack of a colorectal adenocarcinoma consisting of 50 slide images scanned at 20x [68] (g) 3D view from serial histopathological images of renal cortical tissues [40].

MRI and CT images. Table 3 depicts various 3D reconstruction techniques used in the past few years on gastric and other CT and MRI images for improving the efficiency of disease diagnosis.

In Medical imaging, the significance of 3D visualization tools for tissue images lies in their capacity to unlock a new dimension of understanding and analysis in the field of medical research and clinical practice. These resources aid in more accurate diagnosis, better therapy preparation, and better patient outcomes. By offering tools and capabilities to process, align, and visualize the images in three dimensions, 3D visualization software plays a crucial part in the 3D reconstruction of serial section histopathological images. Utilizing 3D visualization tools, the reconstructed 3D volume can be rendered, giving the histopathological data a realistic and immersive depiction. A comprehensive list of some of the 3D visualization software tools available for different medical imaging modalities is given in table 4. The choice of software depends on specific requirements, imaging modalities, and research or clinical needs.

V. COMMON CHALLENGES FACED IN EXISTING WORK AND FUTURE DIRECTION

Future developments and applications for 3D reconstruction of histopathological images are highly promising. First of all, there aren't many studies that discuss image reconstruction techniques for gastric glands. Some of the areas, where the field is expected to have a substantial impact include improved diagnostic accuracy, virtual reality visualization, and quantitative analysis by enabling the assessment of gland size, growth patterns, invasion depths etc. However, obtaining 3D views from histology sections has faced several challenges till date.

Physical destruction is caused during the tissue fixation and tissue cutting processes using microtome [87]. Tissue deformation can occur during the processing of histopathology samples, including fixation, embedding, and sectioning. Accounting for tissue deformation and accurately reconstructing the original 3D structure from distorted 2D images can be difficult. There is always a non-rigid deformation within the location that occurs in different points of the histology images, and this might alter the data information. Another significant challenge related to staining the sample specimen is that uneven stain variations will cause discrepancies in the density of individual tissue components [88], [89]. Variations in staining intensity, image contrast, and image quality across different sections can impact the accuracy of the 3D reconstruction. This paper focuses on two major challenges related with gastric 3D histology image reconstructions: i) Extraction of analyzing area ii) Alignment of serial sections.

i) Extraction of analyzing area from gastric histopathology images is of main challenge. As per the pathologist's knowledge exact parameters for adenocarcinoma is not yet

TABLE 3. Various 3D reconstruction techniques applied on gastric images of different modalities.

Year	Reference	Technique	Input images	Advantages	Future scope
2005	Akemi Tsutsui et. al [69]	Ultrasonic Mini probe (UMP)	Gastric Endosonographic Images	The histology diagnosis and the depth of tumor invasion as determined by the 3D imaging yield same results.	Not specified
2014	Wang et. al [70]	Structure from Motion along with Patch fusion	Gastric endoscopic images	3D depth was constructed from moving gastric endoscopic images and the results obtained were promising in gastroscopic environment	Creation of an enhanced reality image guided system for minimally invasive surgery using a gastroscope that can give the endoscopist reliable 3D in-formation
2015	Kim et al. [59]	Surface Volume Rendering technique	Multi detector CT gastric images	Exact localization of the tumor and accurate tumor staging	Future work can focus to detect color changes in gastric mucosa and make the computation less time consuming
2015	Chen et al. [61]	Hybrid Light-transport-model-based 3D optical imaging	CT gastric image	Better longitudinal and quantitative observation of the development of in situ gastric cancer	Cross validation of in-vivo imaging results with other tools can be done and this technique should be tested on diverse CT datasets
2016	Buisman et al. [60]	Matrix 3D Ultra Sound	MRI Gastric sample	Performed better than dynamic MRI Imaging	Not specified
2018	Zhang et al. [62]	3D Micro-vessel Density	Phase contrast CT gastric images	Provided qualitative understanding of micro vessel distribution	Vessel deformation and information loss should be minimized
2019	Widya et al. [63]	Structure from Motion	Gastric Endoscopic image	Embed color texture information to the reconstructed 3D shape of stomach	Mesh generation process can be refined for better having down sampling and outlier rejection approaches
2020	Ralf Hackner et al. [72]	Depth Estimation Motion Network	Gastric endoscopic images	Produced 3D estimates of stomach components, which was based on pairs of monocular gastroscopic images	The next stage to raise the quality of reconstruction is to retrain the DeMoN network using native endoscopic data
2021	Widya et al [74]	CycleGAN as an image-to-image style translator	Gastric Endoscopic image	Generated VIC images significantly increased the number of extracted	Real-time whole stomach reconstruction by combining VIC

TABLE 3. *(Continued.)* **Various 3D reconstruction techniques applied on gastric images of different modalities.**

				SIFT feature points	image generation and real-time depth and pose prediction as performed in deep-learning-based SLAM methods.
2021	Widya et. al [73]	CycleGAN	Gastric Chromoendoscopic images	The suggested approach could estimate the depth in gastro endoscopy by self-supervised training. It worked well for chromoendoscopic and general endoscopic white-light images	Not clearly specified

fully characterized. One of the parameters for the pathologists is to analyze the nuclei density and gland morphometry. So, a focus on gland section 3D reconstruction for this section will definitely help in early diagnosis. Also, glandular structures in gastric histopathology images can overlap or have touching boundaries, posing challenges for accurate segmentation.

ii) Alignment of histologically thin slices involves registration or mapping of exact coordinates. When registering histology sections with different stains, the challenge is that different stains highlight distinct tissue substances, leading to dissimilar structural appearances on neighboring tissue segments. This complicated impact of distortion makes the recording of histopathological information a more difficult task. Also, the alignment of the slides is a significant problem in the 3D representation, as nonlinear deformation happens during the sampling process of specimen fixation and sectioning [52]. If there is discontinuity of tissue as a consequence of the gaps that appear in the overlapping parts, registration may fail.

Other than the above-mentioned challenges, sectioning artifacts also pose a challenge in 3D reconstruction. Serial sectioning of tissue samples can introduce artifacts such as tissue folds, tears, or missing sections. These artifacts can affect the accuracy and completeness of the reconstructed 3D view.

In light of the endeavor to create three-dimensional views of light microscopic gastric histopathology tissue images, the following important findings have been made. Eminent researchers can take note of these facts, interpret them as a limitation or a challenge, and use them to improve image analysis in this area of research.

1. The automatic registration between SHG and BF images of H&E-stained tissues has shown successful results. However, future work in this area involves developing a normalization approach to correct staining and illumination artifacts in bright field (BF) images [53].

2. The proposed feature-based technique needs enough feature points for registration, and a more reliable matching algorithm can boost the accuracy of registration. Large distortions may cause the tissue extraction process to fail, resulting in unsuccessful scale and registration adjustments. A more reliable tissue extraction technique can improve overall robustness [46].

3. The optimization process of iterative 2D/3D medical image registration involves the time-consuming continuous generation of digitally reconstructed radiograph (DRR) images through projection rendering. Future research should optimize DRR generation using GPU acceleration to reduce time consumption in iterative 2D/3D medical image registration. Additionally, studying non-rigid transformations can improve the accuracy of image registration to meet clinical requirements [90].

4. The SFG (Structural Feature Guided) CNN method for histological image registration faces challenges with tearing regions. Future research can focus on improving its robustness and adaptability in histological image registration scenarios [57].

5. Cross slide registration technique faced challenges like reliance on deep features, which may not be available or effective in all scenarios, and difficulty aligning slides with fatty tissue. Future studies could concentrate on creating stronger alignment methods, especially for circumstances in which slides have a significant quantity of fatty tissue [58].

6. Due to the major differences in tissue architecture, the multi-stain 2D registration approach performs less effectively when there is a bigger gap between sections. There is scope for improvement in the registration process to account for wider section gaps and take tissue structure changes into account [41].

TABLE 4. 3D Visualization tools used in various imaging modalities.

Software and Developer	Features	Supported File Formats	User Interface	Open Source
Voloom (micro-Dimensions) [75, 76, 77]	Using arbitrary cutting planes and direct volume rendering, the visualization module offers a 3D perspective	Histopathology	User friendly	Yes
3D Slicer (Interdisciplinary group of scientists, engineers, and medical professionals) [78, 79]	Interactive Visualization, segmentation, registration, and analysis of 3D models	MRI, CT, US, nuclear medicine, and microscopy	User friendly	Yes
Fiji/ImageJ (Wayne Rasband, National Institutes of Health (NIH) [80, 81, 82]	Image Processing Measurement and Quantification Image Visualization	Bright field microscopy Fluorescence microscopy, Electron microscopy, X-ray, MRI and CT imaging Light Microscopy	User friendly	Yes
Amira (Zuse Institute Berlin Thermo Fisher Scientific) [83]	Scientific visualization, data analysis, and presentation of 3D data	Optical and Electron Microscopy, CT, MRI WSI etc.	User friendly	No
ITK-SNAP Biomedical Imaging Research Group at the University of Pennsylvania [84, 85]	Seamless 3D navigation Segmentation	Magnetic resonance imaging (MRI), cone-beam computed tomography (CBCT) and computed tomography (CT)	User friendly	Yes
3D Histech software (3D Histech) [86]	Advanced visualization options, Measurement tools to assess metric distances, 3D reconstructions	Bright field microscopy, Fluorescence microscopy, Electron microscopy, WSI	User friendly	No

7. The proposed method is validated using synthetic data, highlighting the need for further validation with real tissue samples to assess its performance in realistic scenarios. Additionally, exploring the algorithm's applicability to analyze tissues beyond mammary glands can broaden its usage in biomedical research and clinical applications [49].

Future studies can go beyond visualization and focus on developing quantitative methods to extract meaningful features from 3D reconstructions of gastrointestinal tissue. By measuring morphological metrics, spatial correlations, and cellular heterogeneity within the reconstructed volumes, these techniques can provide valuable insights for understanding gastric pathology and facilitating diagnostic and prognostic evaluations. Additionally, in the course of our extensive survey, it was seen that the dataset of serial section gastric histopathology images obtained from light microscopy is not publicly available. Hence establishing benchmark datasets and standardized validation metrics specific to the 3D reconstruction of gastric histopathology images is of utmost importance. This would enable fair comparisons and assessments of different algorithms and approaches, driving advancements in the field.

VI. CONCLUSION

3D light microscopic histopathology reconstruction of a gastric sample can reveal the tumor characteristics of the gastric

gland, providing extended z axis information. Overlaying approximately 10 to 16 serial sections of 3-micron thickness can produce a 3D texture representing the width of a gastric gland. This process will result in the generation of a tubular structure with a width ranging from 0.03mm to 0.05mm in size. This study examines the importance of 3D reconstruction from light microscopic gastric images, highlighting its advantages over whole slide imaging, primarily in terms of cost and computational complexity. This paper offers a comprehensive review and comparative assessment of various existing survey papers that center around the 3D reconstruction of histopathology images. Also, it thoroughly discusses an inclusive compilation of endeavors pursued by diverse authors across various stages, like registration, 3D visualization etc. inherent in the 3D reconstruction process. Details about some of the latest 3D visualization tools that can contribute to providing high quality 3D visualization of the registered tissue images is also summarized in this piece of work.

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