Review

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The Role of Nonmetastatic Lymph Nodes in the Survival of Colorectal Cancer

A Systematic Review

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Objective: In this review, we aim to provide an overview of literature on lymph node (LN) histomorphological features and their relationship with the prognosis in colorectal cancer (CRC).

Background: Lymph nodes play a crucial role in the treatment and prognosis of CRC. The presence of LN metastases considerably worsens the prognosis in CRC patients. Literature has shown that the total number of LNs and the number negative LNs (LNnegs) has prognostic value in CRC patients. In esophageal carcinoma, LN size seems to be surrogate of the host antitumor response and a potentially clinically useful new prognostic biomarker for (y)pN0 esophageal carcinoma.

Methods: A comprehensive search was performed in Pubmed, Embase, Medline, CINAHL, and the Cochrane library in March 2021. The PRISMA guidelines were followed. Only studies focusing on histomorphological features and LN size and their relation to overall survival were selected.

Results: A total of 9 unique articles met all inclusion criteria and were therefore included in this systematic review. Six of these studies investigated HMF (eg, paracortical hyperplasia, germinal center predominance, and sinus histiocytosis) and 4 studies LNneg size and their relationship with overall survival. The presence of paracortical hyperplasia and an increased number of large LNnegs is related to a more favorable prognosis in CRC.

Conclusion: The results of this systematic review seem to support the hypothesis that there is a relationship between the host antitumor response reflected in different histomorphological reaction patterns visible in LNnegs and LNneg size related to survival in CRC patients.

Keywords: colorectal cancer, lymph nodes, immune system, survival

Colorectal cancer (CRC) is the third most common cancer and the second most common cause of cancer-related death worldwide.[1] Treatment is based on clinical disease stage [tumor, node, and metastasis (TNM) classification]. The presence of metastatic disease in the regional lymph nodes (LN) is one of the most important prognostic indicators determining (neo) adjuvant treatment.[2–4]

A higher number of LN metastases [positive LN (LNpos)] has been associated with a poorer prognosis in CRC patients.[3,5] A review by Kim et al explored alternative factors that can influence survival beyond the number of LNpos such as LN ratio, LN distribution or location of metastatic LN, tumor deposits, and extracapsular invasion.[6] A high LN ratio (LNpos/total number of LN) has been associated with poor prognosis.[7–11] However, there is no consensus on what the universal cutoff value for LN ratio for clinical practice should be, which hinders clinical implementation of this factor.[6] Although there is evidence supporting the use of lymph node distribution (LND) as a classification for metastatic LN,[12,13] LND classification is currently not used in clinical practice for treatment decisions. One of the main reason for this might be that it is a time consuming process for surgeons

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All authors were involved in the conceptualization and design of this review. A.J.P., M.K., and L.F.S.K. designed the search strategy with input from J.M.P.K. A.J.P. and B.A.v.d.V. collected and analyzed the data. A.J.P., B.A.v.d.V., H.I.G., and J.M. were responsible for data interpretation. A.J.P. drafted the first version of the article under supervision of H.I.G. and J.M. All authors were involved in the critical revision and final approval of the version to be published.

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Definitions/abbreviations used

- **TNM stage I**: The primary tumor has grown into the submucosa (T1) or has invaded the muscular layer of the colon or rectum (T2). There are no regional lymph node metastases and no distant metastases (T1 or T2, N0, M0).
- **TNM stage II**: The primary tumor has grown through the muscular layer of the colon or the rectum into the subserosal fat (T3) or through the peritoneal surface (T4). (T3 or T4, N0, M0).
- **TNM stage III**: Irrespective of the extent of invasion of the primary tumor, the cancer has spread to regional lymph nodes, there are no distant metastases (T1-4, N1 or N2, M0).
- **TNM stage IV**: Irrespective of the extent of invasion of the primary tumor and the number of lymph node metastases, the cancer has spread to other parts of the body (presence of distant metastases) (any T, any N, M1).
- **Sinus histiocytosis (SH)**: The presence of large monocytic cells with vesicular nuclei and well-defined, somewhat granular, eosinophilic cytoplasm within the sinusoidal structures of the lymph nodes.
- **Germinal center predominance (GCP)**: Lymph nodes with the presence of an increased number of germinal centers inside the secondary lymphoid follicles.
- **Paracortical hyperplasia (PH)**: Lymph nodes with an expansion of the paracortical region due to an increased number of lymphocytes in these regions.
- **Lymphocyte depletion (LD)**: Lymph nodes showing a paucity of lymphocytes and an absence of germinal centers as well as fibrosis or hyalinization of the cortex region.
- **Unstimulated lymph nodes (ULN)**: Lymph nodes with a thin cortex showing lymphocytic follicles and ill-defined deep cortical regions.
- **Lymph node size (LNS)**: The largest diameter of lymph nodes in millimeters measured in the pathological specimen. Figure 1 shows a schematic view of lymph node structure and the location of immune cells.

and pathologists to process and report findings in LNs by location.[14] Furthermore, there are studies suggesting that pathologic N status (eg, number of positive LN) was more significantly associated with survival than LND.[14] Both tumor deposits and extracapsular invasion are emerging prognostic factors, but although the reporting of tumor deposits is recommended in international guidelines, treatment decisions are currently not using this information.[6]

Most literature about LNs in CRC focuses on the presence of metastasis in the LN. However, it has been suggested that regional, tumor-draining LN play a pivotal role in the initiation of a robust host antitumor response and that an increased LN size might be related with a better prognosis.[15] A recent study by Kloft et al investigating esophageal cancers showed that irrespective of treatment modality, (y)pN0 patients with large LNneg had the best overall survival suggesting that LNneg size might be a surrogate marker of the host antitumor response and a potentially clinically useful new prognostic biomarker.[16]

In this review, we aim to provide an overview of the current literature on LN histomorphological features, their relationship with survival in CRC and the potential clinical value of these features in the diagnosis and treatment of CRC patients.

METHODS

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17,18] The review protocol was registered in the PROSPERO database (CRD42021244847).

Search Strategy

A search was performed in Pubmed, Embase, CINAHL, and the Cochrane database for the period from inception to March 2021. A second search was performed on the December 20, 2022, to assure no new publications were missed. The full search strategy is available in Appendix 1. Two reviewers independently performed the article selection and reviewed all included articles. Discrepancies were either resolved by discussion or by a third reviewer. The primary outcome of this systematic review is overall survival related to negative LN histomorphology. The following inclusion criteria were used: (1) studies that investigated the negative LN histomorphological reaction pattern (eg, sinus histiocytosis (SH), paracortical activity, LN hyperplasia, and LN size) in relation to survival in colorectal cancer patients, (2) study included 10 or more patients, (3) studies reported in English, German, or Dutch. Case reports, animal studies, letters to the editor, meeting abstracts, and expert opinions were excluded.

Data Extraction and Risk of Bias Assessment

Two reviewers (A.P. and B.V.) performed data extraction and risk of bias analysis independently, any differences were resolved by consensus. Data extracted included study characteristics (eg, year of publication, country of origin, design, and tumor type of interest), baseline patient characteristics, what negative LN histomorphology was assessed and survival data (Supplemental Table 1, http://links.lww.com/AOSO/A252). Quality assessment was performed by using the Quality In Prognosis Studies (QUIPS) checklist.[19] Study domains (ie, study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting) were assessed separately as being low, moderate, or high risk of bias.

Data Analysis

Basic descriptive statistics were used to summarize patient characteristics and survival data. The interquartile range (IQR) or the standard deviation was provided, when informative, for the interpretation of medians and means, respectively.

RESULTS

Literature Search

The search was performed in March 2021, and 6870 unique articles were identified of which 70 were included in the full-text analysis. Nine articles met all inclusion criteria and were included in qualitative synthesis. The PRISMA flow-chart is shown in Figure 2.

Baseline Study Characteristics

Two prospective cohort studies[20,21] and 7 retrospective cohort studies[22–28] were included. The baseline characteristics of the included studies and patients are summarized in Supplemental Table 1, http://links.lww.com/AOSO/A252. The primary cancer was located in the colon in 5 studies, in the rectum in 1 study and colorectal in 3 studies. The reported mean or median age of patients ranged from 50 to 71 years. All studies reported sufficient follow-up for our research question.

Seven of 9 studies reported tumor stage using the Dukes classification, which was converted to AJCC/UICC eighth edition for the purpose of the current study.[29] Five studies included TNM stage I CRC patients, 9 included TNM stage II CRC, 5 studies included TNM stage III CRC, and 1 included TNM stage IV CRC. The reported primary outcome was mostly 5-year overall survival, although some studies did not specify outcome range or used cancer-specific survival. Due to heterogeneity, pooling of data was not possible.

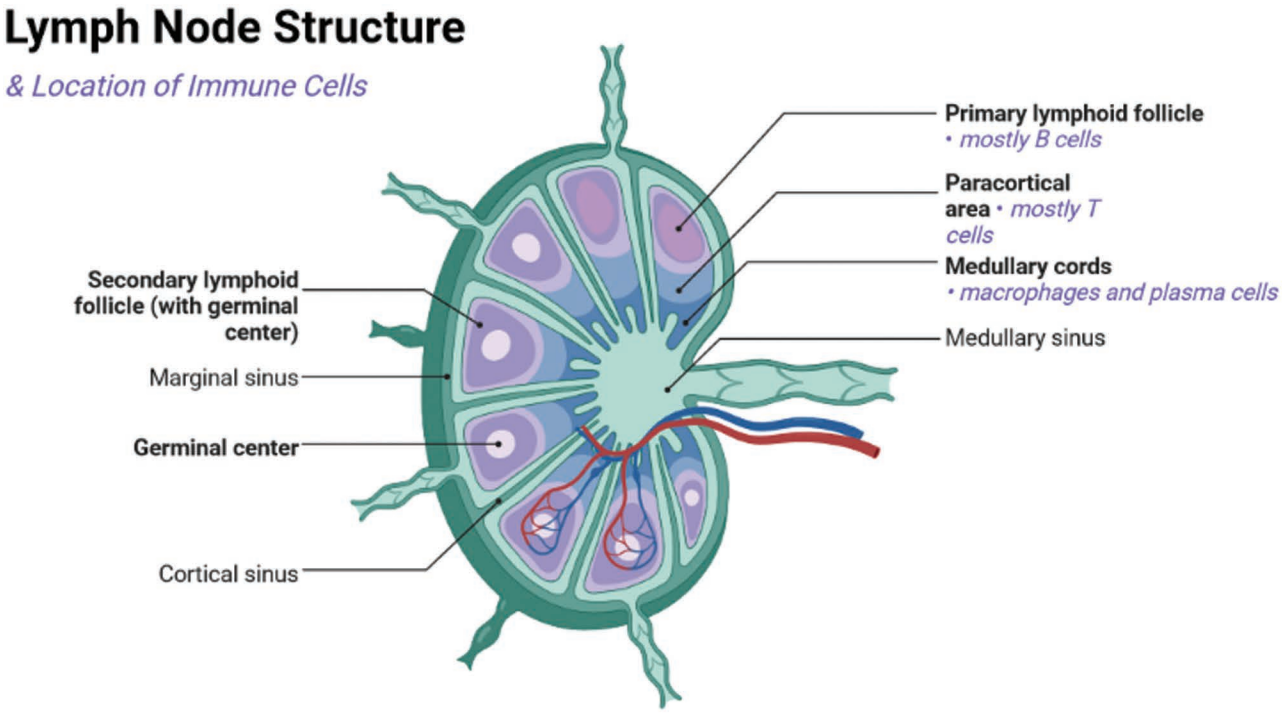

FIGURE 1. Schematic representation of lymph node structure.

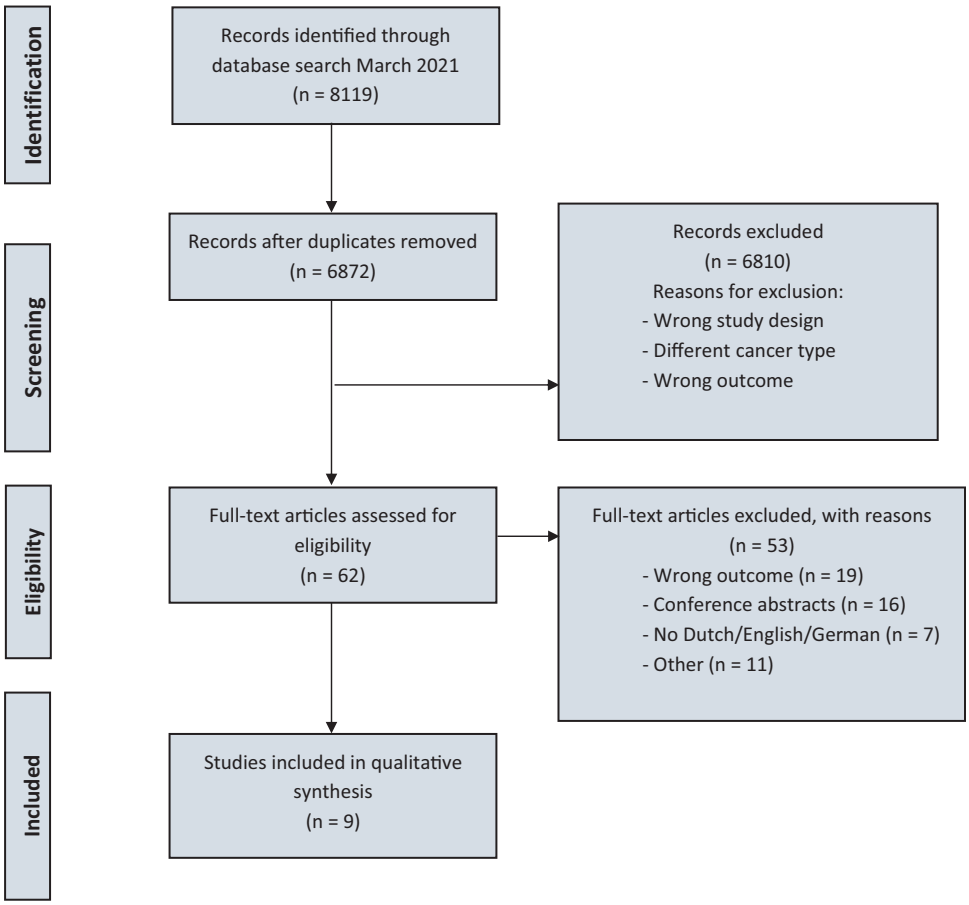

FIGURE 2. Flow diagram of the article selection process.

Sinus Histiocytosis

Three studies[22–24] examined the association between the presence of SH in negative LNs and survival. The studies of Murray et al and Patt et al showed a favorable survival for patients where SH was present in the locoregional LN when all patients were analyzed together irrespective of tumor stage (76.7% vs 58.6%, $P < 0.05$ and 75% vs 50%, $P < 0.05$). However, the study by Pihl et al of stage II CRC patients did not show any association between the presence of SH and survival (Table 1).

Germinal Center Predominance

Five studies[20,23–25,28] examined the relationship between germinal center predominance (GCP) and survival. One study showed that increased GCP was associated with significant longer survival in stage II patients (77% vs 83%, $P = 0.003$)[20] (Table 2). None of the other studies showed a relationship between GCP and survival.

Paracortical Hyperplasia

Fives studies examined the association between paracortical hyperplasia (PH) in negative LNs and survival. Patt et al reported a significant improved survival in stage I to III sigmoid cancer with increased PH (35% vs 74%, $P = <0.05$)[23] (Table 3). Similar findings were reported by Pihl et al for PH in negative LNs and survival in stage II and stage III CRC patients.[20,24] Pihl et al also investigated PH in tumor-involved LN and demonstrated a favorable survival in patients with PH compared with patients without (50% vs 73%, $P = 0.009$).

Lymph Node Size

Four studies investigated the relationship between LN size and survival in CRC patients.[21,24,26,27] LN size was determined by macroscopically measuring the largest diameter of each LN. Two studies divided the patients in 2 groups, those with small LN versus those with large LN based on a self-defined cutoff value. Pihl et al stated that the presence of enlarged negative LN (>4.5 mm) tended to be associated with longer survival in stage II CRC, but this did not reach statistical significance (79% vs 86%, $P = 0.057$).[24] Murphy et al defined LN ≥4 mm as large and showed a significant difference in survival in stage II CRC in favor of patients with large LNneg (73.3% vs 88.0%, $P = 0.0015$).[26]

The 2 remaining studies by Märkl and colleagues,[21,27] investigating colon cancer without LN metastasis used a cutoff value of >5 mm for large LN. In the first study by Märkl et al, patients were classified based on the number of large LNs present. Patients with >7 LNs larger than 5 mm were classified as high (LN5High), and patients with <7 large LNs were classified as low (LN5Low). LN5High patients showed a better survival in comparison with LN5Low patients ($P = 0.024$). This was especially true for patients with higher T category (T1/2 vs T3/4, $P = 0.033$). They also showed a trend toward lower chance of progressive disease in the LN5High group [1 out of 28 (LN5high) vs 17 out of 69 (LN5low); $P = 0.072$).

TABLE 1.

Sinus Histiocytosis and Survival

Study	Stage	Location		Absent SH, n		Survival	Present SH, n (%)		Survival	*P**
		Colon	Rectum	Alive	Dead	%	Alive	Dead	%	
Murray et al[22]	II	63	–	31	14	68.9	17	1	94.4	<0.1
	III	67	–	20	22	47.6	16	9	64.0	>0.2
	II & III	130	–	51	36	58.6	33	10	76.7	<0.05
Patt et al[23]	I	1	–	0	0	0	1	0	100	N.A.
	II	15	–	4	6	40.0	4	5	80.0	N.A.
	III	20	–	5	3	62.5	9	3	75.0	N.A.
	I–III	36	–	9	9	50.0	14	4	75.0	<0.05
Pihl et al[24]	II	71	63	68	23	74.7	32	5	86.5	0.38

*A $P < 0.05$ was considered significant.

N.A. indicates not available; SH, sinus histiocytosis.

TABLE 2.

Germinal Center Predominance and Survival

Study	Stage (n)	Location		Absent GCP*, n		Survival	Present GCP*, n (%)		Survival	*P**
		Colon	Rectum	Alive	Dead	%	Alive	Dead	%	
Tsakraklides et al[28]	I (16)	–	–	–	–	–	14	2	87.5	N.A.***
	II (19)	–	–	–	–	–	16	3	84.2	N.A.
	III (24)	–	–	–	–	–	13	11	54.2	N.A.
	I–III (59)	–	–	–	–	–	42	17	71.2	N.A.
Patt et al[23]	I–III (36)	36	–	–	–	–	–	–	–	n.s.
Pihl et al[24]	II (134)	71	63	21	2	91.3	79	26	75.2	0.21
Pihl et al[20]	I (71)	–	–	32	1	97	31	2	94	0.3
	II (213)	–	–	81	24	77	87	12	83	0.003
	III (163)	–	–	52	21	71	45	19	70	0.4
	IV (72)	–	–	6	24	20	9	21	30	0.09
Nacopulou et al (1981)	I	–	–	–	–	–	12	2	85	N.A.
	II	–	–	–	–	–	28	15	65	N.A.
	III	–	–	–	–	–	2	20	9	N.A.
	I–III	112	42	–	–	–	42	37	53	N.A.

*A $P < 0.05$ was considered significant.

GCP indicates germinal center predominance; N.A., not available.

TABLE 3.

Paracortical Hyperplasia and Survival

Study	Stage (n)	Location		Absent PH, n		Survival	Present PH*, n (%)		Survival	*P**
		Colon	Rectum	Alive	Dead	%	Alive	Dead	%	
Tsakraklides et al[28]	I (9)	–	–	–	–	–	5	3	67	N.A.***
	II (11)	–	–	–	–	–	5	5	55	N.A.
	III (8)	–	–	–	–	–	2	5	44	N.A.
	I–III (28)	33	110	–	–	–	15	13	54	N.A.
Patt et al[23]	I (1)	1	–	0	0	0	1	0	100	N.A.
	II (15)	15	–	2	4	33	7	2	78	N.A.
	III (20)	20	–	4	7	36	6	3	67	N.A.
	I–III (36)	36	–	6	11	35	14	5	74	<0.05
Pihl et al[24]	II (134)	71	63	37	15	71.2	63	13	83	0.04
Pihl et al[20]	I (71)	–	–	31	2	94	32	1	97	0.3
	II (213)	–	–	83	19	81	85	17	83	0.025
	III (163)	–	–	47	24	68	50	16	74	0.047
	IV (72)	–	–	5	28	15	10	17	37	0.09
Nacopoulou et al[25]	I	–	–	–	–	–	9	2	81	N.A.
	II	–	–	–	–	–	13	9	59	N.A.
	III	–	–	–	–	–	4	1	80	N.A.
	I–III	112	42	–	–	–	–	–	–	N.A.

*A $P < 0.05$ was considered significant.

N.A. indicates not available; PH, paracortical hyperplasia.

In the 2016 study, patients were classified as LN5-very low (LN5vl, 0–1 LNs >5 mm), LN5-Low (LN5l, 2–5 LNs >5 mm), or LN5-High (LN5h, >5 LNs >5 mm). Survival analysis of the 3 groups showed a nonsignificant trend toward shorter median overall survival in de LN5vl group compared with both other groups (71 months vs 76 months, $P = 0.230$). The restriction to locally advanced patients (pT3/4) reveals significant survival differences with poor overall survival of the LN5vl group. Median overall survival for LN5vl, LN5l, and LN5h was 40, 57, 71 months, respectively ($P = 0.022$).

Lymph Node Histologic Patterns and Tumor Positive Nodes

Two studies compared LN histomorphological patterns between LNneg and LNpos CRC and their association with 5-year survival.[25,28] Both studies compared the relationship between survival and lymphocyte predominance in de paracortex, GCP, Lymphocyte depletion (LD) in the paracortex, and unstimulated LN. Tsakraklides et al found a more favorable survival in patients with GCP compared with lymphocyte predominance/PH or unstimulated LN (71% vs 54%), but these results were not statistically significant. Nacopoulou et al found that patients with LNs showing lymphocyte predominance/PCP pattern had the best 5-year survival followed by patients with GCP pattern in their LN (68% vs 53%). Patients showing LD or unstimulated LNs had the poorest survival (10% vs 17%, respectively). The difference between histomorphological patterns was statistically significant, $P < 0.05$. When restricting to patients without LN metastasis, the trends for surival became less clear. GCP showed the best overall survival (70%) compared with paracortical predominance (66%), LD (16%), and unstimulated LNs (36%), but this difference was not significant.

Risk of Bias Assessment

A summary of the risk of bias assessment for each included study is shown in Figure 3. Overall, most studies were rated as having low or moderate risk of bias for most items. Possible study confounding appeared to be the most common problem.

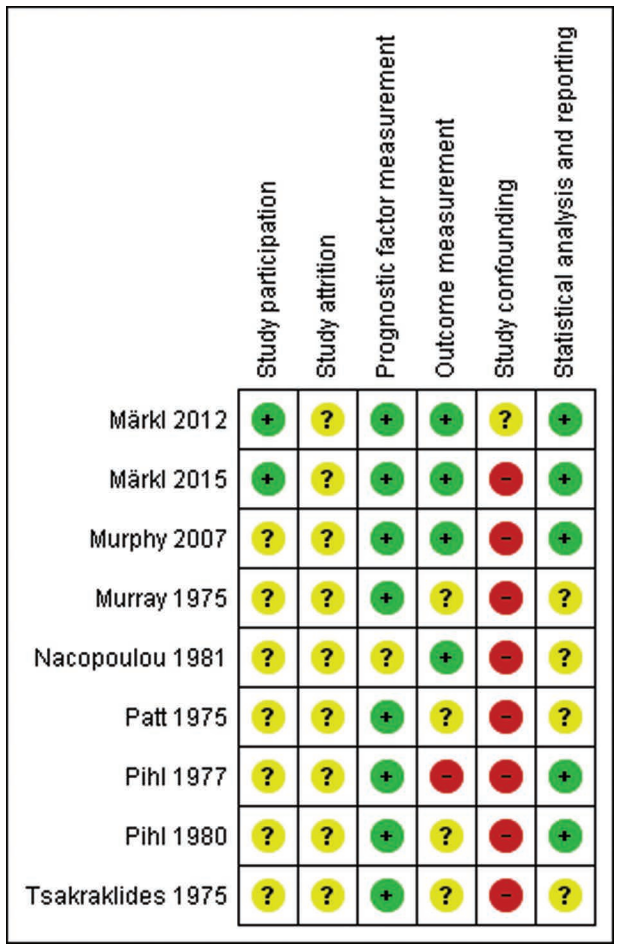

FIGURE 3. Risk of bias assessment using the QUIPS tool. Green, low risk of bias; yellow, moderate risk of bias; red, high risk of bias. QUIPS indicates quality in prognosis.

DISCUSSION

The findings of our review support the hypothesis that changes in LN morphology, for example, paracortical predominance or enlargement of regional LNnegs, might be indicative of an improved survival in stage II colorectal cancer patient. Changes seen in the histomorphology seem to suggest a potential relationship with the host antitumor response.

During the last two decades, no articles were published investigating immunological changes inside LNnegs. However, we were able to identify several old studies suggesting that changes in LN histomorphology may provide a "readout" of the host antitumor response and might provide clinically relevant information. This review shows that an increase in lymphocytes in the paracortex (so called paracortical predominance) seems to be a prognostic feature associated with a better survival.[20,23,24] Matsuno et al reported that tumor antigens can cause immune activation through germinal center hyperplasia, PH, and SH in pancreatic cancer.[30] Based on these results, it can be hypothesized that an increase in lymphocytes in the paracortex could be considered as surrogate for an active immune response of the host against the cancer.[31]

There are various reasons for LNs to grow in size, most common are the presence of LN metastases, immune activation, or the presence of intranodal fat. Immune activation causes enlargement due to hyperplasia of different cellular components in LNs (eg, follicular hyperplasia, PH, and SH).[32] A recent study by Ruisch et al[33] suggested that the size of LNnegs is related to the presence of follicular hyperplasia as well as the presence of intranodal fat in those LNs. In this study, the number of lymphoid follicles seemed to be higher in larger LNnegs. The authors hypothesized that LNneg surface area could be a potential clinical marker for the immunogenicity of the primary tumor and/or successful activation of a host's response to tumor antigens. A study by Okada et al[34] found that the presence high number of natural killer cells in the LNs was associated with a larger diameter of LNnegs and a significantly better survival. Combined, these results seem to support findings reported by Kloft et al in esophageal carcinoma.[16]

The immunogenicity of CRC tumors and the role of tumor-infiltrating lymphocytes (TILs) has seen a rise in interest over the last decades. pMMR tumors responding to ICI showed significant higher levels of T cells with CD8 and programmed death-1 (PD-1) coexpression before treatment, possibly indicating an active host antitumor response. Other studies indicate that certain TILs (CD3+, CD8+, and CD45RO+) play an important role in CRC tumor progression and prognosis.[35–39] In 2005, a study by Pagès et al[40] showed that patients with a high presence of tumor infiltrating and effector T cells (CD45RO+) were less likely to disseminate to regional lymph nodes and to lymphovascular and perineural structures. The Immunoscore (IS) further explores the prognostic value of TILs in CRC. Many studies using the IS showed that CRC patients with a high level of CD3+ and CD8+ had prolonged overall survival, disease-free survival and time to recurrence regardless of microsatellite status.[35,39,41,42] A biopsy-adapted IS could possibly even aid with predicting therapy response in rectal cancer patients.[43,44] Together with our observation, that hyperplasia of the LN paracortex (also known as a T-cell zone) relates to prolonged survival, this underlines that the host antitumor response probably is more than a local response and LNs play an important in the immunological reaction to the tumor.

The NICHE trial is one of the first studies administering neoadjuvant immune checkpoint inhibition (ICI) in nonmetastatic colon cancer and showing impressive responses in 100% (20/20) of dMMR and 27% (4/15) of pMMR patients. Although showing low response numbers in pMMR, an underlying immune activation was visible in the tumor microenvironment suggestive for tumor recognition. A longer duration of treatment can possibly further increase response rates in these pMMR tumors.[45] Another recent study by Cercek et al investigated the use of ICI in the form of PD-1 blockade in dMMR rectal cancer. All 12 patients showed a clinical complete response after 6 months and omitted chemoradiotherapy and surgery.[46] Both these studies show great potential of ICI in especially dMMR CRC. Being able to differentiate between large LNneg and large LN with metastases could aid in the identification of immunoactive pMMR tumors susceptible for pMMR. Future work is required to establish the viability of this concept.

There are several limitations to the current study. First, literature was scarce and several publications were from the 1980s, thus the methodology of these articles can be questionable. Still, valuable information was obtained from these studies. Second, the majority of the included studies were retrospective, single center studies with potential patient selection bias. Third, due to heterogeneous and scarce data and varying cutoff values for LN size, performing a meta-analysis was not possible. Despite these limitations, this systematic review provides the first available assessment of literature on the prognostic value of LNnegs histomorphology in CRC patients.

In summary, literature on the relationship between histomorphological patterns in regional negative lymph nodes and survival of CRC patients is very limited. Nevertheless, the results of this systematic review seem to support the hypothesis that there might be a relation between the host antitumor response reflected in different histomorphological reaction pattern visible in LNnegs, LNneg size, and survival in CRC patients. These findings suggest that it might be clinically useful to differentiate between large LNneg and large LNs with metastases through radiological imaging at diagnosis as large LNneg might indicate a highly immunogenic CRC microenvironment which might be treated differently in the near future. Based on the findings of this literature review, further work appears to be warranted to prospectively relate radiological LN findings to detailed histopathological assessment of LN microarchitecture, which might be achieved through a combination of radiomics and deep learning–based analysis of histological images. This type of study may pave the way to translate the measurable host antitumor reaction into patient-specific treatment decisions ultimately improving personalized care.

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