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Anatomy of the lymphatics in normal stomach and gastric carcinomas

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The lymphatic system is composed of lymphoid organs/tissues and a complex network of lymphatic vessels that transport interstitial fluid, antigens, lipids, immune cells, and other materials in the body. There is growing evidence that lymphatic vasculature is associated with many pathological conditions such as lymphoedema and cancer progression and metastasis. Thus, improved understanding of the anatomical features, the molecular profile, and the function of the lymphatic vasculature may provide innovative approaches for disease prevention and treatment. This article aims to present a comprehensive review of the gastric lymphatic anatomy and its importance in the pathology, treatment, and prognosis of gastric carcinomas. (Folia Morphol 2025; 84, 1: 37–47)

Keywords: lymphatics, stomach, gastric cancer, surgical treatment, lymphadenectomy, skip metastasis

INTRODUCTION

The human lymphatic system is composed of lymphoid organs/tissues (thymus, spleen, lymph nodes, mucosa-associated lymphoid tissue) and a complex network of lymphatic vessels [2, 25, 52, 54, 56, 60, 61, 63]. The lymphatic vasculature transports the lymph, a mix of interstitial fluid, immune cells, lipids, antigens, and other components and is implicated in the homeostasis of fluid balance, the immunosurveillance, and the absorption of nutrients, especially lipids [52, 54, 60].

Recent advances in imaging and the discovery of novel cell biomarkers and single-cell biotechnologies have improved the understanding of the anatomy of the lymphatic vasculature and the molecular profile of the lymphatic endothelial cells [52, 54, 60]. Notably, there is growing evidence that lymphatic vasculature is associated with a great array of pathological conditions including lymphedema (primary and secondary), inflammatory bowel disease such as Crohn's disease, cardiovascular disease (atherosclerosis, myocardial infraction), eye diseases such as glaucoma, neurological disorders such as Alzheimer's disease, metabolism/ /obesity, and cancer progression and metastasis [52, 54, 60].

The lymphatic system provides an important route for the spread of malignancies; thus, the identification of lymphatic vascular pathways and lymphonodal stations of carcinoma spread is important for staging, choice of treatment, and prediction of the prognosis of patients with malignant diseases [11, 18, 19, 42, 57, 67]. For example, in the abdomen, the

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vascular pathways of lymphatic drainage accompany the blood vessels that supply or drain the abdominal organs, and are localised within the peritoneal ligaments, mesocolon, or mesentery [11, 18, 42, 67]. Malignant cells from the abdominal tumours such as gastric and colorectal carcinomas enter lymphatic vascular structures and travel to the lymph nodes (LN) along the lymphatic drainage pathways [11, 18, 19, 42, 57, 67]. This article aims to review the gastric lymphatic anatomy [11, 18, 19, 42, 57, 67] and its importance in the pathology, treatment, and prognosis of gastric carcinomas [1, 3–10, 12–24, 26–51, 53, 55, 57–59, 62, 64–66, 68–70].

BASIC ANATOMY OF THE LYMPHATICS

Before addressing the analysis of the lymphatic vasculature in normal stomach and gastric carcinomas, the general embryology, histology, and macroscopic anatomy of the lymphatic vascular system is summarised [2, 25, 52, 54, 56, 60, 61, 63].

Embryology

The basic concepts of the descriptive and molecular Embryology of the human lymphatic system were reported in previous reviews [25, 54, 56, 61, 63]. The increasing understanding of the molecular mechanisms that dictate the formation of the human lymphatic system in the early developmental stages are useful for gaining further insight in various physiological and pathological processes [56, 63]. The development of the human lymphatic system begins at the end of the sixth gestational week [25, 61]. Lymphatic vessels are lined with lymphatic endothelial cells (LEC), which is an endothelial cell lineage characterised by specific transcriptional and metabolic program [56, 63]. LEC express the transcription factor prospero-related homeobox 1 (PROX1), which is involved in the establishment and maintenance of the lymphatic endothelial transcription program as well as the receptor tyrosine kinase vascular endothelial growth factor (VEGF) receptor-3 (VEGFR-3) [56, 63]. VEGFR-3 and its ligand, VEGF-C, are a crucial growth factor pathway involved in normal and pathological lymphangiogenesis [56, 63]. During mammalian embryonic development, the major population of LEC are derived from transdifferentiation of venous progenitors and give rise to dermal, cardiopulmonary, and hepatic lymphatic vessels [56, 63]. In addition to the venous-derived LEC, progenitors of non-venous origin contribute to the development of the lymphatic vasculature [56, 63]. The heterogeneous origin of LEC and the organ-and tissue-specific microenvironments contribute to the development of the organ- and tissue-specific characteristics and functions of LEC that are observed in adulthood [56, 63].

Histology

The microscopic characteristics of the lymphatic vasculature were reported in previous reviews [2, 56]. Briefly, the lymphatic vessels are divided into 3 subtypes: initial lymphatics (capillary), pre-collectors, and collecting lymphatics [2]. The initial lymphatics are blind-ended, non-contracting vessels with increased permeability, which are composed of a single layer of LEC surrounded by a thin discontinuous basement membrane [2, 56]. The LEC of the collecting lymphatics are connected by continuous cell–cell junctions and are surrounded by a prominent basement membrane and contractile smooth muscle cells [2, 56]. Thus, collecting lymphatics are contractile and display reduced permeability. The accurate histological identification of lymphatic vessels requires the use of immunohistochemistry. Indeed, Adamczyk et al. in 2016 reported that the most important specific immunohistochemical markers for lymphatic endothelium are podoplanin (D2-40), Prox-1, and lymphatic receptor for the extracellular matrix mucopolysaccharide hyaluronan (LYVE-1) [2]. They recommended the use of a panel consisting of one pan-endothelial marker (p.e CD31) and 2 specific lymphatic endothelium markers for accurate identification of lymphatic vessels in normal tissues and the detection of lymphangiogenesis and lymphatic vessel invasion in cancer histopathology [2].

Macroscopic anatomy

The macroscopic anatomy of the lymphatic vasculature is variable and was described in previous reviews [25, 61]. Briefly, 3 major lymphatic vasculature structures can be identified: the right lymphatic duct, the cisterna chyli, and the thoracic duct.

Firstly, the formation of the right lymphatic duct, which is approximately 1–2 cm in length, is a result of the merging of 3 other lesser lymphatic trunks: the right jugular, the right subclavian, and the right bronchomediastinal. Its contents empty in the point of junction between the right subclavian and right internal jugular vein and originate from the right upper

quadrant of the body, including the right arm, right side of the head and neck, right thorax, lung and diaphragm, and part of the heart and right lobe of the liver [25, 61].

Secondly, the cisterna chyli resembles a dilated sac measuring about 5 cm in length, which results from the junction of the right and left lumbar lymphatic trunks and the intestinal trunk, but significant anatomical variations have been noted in its formation [25, 61]. Regarding these variations, it is absent in 40–60% of the population, and in those cases the lumbar and intestinal lymphatics communicate directly with the thoracic duct. It is located on the level of the L2 vertebra, but there are also variations ranging from T12 to L2 level, between the aorta and the inferior vena cava [25, 61]. The lymph that it amasses originates from the abdominal wall area below the omphalic level, the pelvis, the kidneys, and adrenal glands and part of the gastrointestinal tract being perfused by the celiac trunk and the superior mesenteric vessels [25, 61].

Lastly, the thoracic duct, which is a continuation of the cisterna chyli, measures around 45 cm in length and 2–5 cm in diameter [25, 61]. The thoracic duct is responsible for returning to the venous blood circulation 80–90% of the body's lymph, from every region except those that are irrigated from the right lymphatic duct [25, 61]. It starts at the level of the T12 vertebra and ascends through the aortic hiatus at the T10 level, with the aorta to its left and the azygos vein to its right. During its ascent the duct is located anteriorly to the thoracic vertebrae and posteriorly to the oesophagus, diaphragm, and pericardium. During its course at the T7 level the duct crosses the midline of the spine obliquely until the level of T5. After that, being situated at the base of the neck and passing posterior to the common carotid artery, internal jugular vein, vagus nerve, left phrenic nerve and anterior to the vertebral artery and vein and the sympathetic trunk, it continues its course until C7, where it empties its content in the junction between the left internal jugular and subclavian veins. The thoracic duct can be divided into 3 parts: the abdominal, the thoracic, and the cervical part. It should be noticed that the anatomy of the thoracic duct is subject to major variability, whether that concerns the number of ducts, the connections of the duct with other minor veins, or the way the duct empties in the junction of the major veins [25, 61].

LYMPHATICS IN NORMAL STOMACH

For a better understanding of the gastric lymphatic anatomy, the Japanese Classification of Gastric Carcinoma subdivides the stomach into 3 regions: the upper, the middle, and the lower one, each with a different lymph drainage, and the Japanese Gastric Cancer Association classifies regional gastric LN into 33 separate stations [7].

These stations include both perigastric LN, situated along the vessels that feed the stomach, and LN along major vessels and adjacent to the pancreas, the diaphragm, and oesophageal hiatus [7].

The gastric lymphatic flow and the LN stations were presented in previous studies [11, 18, 19, 42, 57]. Briefly, the lymphatic flow of the stomach spreads from the perigastric nodes, via the suprapancreatic nodes and nodes around the celiac artery, to the para-aortic nodes, following which it enters the systemic circulation.

Considering the lymphatic flow with respect to the anatomical division of the stomach, the upper third of the stomach has lymphatics that follow the course the left gastric artery, the posterior gastric artery, the splenic artery, and left inferior phrenic artery, but it lacks lymphatic connection with the retropancreatic nodes which are situated along the posterior surface of the pancreas and with nodes around the superior mesenteric vessels (stations 13 and 14, respectively). The lymphatics of the lower third of the stomach run along the common hepatic and superior mesenteric arteries and ultimately drain into nodal stations 12 and 13 (nodes in the hepatoduodenal ligament and retropancreatic nodes). Finally, the gastric lymphatics drain into nodal station 16 by using 4 different pathways, named lymphatic pedicles. Essentially, pedicles are connections between the lymph pathways and are as follows: a) the left subdiaphragmatic and the celiac pedicles, mainly responsible for the upper and middle portion of the stomach and b) the superior mesenteric and the retropancreatic pedicles, mainly responsible for the middle and lower portion of the stomach, each forming from the connection of lymphatics.

Concerning the lymphatic flow with respect to the curvatures of the stomach, a) nodes of the greater curvature of the stomach mainly drain towards the infra-pyloric nodes and finally the superior mesenteric pedicle, but also towards the splenic artery and hilum nodes and then directly to station 16, and b) nodes of the lesser curvature drain towards nodes along

the celiac trunk and the left gastric artery, along with those located right of the cardia stomach [11, 18, 19, 42, 57].

LYMPHATIC SPREAD IN GASTRIC CARCINOMAS

Gastric carcinoma (GC) is the fifth most common cancer and the third most lethal cancer worldwide [48, 62]. Men are afflicted twice as frequently as women, and regarding the geographical distribution: high risk regions include East Asia, Europe, and South America, as well as developing countries, which account for 50% of the cases [45, 48, 62].

GCs are classified according to morphological classifications that include the World Health Organisation (WHO) classification (papillary, tubular, mucinous, signet ring, and poorly cohesive) and the Lauren classification (intestinal, diffuse, and mixed) [45, 46, 48, 62]. However, there is growing evidence showing multiple genetic and epigenetic alterations resulting in the dysregulation of various oncogenes and tumour suppressor genes, which is considered to be the driver during GC oncogenesis [53, 64]. Therefore, various molecular classifications of GC have been developed, which may have an impact on determining the prognosis an/or predicting the treatment responsiveness [53, 64].

The prognosis of GS correlates with the stage of the carcinoma determined at diagnosis according to the depth of tumour invasion (T), lymph node involvement (N), and metastasis (M) [6]. GC is usually classified into 2 subgroups: early GC and advanced GC [46, 67]. Early CG affects the mucosa or the mucosa and submucosa (T1), irrespective of tumour size and lymph node (LN) involvement and has a 5-year survival rate > 90%, whereas advanced GC affects deeper layers (T2-T4) and has a 5-year survival rate of 7–27% [45, 46, 48, 62, 67].

The basis for the treatment of the GC is the enlistment of a multidisciplinary team with a variety of medical disciplines such as surgery, radiation and medical oncology, and gastroenterology. Based on the guidelines of NCCN published in 2022, new patients should have a complete workup, starting from physical examination and ending with specialised imaging exams such as CT-scans, FDG-PET/CT scans, and endoscopic ultrasonography, with the last being especially useful in early disease [4]. The type of treatment to be implemented is largely determined by the stage of the tumour, with early stage or localised disease (cTis-cT1a) possibly being treated only with endoscopic treatment, locoregional disease (cT1b-cT4a, cM0) with excisional surgery if achievable, and metastatic cancer (cT4b, cM1) with systemic palliative treatment, compromising various pharmaceutical schemes and symptom-alleviating surgery [4]. The recurrence rates after gastric surgery remain high (ranging from 20% to 50%), and LN involvement has the strongest influence on the recurrence and prognosis of GC [4, 9, 45, 46, 48, 50, 62].

The surgical treatment comprises gastrectomy and lymphadenectomy

Four main types of gastrectomy can be performed based on the location of the tumour, as summarised by Maru et al., 2021 [51]. The types are as follows: a) total gastrectomy, for diffuse carcinomas, large distal tumours, and carcinomas involving the body or lesser curvature of the stomach; b) oesophago-gastrectomy, for carcinomas involving cardia and gastroesophageal junction; c) distal subtotal gastrectomy, for carcinomas limited to distal stomach; and d) proximal gastrectomy with excision of lower mediastinal LN, for gastroesophageal junction tumour infiltrating less than 3 cm into the lower oesophagus [51].

The type of lymphadenectomy is a subject of debate because the decision concerning the approach of LN dissection is crucial for the staging and prognosis of the disease. [5, 10, 14, 16, 22–24, 35–38, 43, 47, 49, 53, 58, 59, 64]. The types of lymphadenectomy are the following: D1 lymphadenectomy, which is the removal of perigastric nodes, including stations 1–7 in a total gastrectomy; D1+ lymphadenectomy, which is a D1 excision along with stations 8a, 9, and 11p; D2 lymphadenectomy, which adds stations 8a, 9, 10, 11p, 11d, and 12a to D1 dissection; and D3 lymphadenectomy, which is more extensive than D2, including also nodal stations 13–16 [5, 14, 23, 49, 51, 58, 62].

The question that arises is which of these types of lymphadenectomy are to be implemented. Degiuli et al. [19], reported that nowadays, also in western countries, D2 surgical procedure can be carried out without spleno-pancreatectomy, and several national guidelines suggest D2 gastrectomy as the recommended procedure for patients with advanced GC. Coburn et al. [14], 2018, in a systematic review, showed the increased perioperative danger of D2 lymphadenectomy but also the decrease in disease recurrence compared to D1 lymphadenectomy. Douridas

et al. [23], reported no benefit of D3 lymphadenectomy regarding the overall survival, and in addition, the advanced difficulty of this operation, the extended operation time, and increased probability for reoperation, render D3 lymphadenectomy probably inferior than D2 lymphadenectomy, at least in a routine base. Rosa et al. [58], reported that the resection of at least 16 LN is required for proper staging and that D2 might also be beneficial because it includes a great number of excised LN on average [58]. Other studies have reported that the number of LN harvested after D2 distal gastrectomy can exceed 40 [22, 38, 59]. It has been reported that a greater number of harvested LN is associated with better prognosis [46, 47]. On the other hand, early GC, presenting a metastatic pattern that concerns perigastric LN and stations 7, 8a, and 9 has no benefit from D2 lymphadenectomy, and D1+ lymphadenectomy is sufficient [14]. From these studies, but also from the NCCN guidelines, D2 lymphadenectomy seems to have a place in the cure of advanced disease, due to the more radical disease excision and higher survival rates, and it is a tool to be used by experienced surgeons [4, 5, 14, 23]. Notably, Aiolfi et al. [3] used meta-analysis to evaluate 5 randomised controlled trials (RCTs) to compare the effect of D2 vs. D1 on survival in 1653 patients, of whom 805 (48.7%) underwent D2 lymphadenectomy. The restricted mean survival time difference (RMSTD) overall survival (OS) analysis showed that at 60-month follow-up, patients with D2 lymphadenectomy lived 1.8 months ($p = 0.14$) longer on average compared to D1 patients [3]. Similarly, 60-month disease-free survival (DFS) (0.8 months, $p = 0.53$) and cancer-specific survival (CSS) (1.2 months, $p = 0.72$) tended to be improved for D2 vs. D1 lymphadenectomy [3]. Aiolfi et al. [3] concluded that, in comparison to D1, D2 lymphadenectomy is associated with a trend toward improved OS, CSS, and DFS at 60-month follow-up.

LN metastasis is a common form of metastasis in patients with GC [14, 21, 36]. The relatively high rate of LN metastasis in patients with GC can be, at least in part, attributed to the rich lymphatic network in the stomach, which can be shown by immunohistochemistry [66]. Indeed, Yonemura et al. [66] analysed by immunohistological staining using the D2–40 antibody the topographical distribution of the lymphatic vessels in the normal human stomach. They observed the following: a) lymphatic vessels in the lamina propria of the fundic gland, parietal cell area, and pyloric gland areas; b) abundant lymphatic vessels in the superficial layer of the muscularis mucosa and the upper half layer of the submucosa; c) scarce lymphatic vessels in the lower half layer of the submucosa; and d) many lymphatic vessels in the inner and outer layers of the proper muscle [66]. The rich lymphatic vessel network in muscularis mucosa and submucosa of the stomach could provide an explanation of why LN metastasis occurs even in early GC [66].

The overall prevalence of LN metastases in T1 GC is 8–31%, while the overall prevalence of LN metastases in T2-T4 GC is considerably higher, at 45–90% [16, 43]. Concerning early GC (EGC), a meta-analysis showed LN metastasis in about 3.2% (0.0–20.3%) of mucosal EGC and 19.2% (10.2–33.3%) of submucosal EGC [38].

Concerning the prevalence of LN metastases in the individual LN stations for different T-stages, the results of a meta-analysis were as follows [16]: Concerning LN stations 1 to 7, the LN along the lesser gastric curvature (station 3) show the highest metastatic rate (T1: 5.5%, T2: 21.9%, T3: 41.9%, T4: 71.0%); and concerning LN stations 8 to 20, the LN around the common hepatic artery (station 8) show the highest metastatic rate (T1: 0.8%, T2: 7.9%, T3: 14.0%, T4: 28.2%) [16].

Concerning the frequency of LN metastasis according to the anatomic location of the tumour, GC of the upper third of the stomach present more frequently LN metastasis, ranging from 44% up to 80% of cases, whereas the respective frequencies of the middle and the lower parts range from 37–65% to 50–59% [18, 22, 27, 42, 59].

Concerning the anatomical location of the metastatic LN in relation to the anatomic location of the tumour, a) malignancies of the upper third of the stomach more frequently infiltrate nodes in the lesser curvature and paracardial nodes, b) tumours of the middle third more frequently invade the nodes in both the lesser and greater curvature and in the right paracardial station, and c) tumours of the lower third more frequently infiltrate the infrapyloric nodes and those situated along the lesser and greater curvature, with a preference for nodes along the right gastroepiploic artery [18, 42]. From the 3 parts of the stomach, tumours of the upper third are the most likely to present nodal spread towards paraaortic nodes and nodes of the splenic hilum, and tumours from all the parts of the stomach give metastasis to nodes around the celiac trunk [18, 42].

The prognostic significance of LN metastasis in GC was related to the number of positive LN, the LN density, which is also called the LN ratio (ratio of positive to total examined LN), and the number of negative LN [19, 20, 31, 32, 44, 48, 62, 70]. Indeed, the increased number of positive LN is associated with higher possibility of recurrence and lower survival [19, 20, 48, 62]. Moreover, a meta-analysis of 27 studies (a total of 11,441 patients) showed that higher LN ratios were significantly associated with a shorter OS, and the LN ratio was an independent predictor of survival [70]. Furthermore, the increased numbers of negative LN are associated with better prognosis [8, 15, 21, 65]. For example, Bahardoust et al. [8], studied 639 patients who were divided, based on the number of negative LN, into 3 subgroups, including (0–9 negative LN), (10–15 negative LN), and (≥16 negative LN), removed, including 155, 231, and 253 GC patients, respectively [8]. Their results revealed that the number of negative LN resected ≥16 was associated with an increased 5-year survival rate and a decreased recurrence rate in GC patients after gastrectomy. Similarly, Wang et al. [65] studied 7660 GC patients and provided evidence for the superiority of the ratio of negative to positive LN dissected compared to already used systems, such as the TNM staging system and the ratio of positive to total LN, which did not take into account the number of negative LN. The prognostic significance of the negative LN could be explained by the fact that a larger number of LN is indicative of a higher quality of surgery and by indications that negative LN play a protective and immune-enhancing role in defence potential against the tumour [8, 15, 26]. Interestingly, Li et al. [40] assessed the prognostic value of log odds of positive LN (LODDS) compared to pathological classification and the ratio-based LN system (pN and rN, respectively). This study showed LODDS as a more accurate predictor of the survival of GC patients compared to already established methods. One of the factors that mostly affects the prognostic value of LODDS is that of neo-adjuvant therapy, with patients who received therapy presenting with better OS compared to patients who did not, despite being in the same LODDS group [40].

In addition to the prognostic value of the number of metastatic LN, which determines the nodal stage in the GC TNM staging system [6], the incorporation of the anatomical location of the metastatic LN may also have prognostic impact [28, 29, 69]. In this regard, Jeon et al. [28] analysed 3591 patients with LN metastases, who were classified into perigastric (stations 1–6, group P) or extragastric (stations 7–12) groups. The extragastric group was further subdivided into near-extragastric (stations 7–9, group NE) and far-extragastric (stations 10–12, group FE) groups. No statistically significant survival differences were found between group P and the extragastric group in each N stage. However, in N1 and N2, the FE group showed statistically significant worse survival than the other groups ($p = 0.013$ for N1, $p < 0.001$ for N2), but not in N3. In the subgroup analysis, the FE group had a statistically significant lower OS in N2, regardless of the cancer location. Jeon et al. [28] concluded that, although this big data analysis confirmed the superiority of the current numerical nodal staging system, in N1 and N2 in which there is an upper limit on metastatic LN, attention should be paid to the potential significance of the anatomical information for specific nodal stations [28]. Moreover, Jeong et al. [29] analysed 3350 patients and found that the anatomic region of the metastatic LN (perigastric vs. extra-perigastric) improved the goodness-of-fit of the prognostic model using the TNM stage. They concluded that the anatomic region of metastatic LN has an independent prognostic value in the numeric N stage in the current TNM staging system [29]. Furthermore, Zhao et al. [69], reviewed 1451 GC patients who underwent radical gastrectomy and found that the anatomical location of metastatic LN is an indispensable prognostic factor.

The search for predictors of LN metastasis in GC is an important issue and was recently reviewed in studies using meta-analyses. For example, Li et al. [41] analysed 41 studies (56,182 patients) and showed that machine learning (ML) has excellent diagnostic performance in predicting the LN metastasis in GC patients, and more specifically, models based on radiomics and clinical features showed better accuracy than those including only clinical predictors. The most commonly used predictors were tumour size, depth of tumour invasion, histologic differentiation, imaging techniques, lymphovascular invasion, tumour location, CT reported LN, age, and macroscopic features [41]. Moreover, Jiang et al. [30] sought predictors of LN metastasis and residual tumour in early GC patients after noncurative endoscopic resection. They analysed 12 studies (3015 patients), 7 of which also involved carcinoma residues. Six predictors, including a) size of the tumour > 30 mm, b)

invasion depth of the carcinoma (> 500 μm from the muscularis mucosae), c) macroscopic appearance of the tumour, d) undifferentiated histological type of the carcinoma, e) positive vertical tumour margin, and f) presence of lymphovascular invasion (including lymphatic invasion and blood vessel invasion) were significantly associated with LN metastasis [30]. In addition, tumour size > 30 mm, positive horizontal tumour margin, and positive vertical tumour margin were identified as significant predictors for the risk of residual tumour [30]. Furthermore, Abdelfatah et al. [1], reviewed the LN metastatic risk in early GC according to the expanded criteria in comparison with the absolute criteria of the Japanese Gastric Cancer Association. The review of 12 studies (total 9798 patients) showed that a) differentiated mucosal lesions regardless of size and ulcerated lesions ≤ 3 cm could be endoscopically resected without additional risk of LN metastasis and b) early GC presenting even < 500 μm of submucosal invasion have a much greater LN metastasis risk that should be weighed against the relative risk of a surgery including gastrectomy and lymphadenectomy [1].

There is evidence that the patterns of anatomical distribution of LN metastasis are related to the anatomical location of the primary tumour. Indeed, Brisinda G. et al. [10], analysed 1510 patients, including advanced and early GC patients who underwent a gastrectomy, and they documented that in 162 N+ patients with distal GC (middle and lower thirds) the distribution of LN metastases at individual nodal stations is closely related to primary carcinoma location. Moreover, Han et al. [24], analysed 1510 patients including early GC patients and found that the pattern of LN metastasis depends on the location of GC. For example, in all patients, LN station numbers 1, 2, 3, 7, 10, and 11 metastases were dominant in the GC originating in the upper third, whereas LN station numbers 4, 5, 6 and 8 metastases were dominant in the GC originating in the lower third [24]. On the other hand, de Jongh et al., 2022, analysed 212 patients and observed that although proximal tumours metastasised predominantly to proximal LN stations (no. 1, 2, 7, and 9; $p < 0.05$) and distal tumours to distal LN stations (no. 5, 6, and 8; $p > 0.05$), in addition, distal tumours also metastasised to proximal LN stations, and *vice versa* [17]. They concluded that although the pattern of LN metastases is related to tumour location, all LN stations contained metastatic disease regardless of GC location, cT-stage (including cT1N0-tumors), histological type, or neoadjuvant chemotherapy (NAC) treatment [17].

A mention should be made of the study by Kinami et al. [34], who proposed a new classification system: the nPTD (new proximal — transitional — distal) classification, which results from the correlation between GC anatomical location and physiological lymphatic flow distribution using the dye method of sentinel node biopsy [34]. Kinami et al. retrospectively studied 416 GC patients using the following as inclusion criteria: a single lesion type 0 cancer of ≤ 5 cm in the long axis, clinically node-negative, and pathological invasion within the proper muscle layer. The study by Kinami et al. is based on the concept of the lymphatic basin, which is a certain lymphatic area that drains directly from the primary GC focus. The lymphatic basins were defined as follows: the proximal side was the stomach wall, and the distal side was the most distal dye-stained LN [34]. The main results of this study were the following: a) the carcinomas located in the watershed of the left and right gastroepiploic arteries near the greater curvature of the stomach had extensive lymphatic flow — therefore, a newly circular region with a diameter of 5 cm was set on the watershed of the greater curvature between proximal and transitional zone as the 'n' zone; and b) for carcinomas located in the lesser proximal curvature, lymphatic flow to the greater curvature of the stomach was not found — therefore, the proximal zone was divided into 2 zones, i.e. the lesser curvature side and the greater curvature side [34]. Kinami et al. concluded that the advantage of the nPTD classification is that it provides proper LN dissection and adequate function-preserving gastrectomy [34].

A novel pathologist/surgeon team approach to harvest the maximum number of LN, following radical gastrectomy, was recently reported by Ambrosio et al. [5]. Indeed, both the surgeon and pathologist were present in the operative room and implicated in an on-site macroscopic examination and dissection of a fresh tissue specimen. This protocol identified more LN even in GC patients receiving neoadjuvant therapy. Based on these preliminary results, the pathologist/surgeon team approach allows for the harvesting of a larger number of LN and improves the outcome of the patients thanks to more precise staging and therapy [5]. Nevertheless, a higher number of patients are necessary to confirm these findings and assess the impact of this technique on oncological outcomes.

Although the aforementioned information is essential to understand the nodal metastatic patterns of the GC, a mention should be made of the concept of skip metastasis [18, 42]. Skip metastasis is the presence of a metastatic LN in an extraperigastric area without involvement of perigastric LN [12, 68]. The skip metastasis pattern and the complicated lymphatic drainage may limit the application of sentinel LN biopsy in GC patients [12, 18, 33, 39, 42, 55, 68]. The incidence of skip metastasis ranges from 5 to 14%, concerning mainly LN along the common hepatic artery, the left gastric artery, and the celiac trunk, but this percentage presents variations [12, 18, 33, 42, 68]. Choi et al. [12] analysed 2231 patients and reported that 2231 (37.0 %) had metastatic LN. Specifically, 1137/2231 patients (51.0%) had metastatic LN around the stomach only (Perigastric area), and 988/2231 patients (44.3%) had metastatic LN in both the perigastric area and the extraperigastric area. The incidence of skip metastasis was 4.8% (106/2,231 patients) among the patients having metastatic LN, and 1.8% among the overall GC population [12]. In terms of topography, the commonest location of skip metastasis was nodal station 7 around the left gastric artery (67/106 patients, 63.2%), followed by nodal station 8 (around the common hepatic artery) and nodal station 9 (around the celiac axis) (33.0 and 30.2%, respectively) [12]. The skip metastasis was found in only one nodal station in 83/106 patients (79.2%) [12]. In another study including 1343 GC patients, the incidence of skip metastasis was 3.9% in all examined GC patients, the most common anatomical location of skip metastasis was No. 7 and No. 8a node stations, and the proportion of only one involved node station accounted for 83.0% of all GC cases [68]. The prognosis of the skip group was worse than that of the perigastric-only group and similar to that of the perigastric + extraperigastric group when the tumour stage was considered [12, 68]. Possible explanations for the occurrence of skip metastasis may be aberrant and complicated lymphatic network, occult metastases, and inadequate LN sampling [12, 18, 33, 42, 68]. It is noteworthy that several studies found that the skip metastasis group had fewer retrieved LN than the perigastric-only and perigastric + extraperigastric groups, especially in the perigastric area [12, 33, 55, 68]. Therefore, the impact of inadequate number of retrieved LN on the identification of skip metastasis should be carefully considered.

Finally, it is important to summarise the tools available for the pre-, intra-, and post-operative specific diagnosis of LN metastasis. CT scans, FDG-PET/CT, and endoscopic ultrasonography are the mains tools used to help the surgeon to locate enlarged LN in the perigastric area or in further stations (para-aortic, celiac, mediastinal, etc.). The future tools may be methods to predict the LN metastasis based on the characteristics of the initial lesion including location and molecular markers [36]. Intraoperative biopsy could be implemented in specific cases, such as localised cancer or patients with tumours smaller than 5 cm, but it does not seem to provide additional benefit compared to CT scans regarding the identification of LN spread [35, 36]. Postoperatively, the classification of LN metastasis based on location and number of LN has already been discussed [13, 28, 29, 69]. To harvest a large number of LN there are important LN sorting technologies including a) fine LN sorting, which provides a larger number of LN per specimen and b) regional LN sorting, which is time-saving and examines more LN but is not so widely applied [23].

CONCLUSIONS

Lymphatic vasculature plays a vital role in physiology and is involved in many pathological conditions such as lymphedema and tumour metastasis. The knowledge of the lymphatic drainage pathways from each organ is important for the understanding and the prediction of the site of occurrence of LN metastasis. GC remains the fifth most common cancer and the third most common cause of cancer mortality. Most patients diagnosed with GC still have a poor prognosis due to its advanced presentation at diagnosis, even in countries with developed screening programs. Surgery is the cornerstone of the treatment for GC, often combined with perioperative chemotherapy. LN dissection is an important component of the surgical treatment of GC. D1 lymphadenectomy is currently recommended for early-stage tumours. However, the extent of lymphadenectomy in advanced GC gastric cancer is still a matter of debate between Western and Eastern approaches. Although a D2 dissection is the current standard recommended by most guidelines, there might be a place for more limited dissections such as D1+ in selected cases. This article aimed to present a comprehensive review of the gastric lymphatic anatomy and its importance in the pathology, treatment, and prognosis of gastric carcinomas.

ARTICLE INFORMATION AND DECLARATIONS

Author contributions

Dimosthenis Chrysikos and Panagiotis Kanavaros came up with the concept and design of the article. Panagiotis Kanavaros, Dimosthenis Chrysikos, Ameer Shehade, Alexandros Samolis and Dimitrios Liatsos were in charge of acquiring, analysing and interpreting the data. Dimosthenis Chrysikos, Panagiotis Kanavaros, and Dimitrios Liatsos drafted the initial versions of the paper. Alexandra Barbouti and Theodore Troupis revised the article critically for important intellectual content.

Lastly, all authors equally approved the final version of the manuscript that we are submitting.

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Conflict of interest

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