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The role of the lymphatic network in colorectal cancer: anatomy, molecular drivers and management

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Abstract

Our understanding of the structures and functions of the lymphatic system in colorectal cancer (CRC) has advanced dramatically in recent years. This review aims to outline the information regarding lymphatic drainage of the colon and rectum, as well as our current knowledge of molecular determinants of lymphangiogenesis (e.g., vascular endothelial growth factor-C/-D) and the evaluation of the clinical significance of lymphatic microvessel density in cancer. The review also addresses controversies and innovations in CRC staging, including the impact of lymphovascular invasion on indications for adjuvant chemotherapy, especially in early-stage cancer. A review of current developments in the surgical treatment of CRC (transanal total mesorectal excision and lateral pelvic lymph node dissection) was also conducted, with special reference to the oncological relevance of lymphatic drainage. Knowledge of the complex structures of the lymphatic network is required to establish an individualized risk assessment, and to select the most appropriate surgical strategy in order to optimize the treatment of patients with CRC.

Keywords Colorectal cancer, lymph vessels, lymphatic network, lymphatic anatomy

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Introduction

Colorectal cancer (CRC) continues to affect large numbers of individuals worldwide and remains a major cause of cancer-related morbidity and mortality. Tumor spread to regional lymph nodes has traditionally been used to determine a patient's prognosis, and to decide whether a patient may benefit from adjuvant treatment [1,2]. However, simply treating the lymphatic system as a passive filter for migrating tumor cells may underestimate the complex role that the lymphatic system plays in the disease.

Importantly, beyond the macroscopic identification of involved lymph nodes, the complex network functions as an active, dynamic, and even propagative tumor microenvironment throughout the disease course. Notably, a number of studies have demonstrated that tumors themselves induce the growth of new lymphatic vessels, a process referred to as lymphangiogenesis, which occurs through a number of distinct signaling pathways [3,4]. This process facilitates the early phases of tumor metastasis by increasing the opportunity for intravasation of tumor cells into the lymphatic vessels. Of critical importance in this regard is the recognition that even isolated lymphovascular invasion (LVI) is capable of an independent role in the clinical behavior of CRC [5]. LVI exists as an active, dynamic conduit for the progression of tumor throughout the body, the effects of which can be discerned clinically in terms of the timing of disease recurrence, as well as ultimate patient survival, even in cases of node-negative disease [6,7].

While all these factors determine the disease course, the lymphatic spread of the tumor is increasingly acknowledged to play a crucial role in the clinical behavior of CRC. Thus, there is a paradigm shift in the assessment of lymph node involvement in this disease, from simple nodal count to an assessment of the biological factors that are involved in the lymphatic spread of the tumor. The aim of this review is to translate the information

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from the literature regarding the role of the lymphatic system in CRC into clinical practice and, more importantly, to highlight the importance of assessment of the factors involved in the lymphatic spread in order to provide the best possible treatment for the individual patient.

Methods

A narrative review of the existing literature was conducted in order to adequately describe the role of the lymphatic network in CRC.

Two independent reviewers (DC, NT) conducted a literature search across the PubMed, Embase, Web of Science and Scopus databases. The literature search encompassed articles published from database inception up to January 2026. The final search was conducted on February 3, 2026. The search strategy used the following combinations of keywords and Boolean operators: "lymphatic anatomy" AND "colorectal cancer", "lymphatic network" AND colorectal cancer", "lymphatic drainage", "lymphatic microvessel density" AND "colorectal cancer", "lymphangiogenesis", "lymphatic anatomy" AND "colorectal cancer treatment", "lymph node assessment", in order to collect data that would fit the criteria of our review.

Rigid inclusion and exclusion criteria were used for article selection. Inclusion criteria included: publications in the English language, priority to systematic reviews and meta-analyses, key clinical trials and international recommendations focusing on the anatomy, biology and clinical significance of lymphatic spread in CRC. Additionally, any original peer-reviewed published studies that addressed issues around this topic, were included. Exclusion criteria included: any non-peer-reviewed commentary, abstract-only publications, studies from which a full article was not available. Discrepancies between the 2 independent review authors about article eligibility were resolved through discussion.

Anatomy of lymphatic drainage pathways in CRC

Accurate mapping of the lymphatic anatomy of the colorectum is critical for planning and executing cancer resection, as well as for understanding patterns of metastasis. While the colonic mucosa is highly vascularized, true lymphatic channels penetrate deeper into the bowel wall, surrounding the colon within the submucosal and the muscularis mucosal layers [8]. The routes that the lymphatic fluid takes as it exits the colon vary greatly depending on the specific region of the colon. For a clearer understanding, the colorectum can be divided into 3 distinct regions: colon, rectum (and mesorectum), and anal canal.

The lymphatic drainage from the colon follows a sequential pattern through 4 groups of nodes along the blood vessels that supply the colon. The first group, the epicolic nodes, are located on the surface of the colon. The next group, the paracolic nodes, are found along the inner border of the colon. The intermediate nodes are located along the mesenteric arteries, while the last group of nodes, the main or apical nodes, are found at the origins of the superior and inferior mesenteric arteries [9]. Because colon cancer tends to follow an epicolic to apical pattern of spread, central vessel ligation and a complete mesocolic excision are recommended to remove the entire hierarchical basin of nodes for a potential cure of colon cancer [10-12].

The rectal lymphatic system is a very complex system confined within the tight spaces of the pelvis. The perirectal space can be broadly divided into 3 compartments. The inner compartment is surrounded by the visceral pelvic fascia and the Denonvilliers' fascia, creating the mesorectum. The intermediate space is bounded by the parietal pelvic fascia and the internal iliac vessels, and includes the space of the obturator nodes in the outer compartment [13,14]. The majority of the mesorectal nodes (71.4%) are found above the level of the anterior peritoneal reflection, and are primarily located in the posterior and upper two thirds of the mesorectal envelope, following the branches of the superior rectal artery (SRA). The anterior compartment and the lower third of the mesorectum contain relatively few nodes (Fig. 1) [15-17].

The pathway of lymphatic drainage from the rectum follows a characteristic pattern, and can often be predicted based on the anatomical level of the rectum. The upper and middle rectum are restricted to the inner space of the perirectal region. From here the drainage is primarily upwards within the submucosal layer of the rectum, along the supplying branches of the SRA, terminating in the inferior mesenteric artery basin [17]. In contrast, the lower rectum follows a complex dual pathway that not only includes an upward-directed drainage, confined to the inner space of the perirectal region, but also involves penetration of the lateral ligaments of the rectum, allowing drainage in the intermediate as well as in the outer spaces of the perirectal region. Here, the lymphatic vessels ascending in the intermediate space along the internal iliac artery are distributed to the nodes in the obturator space on the lateral pelvic sidewalls [13]. Importantly, the specific pathway that rectal cancer follows is heavily dependent on the tumor's circumferential location within the rectal wall. Posteriorly located tumors in the rectum follow a characteristic bilateral pathway, traveling on both sides of the SRA, whereas tumors on the lateral rectal wall exhibit a strong predilection for a unilateral pathway that can follow the different subdivisions of the superior and middle rectal arteries, primarily on the ipsilateral (tumor) side (Fig. 2) [16,17].

The lymphatic drainage of the anal canal above the dentate line is similar to that of the lower rectum. In this region, the drainage of the anal canal follows the visceral drainage of the rectum. The primary pathway of the lymphatic vessels of the anal canal below the dentate line drains downward and outward to the superficial inguinal lymph nodes [16] (Fig. 2). The anorectal transition zone at the pelvic floor contains a complex functional micro-network of lymphovascular connections. Studies using indocyanine green fluorescence and/or injecting the tissue with India ink have demonstrated active lymphovascular connections from the longitudinal anal muscle, extending to the hiatal ligament and to the endopelvic fascia covering the *levator ani* muscle [18]. The connection of the lymphatic vessels of the anal canal to the deep fascial layers of the pelvic floor helps to

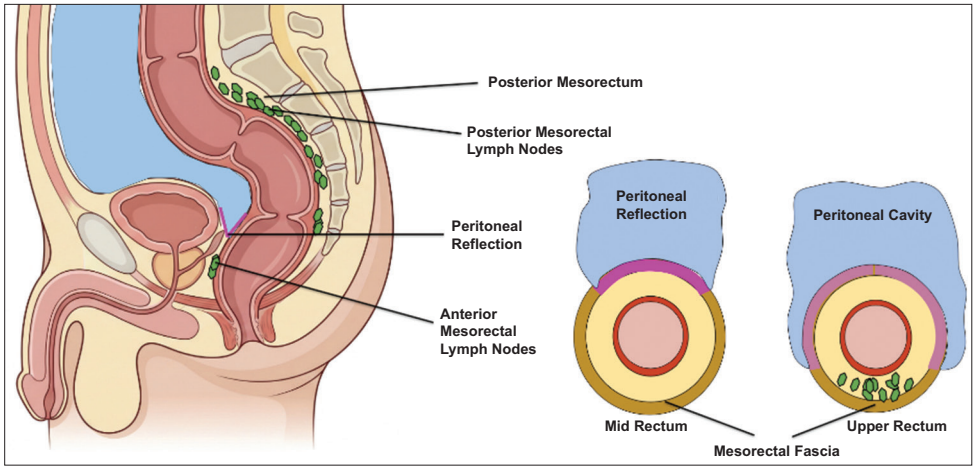

Figure 1 Distribution of the mesorectal lymph nodes

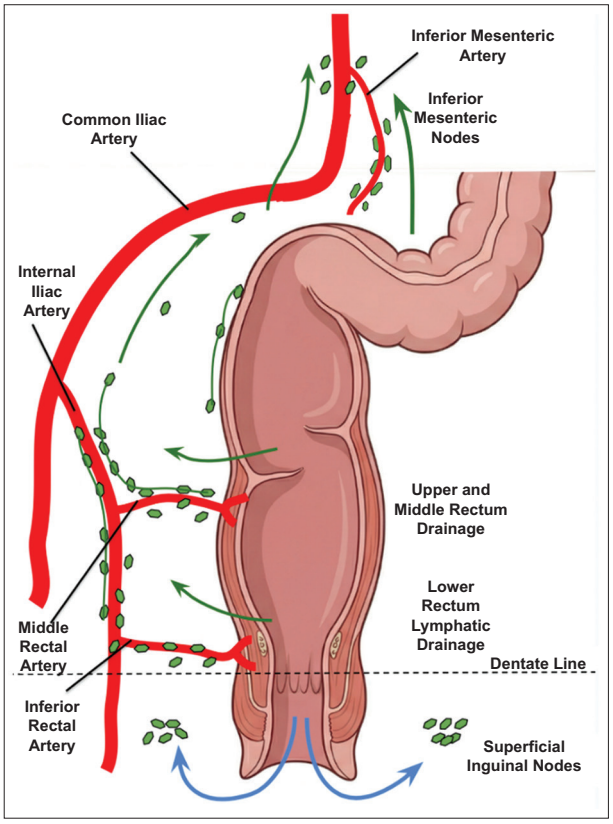

Figure 2 Different lymphatic drainage pathways of the rectum

explain the extensive spread of low-lying tumors throughout the pelvic floor. This spread of tumor may extend beyond the boundaries of standard surgical resection.

Molecular mechanisms

Despite the problems that have been encountered in defining a correlation between neoplastic tumors and the anatomy of the lymphatic vessels, considerable efforts have been made to describe and determine the correlation between lymphangiogenesis and CRC metastasis. Markers that are specifically expressed by typical lymphatic vessels can be used as a starting point. A variety of molecular markers have been described that are specifically expressed by lymphatic endothelial cells, such as vascular endothelial growth facto receptor (VEGFR)-3, Prox-1, and lymphatic vessel endothelial hyaluronan receptor 1. A high specificity for assessment of lymphangiogenesis, however, is often achieved by the use of a very specific marker for lymphatic endothelial cells, i.e., podoplanin [19,20]. This glycoprotein was originally identified in glomerular podocytes and is predominantly expressed by small lymphatic vessels. Recent studies have shown that the process of lymphangiogenesis can be dramatically affected by the absence of podoplanin [3].

It should be noted that multiple molecular factors contribute to the genesis of lymphatic vessels, both peritumorally and intratumorally. Specifically, the upregulation of vascular endothelial growth factor (VEGF)-C/-D is observed in CRC, which facilitates and accelerates lymphangiogenesis through the VEGF-C/VEGF-D/VEGFR-3 signaling axis [3]. Additionally, other variables suspected to be involved, such as epidermal growth factor and transforming growth factors, should be further investigated to determine their precise contribution and role in CRC.

The process of tumor lymphangiogenesis is complex, and involves a number of different factors that interact in a sequence of steps. One group of cells that have been implicated in tumor lymphangiogenesis are circulating endothelial progenitors (CEPs). These cells are incorporated into existing lymphatic vessels, but also have the ability to form new vessels, and are thought to play a role in pathological processes that increase the amount of vasculature in a tumor, potentially increasing its ability to metastasize [3]. CEPs are a subpopulation of circulating endothelial cells that are believed to arise from the bone marrow, and in several pathological states their numbers are increased. Notably, these cells have the ability to maintain a progenitor cell phenotype [21].

Other cell types have been reported to be able to differentiate to lymphatic endothelial cells, thus promoting lymphangiogenesis. For example, macrophages play a part in both promotion and inhibition of tumor metastasis through their dual role in lymphangiogenesis [22].

Lymphatic microvessel density (LMVD) and angiogenic markers

Assessment of LMVD in CRC is considered to be one of the most promising biological variables for prediction of the clinical course and metastatic potential of a tumor. The available literature, however, is characterized by a marked degree of variability, and by a large number of contradictory results that need to be critically analyzed and explained.

Much of the conflicting data regarding the role of LMVD in predicting prognosis for patients with CRC resides in the older anatomic literature, in which studies employed a variety of different immunohistochemical markers. Many of these studies, especially the older ones, used broad-endothelial markers, such as Factor VIII, CD31, CD34, that non-specifically and indiscriminately marked all blood and lymphatic vessels [22]. Such studies estimated generic angiogenesis rather than true lymphangiogenesis, and were confounded by high levels of blood vessel growth (angiogenesis). Utilizing more specific markers for the lymphatic endothelium, such as D2-40 (podoplanin), to specifically and accurately quantify the numbers of individual lymphatic vessels has demonstrated enhanced accuracy compared to routine hematoxylin and eosin (H&E) or older markers in detecting true lymphatic vessels, yielding more reliable prognostic data [23].

The conflicting data may arise from studies that fail to take into consideration the spatial location of the assessed lymphatics. It has been established that lymphatic vessels in different locations of the tumor possess architecturally and functionally distinct features. Zhang *et al* and Liang *et al* demonstrated that intratumoral lymphatics are often small, collapsed and irregular [24,25]. This is a notable observation, since lymphatics are compressed by high interstitial pressure generated by aggressive and fast-growing tumors [24,25], whereas peritumoral lymphatics at the invasive front of a tumor are often large, open and functional. Therefore, studies that average the whole tumor density may arrive at data that are in part contradictory. In contrast, studies that analyzed separate areas of the tumor have indeed found a high density of peritumoral lymphatic microvessels to be a predictive factor for aggressive LVI, positive lymph nodes and a shorter disease-free survival [24,26] (Table 1).

Finally, conflicting data regarding LMVD and tumor stage may be explained by the timeline of tumor progression. For example, in a study by Gao *et al* it was stated that the lymphatic density in Duke's stages C and D tumors is lower than in stages A and B [27]. On the other hand, studies conducted by Barresi and Liang show that LMVD is a very powerful variable that can predict the likelihood of metastasis in early Stage I and even in T1 CRCs [25,26]. It is easy to understand why this contradiction exists. The increased internal pressures and the hypoxic environment associated with advanced tumor stages can compromise the structural integrity of intratumoral lymphatics, leading to their collapse. As a result, the total number of lymphatic vessels within a large tumor would be decreased. Studies that utilized the modern D2-40 staining and focused only on the peritumoral invasive margin of early-stage tumors have identified a high LMVD as a very useful marker that can predict a patient's risk of relapse and, more importantly, can indicate a clinical staging underestimation in many cases [23,24] (Table 1).

Table 1 Summary of studies on lymphatic microvessel density (LMVD) and angiogenic markers

Study [ref.]	Metric investigated	Key finding/association
Zhang *et al* [24]	LMVD (Intratumoral & Peritumoral)	High peritumoral LMVD correlates with aggressive invasion and shorter survival
Moreira *et al* [73]	LMVD	Elevated LMVD in pre-malignant adenomas concurrent with invasive carcinoma
Liang *et al* [25]	LMVD	High LMVD strongly predicts metastasis in early T1 carcinomas
Barresi *et al* [26]	LMVD	Associated with aggressive development in early Stage I CRC
Gao *et al* [27]	LMVD	Lower LMVD in advanced stages (Duke's C/D), likely reflecting pressure-induced vessel collapse
Saad *et al* [23]	LMVD	High peritumoral LMVD identifies high-risk, clinically under-staged patients
Guetz *et al* [28]	VEGF & intratumoral MVD	Predicts worse overall (RR 1.65, 95%CI 1.27-2.14) and disease-free survival (RR 2.84, 95%CI 1.95-4.16)
Wang *et al* [29]	VEGF & MVD	VEGF overexpression doubles death risk and increases distant metastasis risk 4.22-fold

VEGF, vascular endothelial growth factor; MVD, microvessel density; RR, risk ratio; CI, confidence interval

The evaluation of VEGF in addition to LMVD could play an important role in clinical studies of CRC. The assessment of VEGF in combination with LMVD, as outlined in Table 1, can provide crucial information on the prognostic impact of both markers in cancer patients. A systematic review and meta-analysis by Guetz *et al* assessed the impact of VEGF expression and intratumoral microvessel density on patient outcomes [28]. High levels of these variables were found to predict worse overall survival in cancer patients (relative risk [RR] 1.65, 95% confidence interval [CI] 1.27-2.14), as well as disease-free survival (RR 2.84, 95%CI 1.95-4.16) [28]. Similarly, another analysis addressed the same question using hazard ratios, which account for both the number and timing of events, unlike RR [29]. More precisely, the excessive expression of

VEGF was associated with approximately a 2-fold risk of death, while upregulation of LMVD correlated with a 39% increase in the risk of death [29]. Additionally, elevated VEGF expression is associated with more aggressive LVI, increased lymph node involvement, and a 4.22-fold (95%CI 2.93-6.06) greater risk of presenting with distant metastatic sites in comparison to lower VEGF levels [29].

Lymphangiogenesis and lymphatic invasion

Evidence suggests that lymphangiogenesis, or the formation of new lymphatic vessels, is associated with tumor progression and establishment of metastases at specific sites. Increased lymphatic vascular area in the vicinity of tumors is largely due to peritumoral and intratumoral lymphangiogenesis. The interface between growing tumor cell clusters and their surrounding stroma is crucial for invasion of lymphatic vessels by cancer cells, which are then able to migrate through the newly formed connections into surrounding tissue. Although functional lymphatic vessels have been observed within individual CRC tumors, these are mostly non-functional collapsed structures of small diameter [3]. Most of the peritumoral lymphatic structures are a continuation of preexisting vessels in the vicinity of the tumor borders, and are now compacted by the enlarged mass, though newly formed vessels also contribute significantly to this peritumoral density [3].

The process of invasion and metastasis in CRC involves a complex cascade of steps, all depending on the existing lymphatic vessels and their configuration. Invasion of the tumor cells into the vessels of the peritumoral stroma, their transit through the lymphatic channels and their release into the surrounding target tissues within the lymphatic lamina are the main single steps. The fact that enlarged lymphatic vessels with increased lumen diameter are predominantly found in the peritumoral stroma may favor the process of metastasis [30]. Molecules involved in the process of lymphangiogenesis and their potential role in CRC are still a matter of investigation. However, the VEGF-C/VEGF-D/VEGFR-3 pathway has been suggested to play a major role in lymphangiogenesis. Studies in animal models showed that VEGF-C and VEGF-D are capable of increasing the diameter, the proliferation rate and the LMVD of the lymphatic microvessels within the tumors [31]. The sonic hedgehog signaling pathway has also been reported to promote lymphangiogenesis; however, no correlation with CRC has been reported so far [30].

Rather than relying on the overall tumor stage to forecast the cancer's behavior, the assessment of the lymphatic network within a tumor and its connections to possible sites of metastasis can be used to identify high-risk biological behavior. The process of transition from active lymphangiogenesis to actual lymphatic invasion, the microscopic presence of tumor cells within the lymphatic channels, is considered a central point. This distinction is particularly important in Stage II (node-negative) CRC, where the benefit of adjuvant chemotherapy has not yet been widely established by the medical community. While standard Stage II tumors may be managed with surgery alone, the detection of lymphatic invasion can re-categorize patients into a high-risk group, frequently guiding the recommendation for adjuvant systemic therapy [32].

The significance of the exact identification of lymphatic vessel anatomy and function is a key component of patient prognosis. Notably, Betge *et al* showed that definitive lymphatic invasion, as distinct from venous invasion, is an independently significant prognosticator of a poor outcome [1]. In a similar study conducted by Desolneux *et al*, both venous and lymphatic invasion were found to be independent predictors of outcome in patients with node negative CRC. This observation helps in the identification of patients who harbor an occult aggressive disease without any overt lymph node metastasis [32]. Furthermore, expanding upon its implication on survival, Lim *et al* reported a strong connection between the presence of LVI and a reduction in both cancer-specific and disease-free survival, stressing its relevance as a usual criterion in the modern pathological report [33].

The depth and extent of lymphatic invasion in CRC is of great prognostic value, as previously reported by Bianchi *et al* [34]. Thus, the National Comprehensive Cancer Network considers the presence of lymphatic invasion to be a high-risk feature, together with other clinical parameters, such as bowel obstruction or perforation, an inadequate number of examined lymph nodes (<12), positive margins, perineural invasion or a poorly differentiated histology [34,35]. In analogy to other parameters, the prognostic value of lymphatic invasion is strongly related to the degree of lymph node involvement, which is considered as one of the most important factors for the clinical staging and prognosis of CRC [34]. In particular, lymphatic invasion is found in conjunction with adverse histopathological characteristics, such as high-grade tumors, mucinous carcinoma, marked tumor budding, and advanced T and N categories. Notably, lymphatic invasion even allows the early prediction of nodal metastasis in a subgroup of patients with early-stage (T1) primary tumors [34]. While positive N status and an advanced T stage (T3-T4) are recognized as independent prognostic factors, in selected patient groups the presence of lymphatic invasion may have a similar or even higher prognostic value [34]. A meta-analysis performed by Yuan *et al* investigated the prognostic relevance of lymphatic invasion in patients with Stage I-II CRC. While overall lymphatic invasion resulted in a poor prognosis, this effect was largely due to Stage II (T3-T4) tumors, whereas lymphatic invasion was not associated with overall survival in patients with Stage I (T1-T2) cancer [36]. Furthermore, a study by Bianchi *et al* has recently reported the clinical outcome of a series of patients with CRC, which consisted entirely of lymphatic invasion-positive tumors. Remarkably, in the aforementioned group, patients with early T-stage (T1-T2) tumors showed a favorable overall 5-year survival rate of approximately 70% [34]. In marked contrast, patients with T3-T4 tumors and no evidence of lymph node metastasis had a significantly lower overall 5-year survival rate of only 52% [34].

Taken together, these findings indicate that, in early-stage CRC, the presence of lymphatic invasion is not always a poor prognostic sign, but rather a potential biological "upstager",

especially in stages T3-T4. In the context of T2 CRC in particular, with a relatively lower risk of lymph node metastasis, the presence of lymphatic invasion may have a similar or even higher prognostic value than the established parameter of N status. As reported in a comprehensive systematic review by Hartwig *et al*, the overall risk of lymph node metastasis in patients with pT2 colon cancer is 19.3% [37]. Hence, the high proportion of node-negative patients with T2 CRC poses a significant problem in their clinical management, as more than 80% of patients who undergo a standard resection for local disease are found to be node-negative postoperatively [37]. For young and fit patients, a 19.3% risk of metastasis is often considered too high to justify local resection; they are thus candidates for organ-preserving surgery, whereas elderly or frail patients with similar tumors are at higher risk of postsurgical morbidity and mortality [37]. Precisely in the elderly group and in patients with poor performance status, local resection is associated with an 18% 1-year mortality rate. In these patients, the risk of metastasis is considered too high to justify a potentially morbid radical resection. However, local resections are often correlated with a higher risk of inaccurate pathological staging. This may allow for the underestimation of indications for adjuvant therapy, resulting in subsequent relapse and metastatic disease. In view of these considerations, the identification of high-risk histopathological features, such as lymphatic invasion, plays a critical role in the clinical management of CRC patients. The absence of lymphatic invasion may support an organ-preserving approach in frail patients, whereas the presence of lymphatic invasion may guide a more radical surgical strategy.

Lymph node assessment

The understanding of lymph node metastasis in CRC can be enhanced by an overview of current perspectives in tumor staging. The N category of the traditional Western TNM staging system simply states the number of positive nodes found. Recently, the 8th edition of the TNM-staging system includes a more detailed sub-classifications for N1 cancers: N1a (1 single positive node), N1b (2-3 positive nodes) and N1c (tumor deposits), whereas N2-cancers are subdivided into N2a (4-6 positive nodes) and N2b (7 and more positive nodes) [38] (Table 2).

The controversy surrounding the optimal number of examined and processed nodes in CRC patients is still ongoing, and has been addressed in a number of recent studies. Current reports have underlined the importance of nodal proximity, rather than just the total number of processed nodes. It has been stated that the majority of metastatic lymph nodes are found within a 3-5 cm radius of the primary tumor, within the primary nodal basin [39,40]. Therefore, an inadequate assessment of this area is not compensated for by a high number of distally located, non-involved lymph nodes, and thus is not acceptable. To address these problems in tumor staging, recent developments in the field of oncologic pathology have moved from macroscopically dissection of lymph node-containing tissue to a more targeted approach. Through the intraoperative use of dyes or fat-clearing solutions, even the smallest of micro-nodes, which would otherwise not be detected, can be retrieved and processed [39,41]. Moreover, in cases of pN0 status, a second-look approach for the primary nodal basin has been reported to detect a number of cases of micrometastases that would otherwise be subject to stage migration [39].

Table 2 Key prognostic factors in lymph node assessment

Prognostic/ staging factor	Clinical significance
TNM staging (quantitative)	Strictly numeric (N1a-c, N2a-b); explicitly incorporates isolated extra-nodal tumor deposits (N1c)
Nodal yield & proximity	Harvesting the immediate 3-5 cm peritumoral basin is more critical for accurate staging than raw distal node counts
Spatial staging (apical nodes)	Apical node involvement severely reduces 5-year survival (28%), biologically mimicking distant systemic metastasis rather than regional disease
Lymph node ratio (LNR)	Independent survival predictor; effectively rescues risk-stratification in under-staged cohorts with suboptimal yields (<12 nodes)
Extracapsular invasion	Direct tumor extension beyond the nodal capsule strongly correlates with poor differentiation and diminished survival

As opposed to focusing solely on the number of nodes retrieved, there is great international interest in defining a staging system that describes the spatial relationships between cancer and regional lymph nodes. While the TNM staging system currently focuses on quantitative parameters, an alternative Japanese system divides the location of regional lymph nodes into 3 groups: N1 nodes are located near the colon, N2 along the vessels and N3 along the roots of main arteries [42,43]. The pattern of colon cancer spread is frequently determined by the primary tumor's location within the colon. For example, cecal cancer tend to involve the ileocolic nodes, while cancers of the transverse colon involve the middle colic nodes [44,45]. The prognostic utility of this spatial staging is highly evident in apical node involvement (the root of major arteries). Involvement of these nodes has a particularly poor prognosis, with studies indicating a 5-year overall survival rate of only 28% [46]. Because this survival rate closely resembles systemic disease, a contemporary debate questions whether apical nodal involvement should be classified as advanced regional staging, or whether it actually represents a proxy for distant metastasis [42,46] (Table 2).

Because of factors varying from technical considerations to anatomical difficulties, an optimal nodal yield of ≥12 nodes is not always achievable. To better risk-stratify understaged patients, clinicians can opt to use advanced prognostic markers that are known to be able to predict outcomes in CRC. Thus, it is argued that the lymph node ratio (LNR), the proportion of metastatic to total examined nodes, is a significant prognostic indicator [47]. The benefit of utilizing the LNR method over standard N-staging

for predicting outcomes in stage III colon cancer has been well validated [48,49]. There has been some contention about the validity of the LNR method within suboptimal nodal yields, as it was argued that LNR could inflate the statistics artificially, causing a positive prognostic overestimation. However, from the results of prior existing meta-analyses that have involved over 70,000 patients overall, it has been concluded that LNR is a valid independent prognostic factor across different numbers of examined nodes. Finally, an elevated LNR had a robust association with poor prognosis across all cohorts, including the mathematically compromised ones (N<12), in terms of poorer overall and disease-free survival [50] (Table 2).

In addition to the previous mathematical ratios, extranodal disease should also be taken into consideration, as it helps determine the presence of positive or negative prognostic factors. Tumor deposits, defined as discrete neoplastic nodules within the adipose tissue that lack residual nodal architecture, carry significant prognostic weight and are now formally integrated into the TNM staging hierarchy (N1c). Similarly, extracapsular invasion, which is characterized by the direct extension of tumor cells through the lymph node capsule into adjacent soft tissue, is reported to exhibit a strong connection with factors such as advanced disease stage, poor histological differentiation and significantly diminished survival [42] (Table 2). Finally, while the first T1 cancer criteria relied mainly on absolute depth, width and area of submucosal invasion, a modern shift towards more dynamic variables is currently being noted. Since these older aforementioned criteria showed significant variability in predicting nodal metastasis, other factors, such as differentiation, high-grade tumor budding and LVI, are now being considered as more trustworthy for predicting early nodal disease [51-53]. Given its obvious clinical impact, the creation of official evaluation guidelines for diagnosing lymphatic invasion is of great importance. To avoid inaccurate diagnoses, a Delphi consensus allowed Kojima *et al* to introduce formal assessment criteria, supporting the utilization of high-magnification assessment using D2-40 stains [54]. Consequently, diagnosis has improved overall, through the direct identification of tumor cell groups surrounded by D2-40 positive endothelium [54,55]. Overall, the perception of lymphatic spread has changed from the static mapping of anatomical drainage to a more dynamic anatomical framework. As advocated by Zhang *et al*, lymphatic metastasis is a complicated stepwise conduit for dissemination of the disease systemically [56]. High-resolution genetic subclonal mapping illustrates that "skip spreading" directly to distant nodes occurs more frequently than traditionally recognized, and that involved lymph nodes actively "reseed" other nodes or distant organs via the bloodstream, supporting the notion that lymphatic metastasis is an actively propagating biological disease rather than a passive anatomical filter [56].

Adjuvant therapy

The treatment for CRC is characterized as varied, multifaceted and complex. Anti-lymphangiogenic therapy is an intriguing concept focusing on limiting the proliferation of lymphatic growth, and thus limiting metastasis in CRC [3]. The VEGFR-C, VEGF-D and VEGFR-3 pathways, which contribute to the lymphangiogenesis molecular process, make ideal targets for possible future treatment options [4]. CEPs could also be considered an alternative, but care would need to be taken, as they also play a significant role in physiological body function through their influence on the integrity of the vascular endothelium and cardiovascular health. Anti-lymphangiogenic therapy as an approach to cancer has unfortunately made slow progress, as no therapeutic agent is currently in play [3,21].

Instead, contemporary oncologic practice is based on the administration of systemic adjuvant chemotherapy, whose application is heavily reliant on the integrity of the lymphatic barrier [57,58]. The decision about adjuvant therapy in node-negative (Stage II) colon cancer is complex, and focuses on the probability of occult dissemination, a subject also linked with lymphatic biology, given the fact that a lymph node yield of less than 12 is now viewed not only as a surgical quality metric, but also as a biological indicator of inadequate sampling of the regional lymphatic basin, and perhaps the presence of micrometastases [59,60]

More importantly, LVI or perineural invasion indicates a significant parallel, microscopic, non-nodal escape from the primary tumor bed. While standard staging depends on macroscopic nodal counts, perineural invasion, which is present in 18.2% of tumors (according to a meta-analysis by Knijn *et al* of more than 22,000 patients), acts as a powerful parallel route for dissemination, which increases local recurrence while also decreasing 5-year overall survival [6].

When this microscopic escape occurs, Stage II patients with perineural invasion are often placed in the same category as Stage III patients, in terms of disease-free survival, suggesting that this extramural invasion biologically upstages the disease, as these individuals frequently require systemic therapy. This observation was made by Yang *et al*, who highlighted the detrimental effect of this variable on patient outcomes [61]. However, the identification of microscopic lymphatic escape remains challenging, as studies often conflict regarding the prognostic weight of LVI, given its gross diagnostic inconsistencies [62,63].

Moreover, Lee *et al* showed that routine H&E staining often fails to detect collapsed lymphatic channels [57], and when pathologists re-reviewed standard sections with advance dual immunohistochemical staining (such as D2-40, a specific lymphatic endothelial marker), the diagnosis of LVI changed in 33.9% of cases. When identified accurately, this lymphatic invasion was a definite predictor for worse recurrence-free survival. The lack of standardized lymphatic staining protocols means there is considerable under-diagnosis that impacts clinical trial results and proper identification of Stage II patients, who would most benefit from receiving systemic therapy [57].

When correctly defined, however, intramural vascular and lymphatic invasion carry a high prognostic weight comparable to that of nodal metastases. Critical reflection on their respective patterns of spread reveals subtle distinctions that

may have significant clinical implications. According to Bae *et al*, only about 50% of the recurrences in node-positive and vascular-negative cohorts occur rapidly within the first year, in contrast to those with isolated vascular invasion (without macroscopic nodal metastasis), in whom 85% of recurrences present later, after 2 years [7].

This can explain why overt lymph node metastasis and intramural invasion do not merely represent different levels of disease gravity, but rather differences in dissemination that may indicate a need for personalized follow up in the longer term [7]. While the biological effect of microscopic extramural invasion in node-negative disease, leading to upstaging, has been established, it is contentious whether it is powerful enough to be useful in Stage III disease (where the macroscopic barrier of the lymphatics has already clearly been overcome). When clear nodal metastases exist, is the additional (often microscopic) invasion still playing a role in altering the biological profile? A critical synthesis of the current body of literature indicates that it might. While it has been shown that, once overt nodal disease is present, pathological parameters such as perineural invasion play a more prognostic rather than predictive role regarding the efficacy of specific chemotherapies [64], it has been shown recently that LVI in fact serves as a significant independent predictor of disease-free survival reduction in Stage III patients [65]. In node positive disease, LVI does not simply represent the transport of cells into the lymph nodes, but rather suggests active permeation of the lymphatics, and ongoing, more active disease that leads to a higher risk of systemic recurrence and correlates with advanced N-stages [5,65].

Given these poorer outcomes, it is common for patients with evidence of active microscopic lymphatic escape to receive systemic therapy [65]. However, dose-limiting accumulation of chemotherapy-related toxicities (peripheral neuropathy) often reduces the clinical utility of standard adjuvant chemotherapy regimens [2]. Treatment for CRC is now being tailored to the quantity of lymphatic disease, in an effort to strike a good balance between morbidity and oncological control. In those patients with a low lymphatic tumor burden (T1-3N1), the International Duration Evaluation of Adjuvant Chemotherapy collaboration has shown that a 3-month course of CapeOX was non-inferior to the standard 6-month duration. Conversely, in those patients with a high lymphatic tumor burden (T4 and/or N2 disease) or with active microscopic lymphatic permeation, current recommendations favor either a 3-month course of CapeOX or a standard 6-month course of FOLFOX to obtain the best oncological result whilst limiting patient morbidity [2,65]. Thus, the extent of lymphatic spread (both microscopic and macroscopic) not only guides initiating adjuvant therapy, but also guides its appropriate duration.

Surgical management

Although surgical resection for CRC remains the mainstay of treatment, modern operative plans have moved away from the simple removal of the tumor, to clearance of the entire regional lymphatic basin, as well as the performance of complete mesocolon & D3 lymphadenectomy, which represents the *en bloc* resection of the mesocolon along with its embryological planes. This ensures the removal of the whole regional lymphatic drainage network up to the central apical nodes. This reduces the risk of microscopic lymphatic spillage [66]. Despite debates comparing laparoscopic and open techniques, modern trials have shown that these meticulous lymphatic clearances, required for stage II & III disease, can be achieved via minimally invasive techniques without any reduction in oncological outcomes [66,67]. Because of the anatomy of the pelvis, lymph node rich mesorectum is notoriously hard to remove safely in rectal cancer. Total mesorectal excision (TME) is the standard approach across the world; it involves the total removal of the rectum, including its surrounding mesorectal fascial envelope, which contains much of its upward lymphatic drainage pathway. A breach in this fascia risks inadvertent lymphatic spillage and subsequent local recurrence [68,69]. It is for this reason that technologies such as robotic surgery and transanal TME (TaTME) have been developed, and have become popular, offering ergonomic advantages in dissecting the rectum down in the deep pelvis, improving visualization and precise dissection abilities, that all assist in achieving a complete, unbreeched macroscopic TME (Grade 3) and in removing the whole regional lymphatic package [68-70].

Apart from the upward mesorectal drainage, lower rectal cancers present with a complex duality of lymphatic drainage patterns, with a lateral lymphatic spread along the internal iliac and obturator vessels. The management of the lateral pelvic lymph node basin in colorectal surgery continues to be debated internationally. While the Western approach favors management of the basin though neoadjuvant chemotherapy in order to non-operatively sterilize these lateral nodes, the Eastern method prefers prophylactic lateral pelvic lymph node dissection (LLND) to mechanically clear the basin [71]. This was further reinforced by the JCOG0212 trial, where prophylactic LLND was shown to reduce local recurrence when compared with TME alone [72]. However, the lateral lymphatic network is not just an anatomical accessory, but a pathway that potentially leads to local failure. Despite initial concerns with postoperative morbidity, morphological mapping of recurrence demonstrates that, when the lateral lymphatic basin is disregarded in surgery, the lateral pelvic sidewall is the site of a high proportion of local recurrences [71]. Therefore, current surgical concepts view the lateral pelvic nodes not just as distant metastases, but as a regional lymphatic basin, targeted for definitive management [71].

Concluding remarks

Despite the fact that the lymphatic vasculature has long been viewed as a passive, anatomical transport route for the progression of colorectal cancer, new developments highlight its role as a significant driver for cancer invasion and metastases. While microscopic lymphatic escape is an essential precursor to regional lymph node involvement and systemic dissemination, a sound understanding of both macro lymphatic anatomy and

the micro lymphatic spatial environment continues to play an important role. The combination of advanced anatomical mapping, as well as dynamic prognostic markers, is expected to aid clinicians in improving the accuracy of CRC staging. Finally, connecting lymphatic biology and clinical practice is an important step for refining patient risk stratification, organizing appropriate adjuvant therapy schemes, and performing precise, oncologically sound surgical resections.

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