# Review Article: New Findings in the Anatomy of the Human Body

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## ABSTRACT

In recent years, new findings have been made about the anatomy of the human body, which challenged some of the existing information about the structure and function of the human body. Some of the most important findings are the identification of salivary glands on a macroscopic scale as tubarial glands in the nasopharynx, the identification of lymphatic structures in the central nervous system as the meningeal lymphatic system and the glymphatic system, the identification of the mesentery as a continuous structure along the entire abdominal portion of the gastrointestinal tract, and finally, the identification of a new tissue structure called interstitium in some organs of the body. A careful review of these findings is of great importance in terms of understanding the pathogenesis of related diseases, designing treatment methods, basic research, and educating medical students. The purpose of this article was to review the latest findings regarding the anatomy of the human body and their practical importance in the medical sciences.

## 1. Introduction

New findings on the anatomy of the human body generally report a rare phenomenon. In recent years, there have been reports of new organs being identified in the human body. One of these discoveries was the identification of a pair of salivary glands on a macroscopic scale in the nasopharynx called the tubular glands [1]. It is believed that this discovery may help prevent the side effects of radiotherapy in patients with head and neck cancers. Because it is possible that part of the problems of these patients may be due to unwanted injuries caused by radiation therapy of these glands. Another discovery was the identification of a lymphatic structure in the Central Nervous System (CNS). Until now, it was believed that the brain and spinal cord are organs that have no lymphatic system. In this regard, experimental evidence of the existence of a true lymphatic system in the meningeal membranes around the brain and spinal cord has been recorded, which eventually drain into the deep lymph nodes in the neck [2]. Recent studies also have indicated the existence of a structure in the CNS known as the glymphatic system, which is responsible for discharging waste products from nervous tissue [3].

This system is formed by spaces bounded by leptomeninge as well as glial cells around the blood vessels of the brain and spinal cord. The presence of these two lymphatic systems indicates the clearance of metabolic wastes as well as the cycle of immune cells in the CNS.

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Another finding is the anatomical structure of the mesentery in adults and indicates a continuous and integrated extension of the mesentery along the intra-abdominal part of the gastrointestinal tract [4, 5]. Contrary to popular opinion that the mesentery is a discontinuous structure. This finding is very important in the management of intestinal surgeries, especially cancers, as well as developmental disorders. The identification of a new tissue component called the interstitium, a network of sinuses surrounded by collagen fibers in several organs of the human body, is another recent finding [6]. This newly discovered structure has so far been considered as an artifact resulting from the tissue processing in the submucosa of the luminal organs. This system, while providing flexibility in the limbs, also creates ducts to guide immune, inflammatory, and metastatic cells; therefore, these ducts can also be used to treat some diseases [6]. In this article, we reviewed the findings along with the anatomical structure and its clinical importance to better understand the pathogenesis of related diseases.

## 2. Tubarial Salivary Glands

The salivary gland system consists of three pairs of large salivary glands called parotid, submandibular, and sublingual glands, as well as about a thousand small and scattered salivary glands in the submucosal layer of the upper alimentary tract [7]. The tubal gland is one of the small salivary glands located in the submucosal layer adjacent to the Eustachian tube [8]. Recently, researchers have developed a molecular imaging technique called positron emission tomography or computed tomography by the radio-labeled ligand to detect prostate-specific antigens called PSMA1 PET/CT, which also can detect highly sensitive salivary glands [9]. In disbelief, the researchers while identifying prostate-specific antigens using the PSMA1 PET/CT technique, they also identified a pair of unknown structures behind the nasopharynx through absorbing ligands similar to the large salivary glands (Figure 1).

Initially, it was assumed that these organs could contain large amounts of seromucinous ascites to aid in swallowing. Accurate knowledge of the nature of these organs was of particular importance because of its close association with the treatment of head and neck cancers, as high-dose external beam radiotherapy in head and neck cancers can damage the salivary glands and result in dysphagia [10]. Therefore, a comprehensive study was performed to investigate the anatomical structure and its clinical relationship with radiotherapy [1].

The results of this study (imaging by PSMA1 PET/CT in 100 patients) confirmed the presence of a pair of PSMA-positive anatomical structures in the posterolateral wall of the nasopharynx. The autopsy also revealed a mass of mainly mucous glandular tissue with macroscopic drainage ducts that opens into the posterolateral wall of the nasopharynx. These glands are called tubarial glands because of their position relative to torus tubarius. Anatomically, these glands extend downward to the pharyngeal wall and upward to the Rosenmuller cavity. Histologically, the cells of these glands have a high expression of cytoplasmic marker PSMA.

There are reasons why such a structure was not previously known as a macroscopic gland. Firstly, the presence of a group of acini cells in the nasopharynx has been previously reported but not as a unique macroscopic structure. Secondly, it was not possible to observe such a submucosal structure as a pair of salivary glands due to its special position and limited access to the base of the skull in conventional imaging. Overal, compared to the known major salivary glands, the tubarial glands had the most similarities with the sublingual glands based on the predominant mucous acini. It is also physiologically accepted that the tubarial glands moisten and lubricate the nasopharynx and oropharynx. However, no centralized research has been done on their microscopic structure as well as their origin and embryonic development.

## 3. Meningeal Lymphatic System

Although it is said that the CNS is inherently safe due to the lack of lymphatic system and the presence of a blood-brain barrier [11, 12], for the first time in 1816, an Italian anatomist named Paolo Mascagni suggested the existence of lymphatic vessels in the meninges of the brain [13]. However, this hypothesis was not considered by other researchers until 2015 due to the presence of immune cells in the CNS and cerebrospinal fluid, as well as the role of these cells in the pathogenesis of many CNS disorders. In this regard, Louveau et al. reported the presence of lymphatic vessels around the dural venous sinuses of the brain [2].

The results of this study showed that these structures while expressing specific macromolecules of lymphatic endothelial cells, such as lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1), Prospero homeobox 1 (PROX1), podoplanin (PDPN), and vascular endothelial growth factor receptor 3 (VEGFR3) can transfer fluid and immune cells from cerebrospinal fluid and eventually, drain into the deep cervical lymph nodes. On the other hand, the results showed that the obstruction of the af-

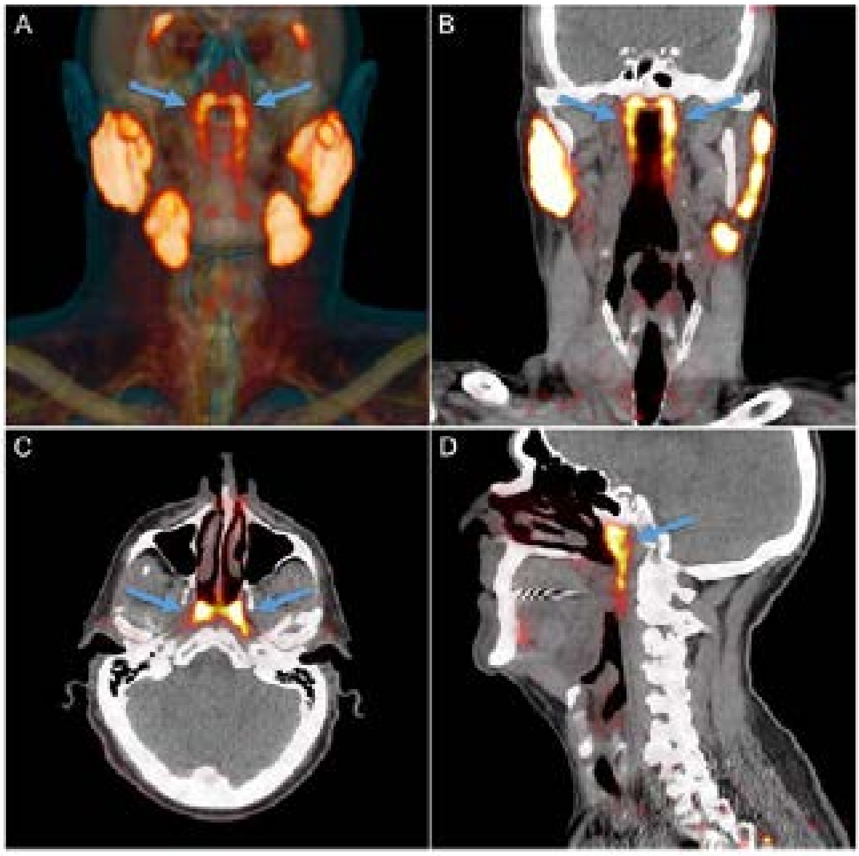




**Figure 1.** PSMA1 positron emission tomography-computed tomography (PET/CT) imaging shows a pair of macroscopic salivary glands (arrows) in the nasopharynx
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ferent lymph vessels of the deep cervical lymph nodes causes dilation of the meningeal vessels. Aspelund et al. also showed that the dural lymphatic vessels are responsible for the uptake of cerebrospinal fluid from the adjacent subarachnoid space as well as the interstitial fluid from the brain through the glymphatic system [3]. These vessels, on the other hand, carry a mixture of cerebrospinal fluid as well as interstitial fluid through the skull base foramina to the deep cervical lymph nodes. To investigate the presence of lymphatic vessels inside the CNS and the meningeal membranes, the researchers evaluated the expression of specific markers of lymphatic and blood vessels in mice. In this study, the expression of PROX1 and CCL21 markers was observed in meningeal membranes adjacent to dural blood vessels. On the other hand, immunofluorescence examination of the superior sagittal lymphatic vessels showed that these vessels, like other lymphatic vessels, express very small amounts of PECAM1.

The abundant expression of LYVE1, PDPN, VEGFR3, CCL21, and PROX1 markers indicates that these vessels are lined by differentiated lymphatic endothelium. The researchers also hypothesized that the dural lymph vessels may carry some macromolecules so that following complete aplasia of the lymph nodes in transgenic mice, the clearance of these macromolecules and their transfer from the subarachnoid space to the deep cervical lymph nodes stops. Studies have shown that the dural lymphatic network in the basal parts of the brain is wider than the upper part and also has valves with unknown functions [2]. Contrast-phase imaging studies confirmed the presence of very delicate lymph vessels in the meningeal membranes around the brain. In this regard, Absinta et al. identified meningeal lymphatic vessels in humans and monkeys using high-resolution Magnetic Resonance Imaging (MRI) and also using a special contrast called Gadobutrol (Figure 2) [14].

These findings were also confirmed by immunohistochemical identification of specific endothelial markers of lymphatic vessels [14]. On the other hand, Eide et al. after intrathecal injection of contrast agent and MRI showed that the lymph vessels of the CNS are drained into the deep cervical lymph nodes [15]. Despite the re-

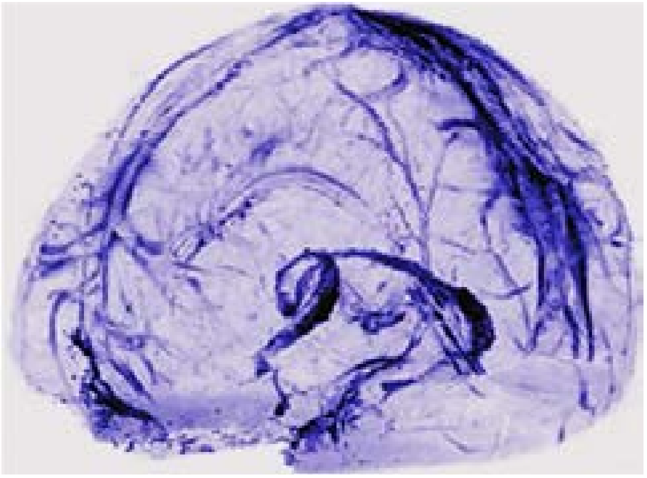



**Figure 2.** Identification of lymphatic vessels in human brain scans using Gadobutrol contrast (300×300 DPI)
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ports, researchers still believe that more studies are needed to identify the exact location and characteristics of the meningeal lymph vessels as well as their relationship in cerebrospinal fluid. Identification of lymph vessels in the CNS justifies the role of the immune system in the pathogenesis of some CNS disorders and inflammatory diseases [16, 17]. Research on the role of immune peripheral cells (T lymphocytes) that enter the brain has shown that the removal of deep cervical lymph nodes in mice causes changes in cognitive behaviors, such as spatial learning and memory [18]. It is also believed that there is a mechanism similar to the cognitive decline mechanism caused by the chemotherapy, dementia, and AIDS [18].

## 4. Glymphatic System

It is believed that there are pseudolymphatic channels around the blood vessels of the CNS that direct interstitial fluid containing metabolic wastes from the brain and cerebrospinal fluid to the cervical lymph nodes [19]. In this regard, experimental evidence confirms the existence of a closed circular system consisting of spaces around blood vessels in the CNS [3, 20]. It is called the glymphatic system because this system is completely dependent on aquaporin channels in areas bounded by glial cells (spaces surrounded by astrocyte appendages around the blood vessels of the brain) and also plays a role in clearing the interstitial fluid of the CNS (Figure 3 shows the cycle of the glymphatic system) [19].

Based on available data on the glymphatic system and meningeal lymphatics, it can be assumed that there is a relationship between them through brain fluids without any obvious anatomical connection. Functionally, the glymphatic system is connected to the meningeal lymphatic system and is thought to be the main route of transport of immune cells to the cerebrospinal fluid and also from the cerebrospinal fluid to the brain parenchyma [3]. The space around the blood vessels inside the brain tissue is called the Virchow-Robin (V-R) space [19, 20]. The V-R spaces around the jugular veins receive interstitial and cerebrospinal fluid collected from the brain and then, direct them to the deep cervical lymph nodes [19, 21].

Today, it is believed that the glymphatic system is the main route of discharge of metabolic wastes from the CNS, and disorders in this system are one of the causes of Alzheimer's disease [16]. On the other hand, it was found that this system is mainly active during sleep to discharge metabolic wastes of the CNS. Two-photon imaging of the glymphatic system in mice showed that the cerebrospinal fluid flow in the awake state is about 90% less than in the anesthetized state [22]. A recent study has also identified perivascular spaces around the retinal vessels as well as the optic nerve [23].

## 5. Continuous Mesentery in Adults

Contrary to popular belief, considering the mesentery as a discontinuous structure [11, 12], recent studies have indicated that there is a disagreement among researchers about its continuity or discontinuity [4, 5, 24]. Radiological and surgical evaluations showed that the mesentery is a continuous structure from the duodenojejunal flexure to the anorectal junction [25]. The results of a study on 109 patients undergoing abdominal colectomy showed that the mesocolon expanded regularly and uniformly from the ileocecal to the rectosigmoid junction [26]. In another study, while identifying continuous and integrated mesentery in abdominal CT scan images, a digital model

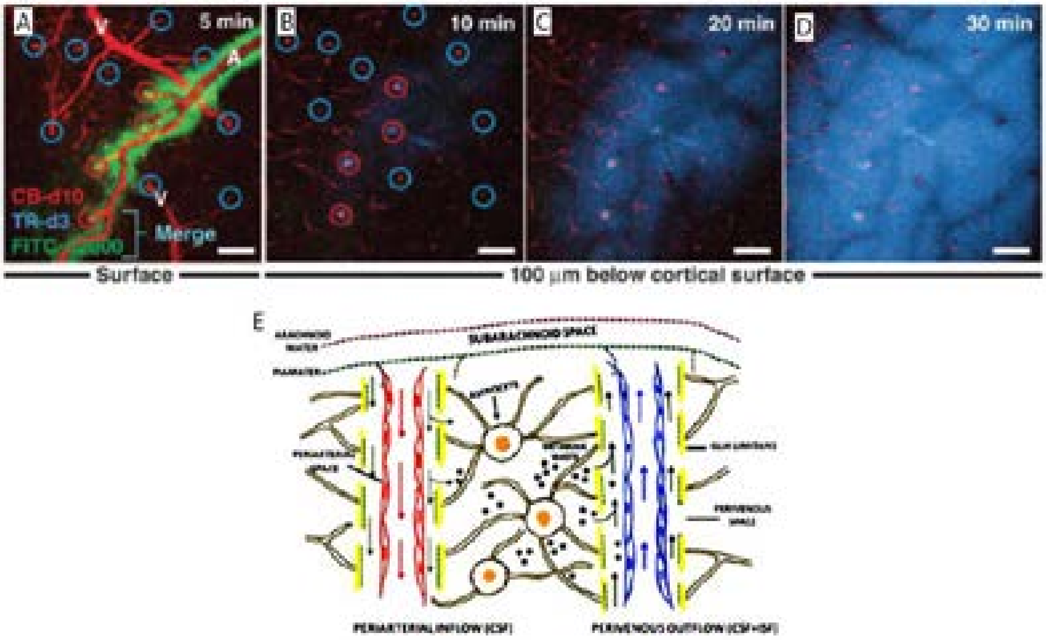




**Figure 3.** Two-photon imaging of the glymphtic cycle in the brain

The cycle of tracers injected into the subarachnoid space is determined by a two-photon microscope. A: The imaging of the superficial part of the cerebral cortex 5 minutes after the injection of the TR-d3 (blue) and FITC-d2000 (green) tracers; B, C, and D: Imaging at a depth of 100 μ from the surface of the cerebral cortex, 10, 20, and 30 minutes after the injection of the tracers, respectively. E is a schematic diagram of the glymphatic cycle. Reproduced with permission from Jessen lab, NIH/NIDS.

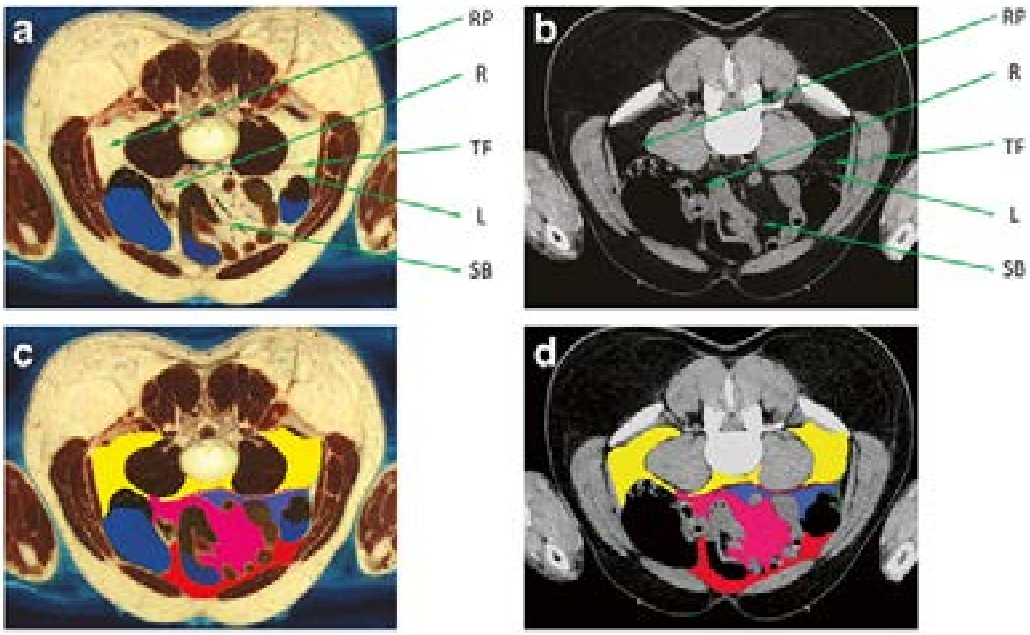


**Figure 4.** Continuous mesentery in the human body



A: The left (L) and right (R) mesocolons, the small intestinal mesentery (SB), the Toldt,s fascia (TF), and the retroperitoneum (R); B: The CT scan image of the same surface as the previous section, which shows similar structures; C: The digital overlap on A, in which the left and right mesoclon (blue), small intestinal mesentery (pink), retroperitoneum (yellow), Toldt's fascia (red dotted line), left lateral peritoneal fold (green crease point), and greater omentum (red) are marked; D: The same digital overlap on figure B. Reproduced with permission from Springer, copyright 2016.

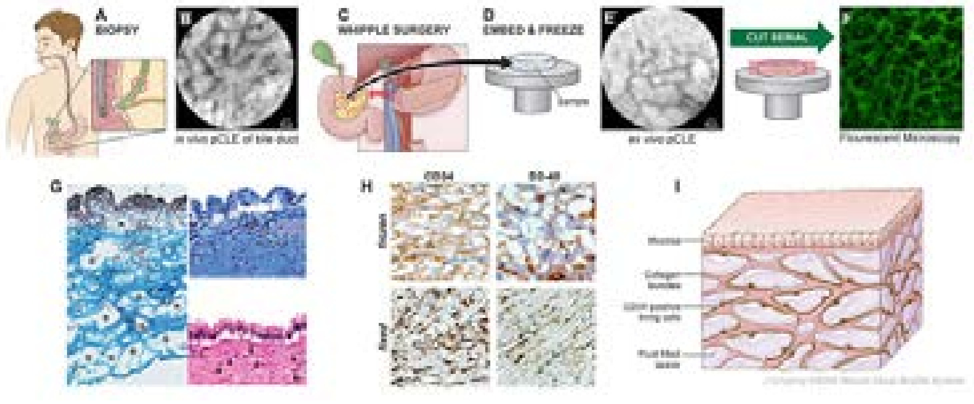


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**Figure 5.** Identification of interstitium.

A: BIOPSY; B: (pCLE in vivo); C: Whipple; E: (pCLE ex vivo); F: (immunofluoresence staining); G: (Mason trichrome staining); H: (CD34 and C2-40 immunohistochemical staining) represent a reticular structure in the wall of the bile duct. Figure 1 also shows a schematic diagram of the interstitium.

of continuous mesentery was presented using these data (Figure 4) [24]. Toldt,s fascia, a connective tissue separating the mesocolon from the retroperitoneum, was also identified along the gastrointestinal tract [24, 25]. On the other hand, histological and electron microscopy studies confirmed the integrity observed in the mesocolon as well as Toldt,s fascia [27]. Another group of researchers described the exact shape of the mesentery from the duodenum to the rectum through dissection [5]. Studies have shown that due to the presence of food and drug-metabolizing enzymes and their carriers in the mesenteric tissue, this tissue can be effective in the pharmacokinetics of drugs [28]. Mesentery also plays an important role in the etiogenesis of diseases, such as Crohn's disease due to abundant blood and lymph vessels, abundant accumulation of immune cells, and large amounts of adipose tissue [29]. Therefore, accurate knowledge regarding continuity or discontinuity of mesentery in surgical methods to improve gastrointestinal disorders, such as cancer and its prognosis is very valuable.

## 6. Interstitium

Researchers have recently identified a unique structure called interstitium in the luminal organs using a probe-based confocal laser endomicroscopy (pCLE) [30]. In other words, what had so far been known as an artifact in the submucosal layer of these organs, Benias et al. identified as a real anatomical structure (Figure 5) [6]. The pCLE technique allows for the preparation of histological images of the target tissues at a depth of 60 to 70 μ during endoscopic surgery. During the pCLE technique with fluorescein injection for extrahepatic bile ducts, the researchers also observed a network of fluorescein-laden sinuses that had not yet been described [6]. In order to better understand interstitium and also to preserve its natural three-dimensional structure, tissue sampling was performed by freezing biopsy method. Due to drain tissue fluid in conventional sampling methods, collagen fibers collapse and stick to each other; therefore, their natural three-dimensional structure will change. A network of fluorescein-stained bundles was detected in the prepared tissue sections. Also, such spaces were detected with Mason,s trichrome staining in the submucosal layer. To isolate these spaces from lymphatic-vascular spaces, immunohistochemical staining was performed with relevant markers. Immunohistochemical staining showed a positive reaction to Vimentin, CD34, and D2-40 on the inner surface of collagen bundles, as well as a negative reaction to other lymphatic-endothelial markers, such as CD31, ERG, and LYVE-1. Immunohistochemical reactions were also negative for actin as a smooth muscle myopathy marker and CD117 as a stem cell marker. This network has been confirmed in ultrastructural studies by electron microscopy as well as second-harmonic generation (SHG) microscopy [6]. On the other hand, the researchers also identified this structure in other tissues that are under intermittent pressure, including the submucosal layer of the entire gastrointestinal tract, soft tissues around the bronchi and arteries, bladder, dermis, and fascia [6]. Accordingly, the researchers believe that this structure may be present in many (or all) organs of the body; however, more research is needed to prove this. It is said that the presence of interstitium in the wall of an organ is likely to be physiologically and functionally important and can act as a shock absorber and support the mechanical function of the tissue. It may also act as a conduit for immune-dependent cells, microorganisms, and metastatic cancer cells. Therefore, sampling of interstitium and analysis of its fluid can be useful to know the prognosis and diagnosis of inflammatory and infectious diseases as well as some cancers [6].

## 7. Conclusion

Advances in imaging techniques, such as endoscopy and microscopy have provided a new and more accurate understanding of organs of the human body. Although the discovery of a new organ on a macroscopic scale seems unlikely, the discovery of new structures at the microscopic level can be expected. On the other hand, the discovery of new organs or a more realistic view of existing structures provides the basis for a more accurate understanding of their physiological functions. Such discoveries are very important in understanding the pathogenesis of related diseases as well as their appropriate treatments.

## Ethical Considerations

### Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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### Conflict of interest

The authors declared no conflict of interest.

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