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Microvasculature of the esophagus and gastroesophageal junction: Lesson learned from submucosal endoscopy

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Abstract

Advanced therapeutic endoscopy, in particular endoscopic mucosal resection, endoscopic submucosal dissection, per-oral endoscopic myotomy, submucosal endoscopic tumor resection opened a new era where direct esophageal visualization is possible. Combining these information with advanced diagnostic endoscopy, the esophagus is organized, from the luminal side to outside, into five layers (epithelium, lamina propria with lamina muscularis mucosa, submucosa, muscle layer, adventitia). A specific vascular system belonging to each layer is thus visible: Mucosa with the intra papillary capillary loop in the epithelium and the sub-epithelial capillary network in the lamina propria and, at the lower esophageal sphincter (LES) level with the palisade vessels; submucosa with the drainage vessels and the spindle veins at LES level; muscle layer with the perforating vessels; peri-esophageal veins in adventitia. These structures are particularly important to define endoscopic landmark for the gastro-esophageal junction, helpful in performing submucosal therapeutic endoscopy.

Key words: Microvasculature; Esophageal anatomy; Submucosal endoscopy; Per-oral endoscopic myotomy; Advanced imaging

Core tip: In the last years advanced endoscopic technology and techniques allowed the possibility to *in vivo* evaluate the esophageal vasculature. We aimed to

review the endoscopic endoluminal and transluminal appearance of the esophageal vascular structures. This paper will allow the reader to deeply understand mucosal, submucosal and muscular layer vessels by a direct endoscopic visualization. The authors' knowledge of the characteristic changes in health and disease, as well as descriptions of anatomical landmarks, will serve to inform the practice of endoscopic surgery in the future.

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INTRODUCTION

Flexible endoscopes were first introduced in 1950s and since that time physicians have been able visualize the gastrointestinal tract. In the past 10 years endoscopy benefited from several technologies such as high-definition television, high-resolution endoscopy, magnification and narrow band imaging (NBI)[1]. Results from the anatomical *ex-vivo* studies have informed the approach to endoscopic examination, but these technologies herald a new era of observation, where the direct visualization of living tissue can confirm, and add to, the observations of the past.

In this article we aimed to review the endoscopic endoluminal and transluminal appearance of the esophageal vascular structures, with particular attention to the state-of-the-art endoscopic equipment and techniques now available.

Advanced diagnostic endoscopy: Magnification endoscopy and NBI

Magnification endoscopy up to 80x (GIF-H260, Olympus Medical Systems Co. Tokyo, Japan) is an excellent tool for the visualization of the normal esophageal mucosa and in the diagnosis of early esophageal cancer[2]. Using magnification, one can begin to visualize the esophageal microvasculature, with the surface capillaries displaying a looped configuration[3]: The intra-papillary capillary loops (IPCLs).

NBI is a relatively recent modality employing narrow-bandwidth filters [red-green-blue (R/G/B) sequential system][4], to increase the contrast between the mucosal surface and the underlying vascular pattern[5]. The depth of penetration, and thus the color seen in the screen, depends on the wavelength used: It is superficial for the blue band, deep for the red band and intermediate for the green band. The blue filter in particular has been designed to be similar to the peak absorption of hemoglobin, in order to emphasize capillary vessels at the mucosal surface[6]. Magnification endoscopy with NBI (M-NBI), therefore, has been developed for two distinct applications: The analysis of the architecture of the epithelium (or microsurface) and analysis of the microvasculature[7].

Advanced diagnostic endoscopy: Endocytoscopy and Endomicroscopy

New optical imaging modalities to enable *in vivo* characterization of suspicious lesions involves both endogenous optical contrast as well as the use of contrast agents targeted against biomarkers that are associated with early and superficial neoplasias[8].

Recently the confocal laser endomicroscopy (CLE) has been studied in the evaluation of the gastrointestinal (GI) tract. Fluorescence diagnosis can be achieved by measuring the tissue fluorescence following administration of an agent (usually fluorescine).

The typical resolution achievable with CLE is on the order of 1-2 μm with a field of view of approximately 500-700 μm^2. It allows for the immediate evaluation of the superficial GI layers and can be used for morphological diagnosis because of the recognition of morphological changes in cells and nuclei[9].

Several studies have compared the performance of confocal microendoscopy to white light endoscopy examination and NBI in the esophagus and colon. In particular in the esophageal field, most of these papers were focused on Barrett Esophagus changes.

More recently the endocytoscopy was introduced. A prototype gastroscope (Olympus Medical Systems Corp., Tokyo, Japan) with a high-power magnifying endocytoscope (450 × magnification) was used to compare the size and appearance of nuclei and cytoplasm ratio, without the need of a contrast agent. In the esophagus the endocytoscopic images has been classified into five grades of endocytoscopic atypia (ECA) from healthy squamous epithelium (ECA 1) to lesion recognized as malignant (ECA 5)[10].

Advanced therapeutic endoscopy

Advanced operative endoscopy, ranging from endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), per-oral endoscopic myotomy (POEM), submucosal endoscopic tumor resection (SET), has open the door to the direct view of the submucosal virtual space and its anatomy. If with diagnostic endoscopy the interest was related only in understanding "superficial" findings and in wondering the submucosal subsequent meanings, the current procedures let the physician to watch from "inside" with his/her eyes a real, true anatomy of submucosal space, until now only imagined by both diagnostic endoscopists and surgeons. EMR and ESD are performed as indicated by local clinical guidelines for early esophageal cancers, POEM for esophageal achalasia[11-15] and SET for subepithelial tumors[16]. These procedures enable clear and direct visualization of the layers of the esophageal wall, as therapy progresses.

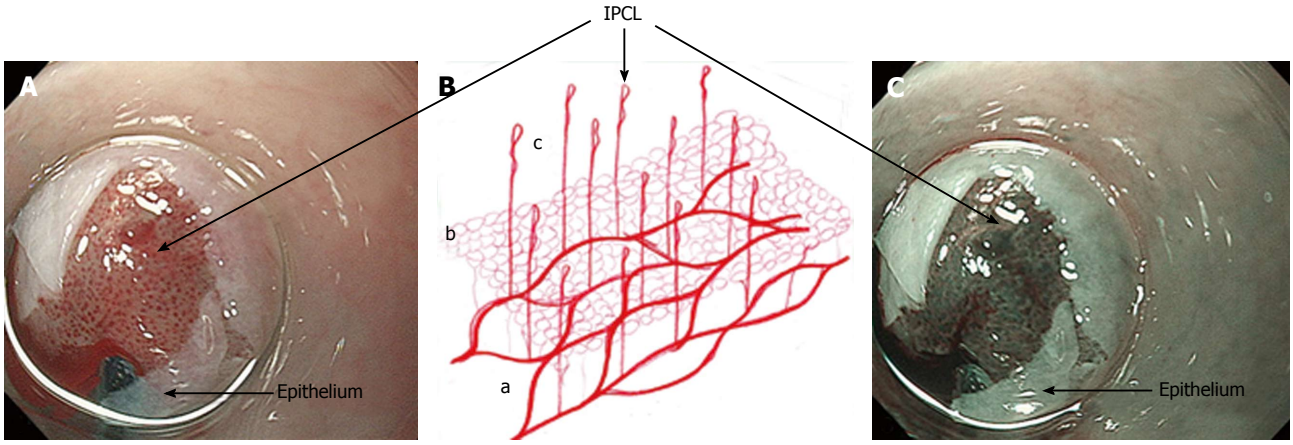


Figure 1 Mucosal vessels. A and C: Endoscopic images during per-oral endoscopic myotomy procedure (high magnification images); after unintentional removal of the epithelium (white layer), top half of epithelium was peeled off, and IPCLs were exposed. IPCLs appear as regularly-arranged, red dots (A: White light) or dark green spots (C: NBI); B: A schematic representation of the vascular network of esophageal mucosa: a: Branching vessels; b: SECN; c: IPCL. IPCL: Intrapapillary capillary loop; SECN: Sub epithelial capillary network; NBI: Narrow band imaging.

Esophageal vasculature: Endoscopic appearance

Combining the information gained from the therapeutic endoscopy, the esophageal wall is organized, from the lumen to outside, in five different layers: Epithelium, lamina propria with lamina muscularis mucosa, submucosa, muscle layer, adventitia. Different vascular system are recognize, belonging to each layer and connecting each other: In the mucosal layer we can find IPCL in the epithelium and sub-epithelial capillary network (SECN) in the lamina propria (Figure 1); at the lower esophageal sphincter (LES) level, we can recognize palisade vessels running in this layer; in the submucosa we find drainage vessels and the spindle veins just under the LES; in the muscle layer are present perforating vessels and peri-esophageal veins in Adventitia. In particular, considering the vasculature by each layer we can find the following structures (Figure 2)[16].

Mucosa: IPCLs and the SECN can be visualized laying all along the esophagus, from the upper esophageal sphincter (UES) to the LES (Figure 3). IPCLs are terminal vessels laying in the epithelial papilla and they drain into the branching vessels located within the lamina propria; they can be clearly demonstrated with M-NBI, although they are visible even with magnification alone. The branching vessels finally drain into the submucosal drainage vessels.

Submucosa: It is a connective "space" between the mucosa and the muscle layer. In this layer drainage vessels can be found running in the entire esophageal length; at the esophagogastric junction (GEJ) level the drainage veins become elongated.

Muscle layer: It is a double layer composed by muscular fibers running circularly in the inner layer and longitudinally in outer part. It is crossed by a venous network running in the intramuscular space. The muscle layer is also crossed by additional perforating vessels, large veins connecting the submucosal drainage veins/arteries with the main longitudinal arteries and veins of the adventitia, the outer esophageal layer.

Adventitia: It is the outermost connective tissue layer, enclosing the esophagus in all its length. The peri-esophageal vessels are clearly demonstrated during submucosal endoscopy for POEM, after the myotomy.

From the early 90s several studies focused on IPCL changes relevant to malignant tumors[2]. These studies led to the development of the IPCL classification[1]: IPCLs show characteristic changes in carcinoma *in situ* (irregular caliber, weaving, dilatation and different shape of IPCL). Analyzing grades of IPCL changes, the mucosa can be differentiated from normal (Type Ⅰ) to carcinoma (Type Ⅴ). By this classification, infiltration depth of the esophageal lesion can also be evaluated.

ESOPHAGEAL VASCULATURE ON HISTOLOGY

The immunohistochemical analysis on non-pathological esophageal specimens using CD34, specific for the vascular endothelium, and D2-40, specific for lymphatics, shows a high expression of CD34 in the areas corresponding to the IPCLs, SECN and branching vessels (Figure 4). IPCLs and SECN stained with CD34, but they are negative for D2-40 staining.

GEJ: ENDOSCOPIC LANDMARKS

The GEJ is usually endoscopically defined as that area where the palisade vessels encounter gastric longitudinal mucosal folds[17-19]. These structures can be directly seen by entering in the submucosal space: From this internal point of view, on the mucosal side, the branching vessels appears neighboring with palisade vessels, running in the

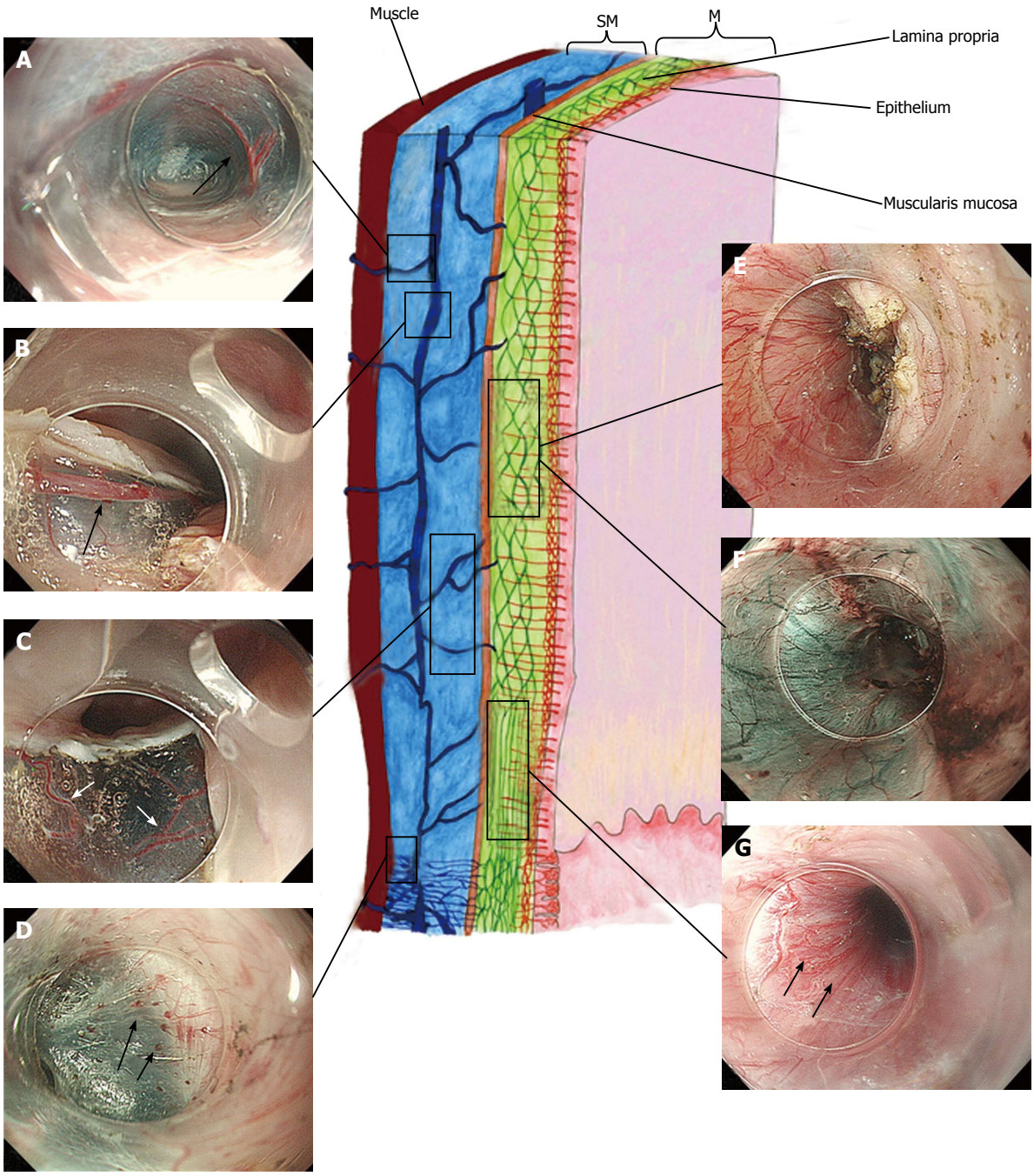


Figure 2 Esophageal wall and esophago-gastric junction vasculature: Schematic illustration and endoscopic corresponding images (high magnification images). Black arrow indicates vessels. This image was originally published in "Treatment Strategies Gastroenterology"[28]. A: Perforating vessels from the outer esophagus to the submucosal vessel; image captured during tunnelization in POEM (bottom side muscle layer, left side submucosal lifting); B: Submucosal drainage vessel (mucosal layer lifted on during ESD). These veins can become esophageal varices in portal hypertension; C: Submucosal vessels connecting the drainage veins to the mucosal branching vessels (in the lamina propria); D: Spindle veins immediately below the GEJ (in left side of the image, in blue, the submucosa and in the right side the muscle); E and F: Whitet light and NBI of the branching vessels (seen from inside the submucosal tunnel). Backside of the mucosa on the left; muscle-already cut-on the right; G: Passage between lower esophagus and GEJ. In the image is possible to recognize, in different planes, all the vessel of the submucosa and lamina propria (palisade vessels). POEM: Per-oral endoscopic myotomy; ESD: Endoscopic submucosal dissection; GEJ: Esophagogastric junction; NBI: Narrow band imaging; M: Mucosa; SM: Submucosa.

same plane, just above the muscolaris mucosae.

In the submucosal layer, immediately below the GEJ, small veins are laying, running regularly and parallel to each other, perpendicularly to the muscular layer, found in most of the patients (Figure 5). These "spindle veins" can be considered a reliable landmark of the GEJ already been passed through.

DISCUSSION

The first descriptions of the esophageal vasculature and its connection with the portal system span from Vesalius in 1543 to Bartholin in 1673 and Dionis in 1703. In 1951 Butler recorded a more detailed description, categorizing the intramural esophageal vessels into intrinsic veins,

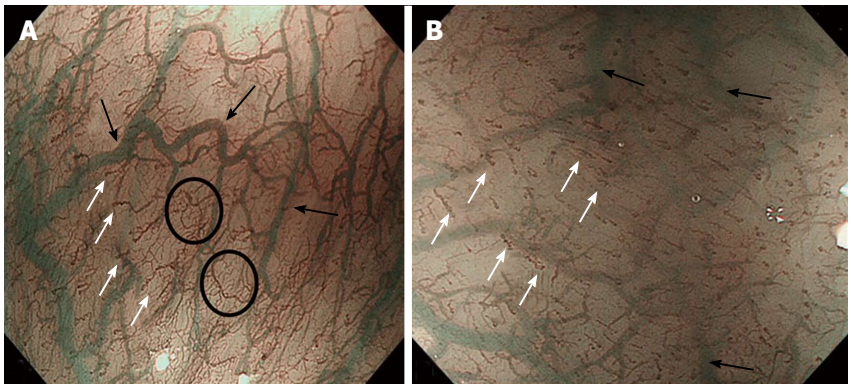
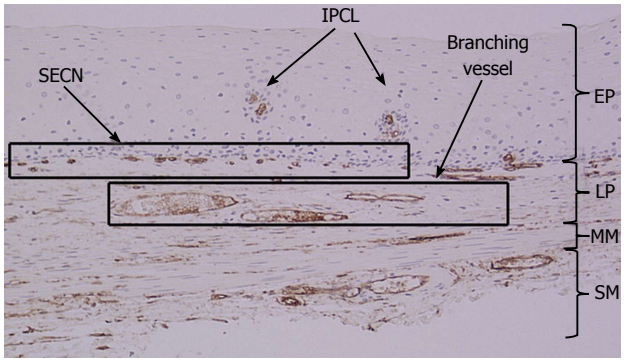


Figure 3 High magnifying narrow band imaging image of normal esophageal mucosa (luminal side). A: Soft pressure of the endoscope distal attachment ("hood") onto the mucosal surface demonstrates SECN, hard pressure onto the mucosa compresses horizontal vessels, allowing clear observation of IPCLs; B: In the circle the SECN located at the top layer of lamina propria mucosae, just beneath the epithelium. The black arrows indicate the branching vessels into the lower lamina propria; white arrows indicate the IPCL located in the epithelial papilla, which is a projection of lamina propria mucosae into the epithelium. SECN: Sub-epithelial capillary network; IPCL: Intrapapillary capillary loop.



Endoscopic procedure	Esophageal "depth" observed	Vascular system mainly focused
magnifying Endoscopy	Epithelium Lamina propria mucosae	IPCL SECN
Regular (non-magnifying) endoscopy	Muscularis mucosae	Branching vessel network
Advanced therapeutic endoscopy	Submucosa and or muscle layer	Sumucosal veins Spindle veins perforating artery and veins

Figure 4 The figure shows the histology of a non-pathologic esophageal specimen. The vessels' wall has been colored by CD34, showing superficially the IPCLs (upper part of the lamina propria, arising the epithelium) and the SECN; deeply in the lamina propria the branching vessels. In the sumucosal layer also the drainage veins are evident. The table summarizes the vascular system observed and its own esophageal layer according to the different endoscopic procedure performed. SECN: Sub-epithelial capillary network; IPCL: Intrapapillary capillary loop; EP: Epithelium; LP: Lamina propria; MM: Muscolaris mucosa; SM: Submucosa.

venae commitantes of the vagus and extrinsic veins[20].

Subsequent descriptions have concentrated largely on abnormalities due to esophageal varices, but these were limited to post-mortem, *ex vivo* analysis, frequently employing the corrosion-cast technique, or scanning electron microscopy (visualizing vessels down to 200 μm)[21]. These studies demonstrated the existence of a SECN, a draining submucosal venous plexus, and the anastomoses between these two.

Advanced therapeutic endoscopy allows, for the first time, the direct *in vivo* observation of the deeper layers of the esophageal wall. Many of these structures are of interest and key importance to endoscopists undertaking advanced therapeutic procedures.

Previous studies of the esophageal vasculature have yielded conflicting observations. Palisade vessels were first described using microangiography, then in 1984 endoscopically identified as "sudare-like veins" [19]. In 1987 Vianna *et al*[22] performed a study on the normal esophageal venous circulation and defined in particular the palisade zone located at the gastroesophageal junction. The veins in this zone were distributed uniformly, running longitudinally and parallel to each other. The submucosal veins of the gastric zone were described as piercing the muscularis mucosae at the GEJ, running in the lamina propria, with the exception of a small number which seemed to remain in the submucosal space[22]. In contrast, Aharinejad *et al*[23] demonstrated that submucosal veins maintain their general longitudinal course when passing through the GEJ. Using M-NBI, Kumagai and colleagues observations of the GEJ and its vessels corresponded to the *ex vivo* description of Kagaries and Butler: They described in the lamina propria a longitudinal plexus of small vessels and in the submucosa at the GEJ, the palisade vessels, with a caliber of 150-170 μm. They demonstrated that the density of palisade vessels is highest near the squamo-columnar junction and that starting form their proximal ends they gradually increase in thickness and become confluent[24]. Using M-NBI, our endoscopic findings, approaching the submucosal space, correspond most closely to those of Aharinejad, with the palisade vessels at the GEJ lying in the lamina propria. In other words, the palisade vessels are continuations of the branching vessels, but we postulate that the vessels appear elongated as a result of the high pressure forces present at the GEJ. This is supported by the presence of similar vessels at the UES level (Figure 6).

The GEJ has previously been divided into four distinct zones (the first two immediately below and the second two above the "Z" line). In zone 1, the most caudally zone directly connected with the gastric side, a complex

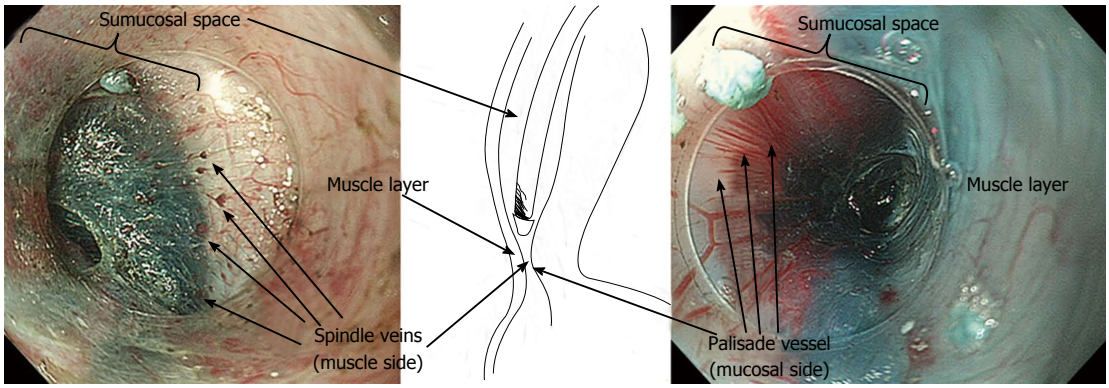


Figure 5 In the center a scheme of the submucosal view at the gastro-esophageal junction during per-oral endoscopic myotomy. At the muscle side (left endoscopic image) the spindle vein are clearly visible; at the mucosal side (seen on its backside, right endoscopic image) the palisade vessel are recognized. High magnification images.

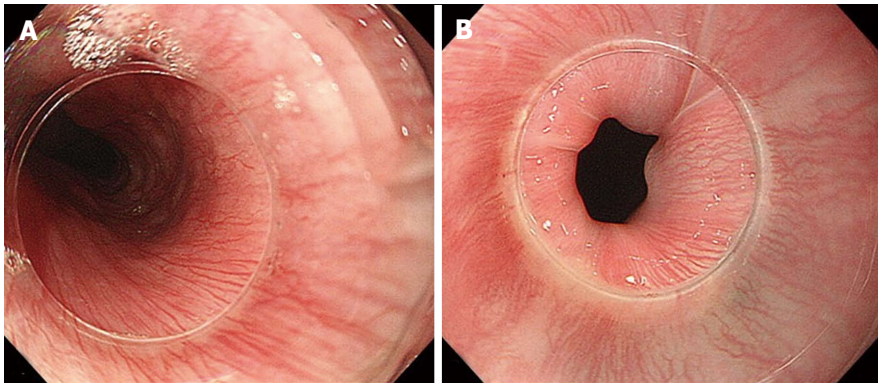


Figure 6 Palisade vessels at the esophageal sphincter. A: Palisade vessels at the upper esophageal sphincter; B: In the lower esophageal sphincter, the vessels, located in the lamina propria, are continuation of the branching vessels, "stretched" by the high pressure present in the area. High magnification images.

of small twisted veins, with circumscript, ampullar bulges[21] - has been found. These veins correspond to the so-called "spindle veins", found in more than 70% of the total cases of our personal series and clearly visible during submucosal endoscopy.

The architecture of IPCLs has been evaluated *ex vivo* in the normal esophagus, with microfilm[19]; comparing these stereoscopic microscopic images with magnifying endoscopic images, at a magnification of approximately 80 times, small vessels coming up from the mucosal vessels could be seen originating and running obliquely upward toward the epithelium and then toward to the intrapapillary capillaries. At a magnification of more than 100 × each intrapapillary capillary can be observed as a single distinct loop[25].

As endoscopists have become more familiar with M-NBI, it became apparent that characteristic morphological changes were associated with the development of malignancy[26]. These observations finally led to the development of the IPCL classification[1,27].

Esophageal vasculature is now *in vivo* evaluable with advanced endoscopic technology and techniques. Our knowledge of the characteristic changes in health and disease, as well definition of anatomical landmarks, will serve to the practice of endoscopic diagnostics and treatment in the future.

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