Colorectal Lymphoma: A Review

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Abstract

Keywords

- ▶ primary colorectal lymphoma
- ▶ extranodal
- ▶ gastrointestinal
- ▶ large bowel

Non-Hodgkin lymphoma (NHL) that primarily involves the colon is rare and should be distinguished from the more common systemic nodal lymphoma. It has unique clinical expectations and management consideration. Different histologic subtypes of NHL involve the colon, which varies in the clinical behavior and likelihood of obtaining durable remissions with treatment. This article will review the current understanding of the different histologic subtypes of primary colorectal lymphoma and propose management algorithms.

Epidemiology

Non-Hodgkin lymphoma (NHL) comprises a large diverse group of malignant neoplasms that are derived from cells of the immune system. The 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms recognizes more than 60 different types of lymphoma.¹ While a majority of NHLs present with adenopathy, primary extranodal lymphomas account for ~10 to 34% of all cases.² Although the gastrointestinal (GI) tract is not commonly considered a lymphoid organ, the gut-associated lymphoid tissues contain the largest number of lymphocytes in the body.

The GI tract is the most common site for extranodal lymphoma and accounts for 30 to 40% of all cases.^{3,4} Primary lymphoma of the colon and rectum is the least common GI location, and accounts for ~10% of GI lymphomas and < 1% of all large bowel malignancies.^{5–14} Distribution of the six most common subtypes of GI lymphoma, based on the two largest GI lymphoma studies, is represented in ▶ **Table 1**.^{12,13} Incidence of colorectal lymphoma is highest between the ages of 50 and 70 years, and is predominantly male, with an approximate ratio of 2:1.^{12,15–18}

Although rare, lymphoma of the colon and rectum presents unique management challenges, stemming primarily from the high risk of radiation to the bowel in contrast to nodal beds elsewhere in the body. Thus, in early-stage disease, definitive local control relies more commonly on surgical resection that is otherwise rarely used for treatment of lymphoma. Given the limited data to guide decisions, the

best approach to the management of localized disease can be challenging, and we suggest a multidisciplinary approach with early involvement of surgical oncology, gastroenterology, radiation oncology, and malignant hematology.

In this article, we review the epidemiology, clinical presentation, diagnosis, pathology, and staging of primary colorectal lymphoma. We outline the evidence and suggest approach to management of several of the most common histologic subtypes of primary colorectal lymphoma.

Risk Factors

Etiology and risk factors, specifically for primary colorectal lymphoma, remain largely unknown. It is reasonable to suspect that established risk factors for NHL will also increase risk for primary colorectal lymphoma. These risk factors include a family history of lymphoma, past radiation or chemotherapy treatment, immunosuppressive medications, organ transplantation, viral infections (e.g., human immunodeficiency virus, hepatitis C virus, human T-cell leukemia virus 1, Epstein–Barr's virus, and hepatitis B virus), and toxic exposures (e.g., agricultural pesticides and Agent Orange).^{19–29} In addition, several medical conditions are associated with an increased risk of NHL, including autoimmune disorders, immunodeficiency disorders, mixed cryoglobulinemia, multicentric Castleman's disease, and obesity.^{30–34} Colitis from inflammatory bowel disease has not been shown to increase risk of lymphoma; immunosuppression with azathioprine or mercaptopurine, however, has been associated with an increased risk of GI lymphoma.^{35,36}

Table 1 Most common GI lymphoma subtypes

Subtype	Proportion
Extranodal marginal zone B cell lymphoma	~45%
Diffuse large B cell lymphoma	~45%
Follicular lymphoma	< 5%
Mantle cell lymphoma	<5%
Burkitt's lymphoma	<5%
T cell lymphoma	<5%

Abbreviation: GI, gastrointestinal.

Clinical Presentation

Presenting symptoms may include weight loss, fevers, night sweats, and lethargy, as well as symptoms of colorectal anatomical compromise, including palpable abdominal mass, occult or apparent GI bleeding, diarrhea, abdominal pain, intussusception, or bowel obstruction.^{7,9,12,35,37,38}

Diagnosis

Primary extranodal NHL should be considered when lymphoma is observed pathologically in an organ with no other clinical evidence of spread from distant lymph nodes or other primary organs. Diagnostic criteria for primary GI lymphoma has varied over the years but was initially established in 1961 by Dawson.^{36,39} It required a dominant bowel lesion with only local lymph node involvement upon laparotomy, no palpable superficial lymphadenopathy on presenting clinical exam, no chest X-ray evidence of lymphadenopathy or mediastinal mass, normal peripheral white blood cell count and differential, and that liver and spleen were free of lymphoma at laparotomy.³⁶ Since then, others have used more liberal criteria that include higher stage disease with an extranodal dominant site after clinical staging is complete.^{2,7,40–44}

Histologic diagnosis is usually obtained upon pathologic examination of endoscopic or surgically resected tissue. Findings on endoscopic examination are varied and include mucosal nodularity, mucosal induration, mucosal ulceration, and mass with or without ulceration.⁴⁵ Follicular lymphoma typically has no erosions or ulcers, and can often be macroscopically observed as papular, polypoid, or flat elevated lesions.⁴⁶ T cell lymphomas are more commonly associated with ulcerative lesions and perforation than B cell lymphomas.³⁹

Imaging with endoscopic ultrasound and computed tomography may demonstrate ulcerative or nodular patterns on imaging.⁴⁷ Double-contrasted barium enema may reveal various findings, including polypoid masses, circumferential infiltrative mass (with or without ulceration), cavitory masses, mucosal nodularity, and fold thickening.⁴⁸ More rarely, focal strictures, aneurysmal dilatation, and ulcerative forms with fistula formation may also be seen. Lymphoma is more likely than adenocarcinoma to show extension into the terminal ileum, have well-defined margins, preservation of fat planes, an absence of invasion into adjacent structures,

and perforation with no desmoplastic reaction.⁴⁸ Ultimately, diagnosis is based on histologic, flow cytometric, and molecular evaluation of an adequate tissue specimen. This may require multiple needle biopsies, partial resection, or complete resection. Fine needle aspiration is usually inadequate to determine the specific lymphoma subtype.

Pathologic Classification

The vast majority of GI lymphomas, including colorectal lymphomas, are NHLs. There are only a few case reports of primary GI Hodgkin lymphoma.^{49,50} Most of the different histologic subtypes of nodal NHL may arise in the GI tract, and various classification systems have been used in the past. Most commonly, classification is based on the updated WHO classification of lymphoid neoplasms, which is based on a combination of clinical, histopathologic, and genetic/molecular characteristics.¹ Determining the specific histologic subtype of NHL of primary GI lymphoma is important, as it represents specific tumor biology, treatment options, and expected outcomes.

The most common WHO subtypes of primary colorectal lymphoma are diffuse large B cell lymphoma (DLBCL), follicular lymphoma, mantle lymphoma, T cell lymphoma, Burkitt's lymphoma, small lymphocytic lymphoma, and mucosa-associated lymphoid tissue (MALT) lymphoma.^{15,51} Most colorectal lymphomas are of B cell origin, with T cell potentially occurring more commonly in Eastern populations.^{45,52–58} As opposed to the stomach, large intestine MALT lymphoma does not appear to be associated with *Helicobacter pylori* (*H. pylori*) infection and has a distinct natural history.¹⁴

Staging

Historically, staging of primary colorectal lymphoma has been based on the Ann Arbor classification system, with modification for extranodal status (→Table 2).^{59,60} The effectiveness of this staging system to capture relevant features of primary extranodal lymphoma has been brought into question, and in 2003, the European Gastrointestinal Lymphoma Study Group proposed a modified TNM staging system aimed at more accurately describing the depth of tumor infiltration, along with extent of nodal spread (→Table 3).⁶¹ This TNM staging system may be more useful when considering treatment strategy in localized extranodal lymphomas that more commonly involve a multimodality approach with curative intent, as compared with advanced nodal NHL. The St. Jude/Murphy system may also be useful in primary colorectal Burkitt's lymphoma.

Management Overview

Different types of NHL have variable responses to chemotherapy, based on proliferation rate. Rapidly proliferating lymphomas, such as DLBCL and Burkitt's lymphoma are usually quite sensitive to multiagent immunochemotherapy, which can be curative, even in advanced-stage disease. In contrast, advanced-stage indolent lymphomas typically

Table 2 Ann Arbor staging for lymphoma

Stage	Description
I	Involvement of a single lymph node region or lymphoid structure
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph regions or structures on both sides of the diaphragm
IV	Involvement of extranodal site(s) beyond that designated E
A	No symptoms
B	Fever (38°C), drenching sweats, weight loss (10% body weight over 6 mo)
E	Involvement of a single, extranodal site contiguous or proximal to known nodal site

respond less robustly, and high-dose chemotherapy usually does not change long-term outcomes.⁶² For both aggressive and indolent lymphomas that are localized/early stage, definitive local therapy with surgery and radiation plus or minus adjuvant immunochemotherapy can establish a long-term cure. This concept of early-stage curability with multimodal therapy applies to colorectal lymphoma as well, regardless of the primary histology or grade involved.

Surgical Management

The role of surgery in the initial management of colorectal lymphoma has been a matter of historical debate. Patients with colonic lymphoma do not uncommonly present with acute surgical indications, including bleeding, obstruction, or

perforation, necessitating upfront surgical resection.⁵¹ A first paradigm in surgical intervention for local disease has been advocated for with the argument that it may, in larger lesions, decrease rates of perforation and bleeding that can be seen when chemotherapy is initially used. It may also increase long-term remission rates over chemotherapy alone.⁶³

In a large retrospective analysis that included 345 patients with intestinal DLBCL, patients with limited-stage I/II disease and surgery plus chemotherapy demonstrated a lower recurrence rate of 15.3%, when compared with chemotherapy alone, at 36.8%, with an improved 3-year overall survival (OS) rate of 91%, compared with 62% with chemotherapy alone.⁶⁴ In addition, a prospective nonrandomized trial that included 40 patients with stage I/II GI DLBCL (44% large bowel) who received primary surgical resection followed by cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy demonstrated favorable outcomes with a 5-year disease-free survival rate of 83%.⁶⁵ Unfortunately, there are no randomized comparative studies between the two approaches to better determine the optimal treatment approach.

Diffuse Large B Cell Lymphoma

DLBCL is the most common nodal lymphoma histology found in colonic lymphoma. High (>80%) long-term remission rates can be obtained in nonbulky (< 7.5 cm), limited-stage, nodal DLBCL treated with either abbreviated (three cycles) or full (six cycles)-course systemic, multiagent immunochemotherapy with rituximab-CHOP (R-CHOP) plus or minus involved-site radiation therapy (RT).^{66–69}

In contrast to nodal lymphoma, treatment of localized colorectal DLBCL includes consideration for surgical resection, due to risk of both acute and chronic radiotherapy-induced gut toxicity. The efficacy of surgical resection followed by chemotherapy has

Table 3 Paris staging system for primary GI lymphoma

Tumor		Node		Metastasis		Bone marrow	
Tx	Extent not specified	Nx	Not assessed	Mx	Not assessed	Bx	Not assessed
T0	No lymphoma	N0	No involvement	M0	No extranodal dissemination	B0	No involvement
T1	Confined to the submucosa	N1	Involvement of regional LN	M1	Noncontinuous involvement of separate site in GI tract	B1	Involvement with lymphoma
T1m	Confined to the mucosa	N2	Involvement of intra-abdominal LN beyond the regional area	M2	Noncontinuous involvement of other tissues or organs		
T1sm	Confined to the submucosa	N3	Spread to extra-abdominal LN				
T2	Infiltrates muscularis propria or subserosa						
T3	Penetrates serosa without invasion of adjacent structures						
T4	Invades adjacent structures or organs						

Abbreviation: GI, gastrointestinal.

Fig. 1 Treatment algorithm for primary colorectal diffuse large B cell lymphoma. Management of diffuse large B cell lymphoma involves treatment with an R-CHOP-like regimen. Surgery for limited-stage disease allows less chemotherapy use, thus reducing chemotherapy-related toxicities.

been assessed in several retrospective and one prospective analysis with high (>80%) 3-year disease-free survival rates, and was superior to immunochemotherapy alone.^{64,65,70,71}

For unresectable DLBCL of the colon or rectum, treatment with a full six cycles of an R-CHOP-like regimen is generally used. In nodal lymphoma, radiation is considered for incomplete positron emission tomography (PET) response after completion of upfront systemic chemotherapy for bulky disease. Adjuvant/consolidative involved field or involved site RT can be considered in primary colorectal lymphoma; risks associated with bowel radiation, however, often preclude treatment (►Fig. 1).⁷²

Follicular Lymphoma

Follicular lymphoma is one of the more common primary colorectal lymphoma subtypes. In nodal follicular lymphoma, patients with localized low-grade (grades 1–3a) disease are candidates for curative mono- or multimodality therapy, as opposed to advanced disease which is considered incurable, and is generally managed with palliative systemic therapy plus or minus RT. Patients with grade 3b follicular lymphoma are treated as aggressive lymphoma and are generally considered curable.^{73,74} Comprehensive staging with PET scan and bone marrow biopsy should be obtained to assess for more advanced disease, as this would dramatically change management from aggressive upfront local therapy with surgery or radiation plus or minus chemoimmunotherapy to a palliative-only approach, which often only managed with upfront observation.

Long-term disease-free survival can be obtained in primary colorectal follicular lymphoma with aggressive upfront local therapy.⁷⁵ Given the complexities of assessing risk and feasibility of upfront colorectal radiation or surgery, we suggest multidisciplinary evaluation of all patients with early-stage primary colorectal follicular lymphoma. Large bowel radiation

Fig. 2 Treatment algorithm for primary colorectal follicular lymphoma. Management of localized early-stage disease would include resection or radiation. Advanced-stage disease is best managed with immunochemotherapy.

sensitivity and risk of long-term complications from RT makes surgical resection an attractive upfront treatment of choice. Adjuvant immunochemotherapy in the treatment of primary colorectal follicular lymphoma is of unclear additional benefit. There are single case reports and series that report long-term disease-free survival with surgery with or without adjuvant chemoimmunotherapy.⁷⁵ Adjuvant immunochemotherapy will reduce any postsurgical residual disease, but it is unlikely to completely eliminate it. If there are negative margins upon surgical resection, we suggest clinical monitoring only. If there is residual disease after resection, local RT can be considered in an attempt to establish cure; given the indolent nature of most follicular lymphoma, however, observation would also often be appropriate (►Fig. 2). Initial treatment with immunochemotherapy can result in good disease control and long periods of asymptomatic disease, and would be a reasonable treatment option for patients who have contraindication for surgery or radiation, or where disease control is an appropriate treatment goal.

Colorectal Mantle Lymphoma

Limited-stage mantle cell lymphoma (MCL) is rare, and the optimal treatment algorithm is not clear. In one retrospective analysis that included 26 patients with stages IA to IIA nodal disease, 65% of patients were managed with involved field radiation with or without chemotherapy. The other 35% were treated with observation alone. The 5-year progression-free survival (PFS) was 65% in the intervention group, and 46% in the observation group, and OS was 86 and 70%, respectively.⁷⁶ PFS was statistically and significantly improved when RT was included, compared with not, with a trend toward improved OS.

Fig. 3 Treatment algorithm for primary colorectal mantle cell lymphoma. Aggressive treatment of mantle cell lymphoma involves use of a cytarabine-based multiagent immunochemotherapy regimen. Surgical resection of early-stage disease may improve clinical outcomes and reduce the need for an extended immunochemotherapy treatment course.

In a more recent and larger retrospective study that included 2,539 patients with stages I to II MCL, estimated 3-year OS for patients receiving chemotherapy, RT, or chemotherapy plus RT were 67.8, 72.4, and 79.8%, respectively, which was statistically significant, and appeared to support the idea that combined therapy may improve survival.⁷⁷

Extrapolating these data from patients with early-stage nodal MCL to patients with primary colorectal MCL, we again confront the issue of both short- and long-term toxicities of bowel irradiation. If limited-stage disease involves an area of the colon that cannot be safely irradiated, we suggest upfront surgical resection, with adjuvant RT plus or minus chemoimmunotherapy, depending on surgical margins (→ Fig. 3).

Mucosa-Associated Lymphoid Tissue

GI MALT lymphoma most commonly occurs in the stomach and small intestine but can occur in the colon and rectum (< 1% of cases).^{78,79} Common clinical presentations include rectal bleeding, iron deficiency, and incidental discovery on screening endoscopy. Endoscopically, large bowel MALT lymphomas can have a variety of appearances, but are usually elevated polypoid or submucosal tumor-like lesions that rarely have ulceration, as opposed to gastric MALT, which more frequently shows ulceration.

Helicobacter pylori infection is less common in rectal MALT lymphoma, occurring in only the minority of cases, when compared with gastric MALT lymphoma, where it contributes to 90% of cases. In addition, eradication of *H. pylori* does not have the clear efficacy in rectal MALT lymphoma that it does in the stomach. In one study, antimicrobial irradiation showed a response in only 1 out of 15 cases.^{80,81}

Pathology of colorectal MALT lymphoma is characterized by infiltration of centrocyte-like cells with immunohistochemistry, demonstrating expression of CD19, CD20, and CD79 without expression of CD5, CD10, CD23, and cyclin D1.⁸²

There is a paucity of data on ideal management of colorectal MALT lymphoma. There are case reports describing successful treatment of colorectal lymphoma with radiation only, surgical resection, or endoscopic mucosal resection.^{80,83–85}

Management of localized lesions depends on depths and size of lesion. Small, shallow lesions may be amenable to endoscopic submucosal resection. Deeper and larger lesions typically require surgery and/or RT. Adjuvant systemic chemoimmunotherapy can be considered if the setting or positive margins are not amenable to RT.

Disseminated MALT lymphoma is treated primarily with chemotherapy. Successful use of a variety of regimens, including alkylators, purine analogs, and anthracyclines has been demonstrated.⁸⁶

Summary/Conclusion

Colorectal lymphoma is rare and pathologically heterogeneous. Both high-grade and low-grade lymphomas can occur with NHL subtypes of DLBCL, follicular, mantle, with MALT lymphomas being the most common. Appropriate staging with PET/CT scan and bone marrow biopsy is critical to assure accurate stage and confirm localized disease. For all subtypes that present with localized disease, a multidisciplinary approach should be undertaken, as surgical resection and RT with or without systemic chemoimmunotherapy may be appropriate, and result in long-term disease-free survival. This stands in contrast to advance NHL, which is primarily treated with systemic chemoimmunotherapy.

References

- 1 Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016;127(20):2375–2390
- 2 Krol AD, le Cessie S, Snijder S, Kluin-Nelemans JC, Kluin PM, Noordijk EM. Primary extranodal non-Hodgkin's lymphoma (NHL): the impact of alternative definitions tested in the Comprehensive Cancer Centre West population-based NHL registry. *Ann Oncol* 2003;14(01):131–139
- 3 Herrmann R, Panahon AM, Barcos MP, Walsh D, Stutzman L. Gastrointestinal involvement in non-Hodgkin's lymphoma. *Cancer* 1980;46(01):215–222
- 4 d'Amore F, Brincker H, Grønbaek K, et al; Danish Lymphoma Study Group. Non-Hodgkin's lymphoma of the gastrointestinal tract: a population-based analysis of incidence, geographic distribution, clinicopathologic presentation features, and prognosis. *J Clin Oncol* 1994;12(08):1673–1684
- 5 Blackledge G, Bush H, Dodge OG, Crowther D. A study of gastrointestinal lymphoma. *Clin Oncol* 1979;5(03):209–219
- 6 Contreary K, Nance FC, Becker WF. Primary lymphoma of the gastrointestinal tract. *Ann Surg* 1980;191(05):593–598
- 7 Lewin KJ, Ranchod M, Dorfman RF. Lymphomas of the gastrointestinal tract: a study of 117 cases presenting with gastrointestinal disease. *Cancer* 1978;42(02):693–707
- 8 Dragosics B, Bauer P, Radaszkiewicz T. Primary gastrointestinal non-Hodgkin's lymphomas. A retrospective clinicopathologic study of 150 cases. *Cancer* 1985;55(05):1060–1073

- 9 Henry CA, Berry RE. Primary lymphoma of the large intestine. *Am Surg* 1988;54(05):262–266
- 10 Jinnai D, Iwasa Z, Watanuki T. Malignant lymphoma of the large intestine—operative results in Japan. *Jpn J Surg* 1983;13(04):331–336
- 11 Kashimura A, Murakami T. Malignant lymphoma of large intestine –15-year experience and review of literature. *Gastroenterol Jpn* 1976;11(02):141–147
- 12 Koch P, del Valle F, Berdel WE, et al; German Multicenter Study Group. Primary gastrointestinal non-Hodgkin's lymphoma: I. Anatomic and histologic distribution, clinical features, and survival data of 371 patients registered in the German Multicenter Study GIT NHL 01/92. *J Clin Oncol* 2001;19(18):3861–3873
- 13 Papaxoinis G, Papageorgiou S, Rontogianni D, et al. Primary gastrointestinal non-Hodgkin's lymphoma: a clinicopathologic study of 128 cases in Greece. A Hellenic Cooperative Oncology Group study (HeCOG). *Leuk Lymphoma* 2006;47(10):2140–2146
- 14 Zighelboim J, Larson MV. Primary colonic lymphoma. Clinical presentation, histopathologic features, and outcome with combination chemotherapy. *J Clin Gastroenterol* 1994;18(04):291–297
- 15 Bairey O, Ruchlemer R, Shpilberg O. Non-Hodgkin's lymphomas of the colon. *Isr Med Assoc J* 2006;8(12):832–835
- 16 Stanojević GZ, Stojanović MP, Stojanović MM, et al. Non-Hodgkin's lymphomas of the large bowel—clinical characteristics, prognostic factors and survival. *Acta Chir Jugosl* 2008;55(03):109–114
- 17 Fan CW, Changchien CR, Wang JY, et al. Primary colorectal lymphoma. *Dis Colon Rectum* 2000;43(09):1277–1282
- 18 Cho MJ, Ha CS, Allen PK, Fuller LM, Cabanillas F, Cox JD. Primary non-Hodgkin lymphoma of the large bowel. *Radiology* 1997;205(02):535–539
- 19 Goldin LR, Björkholm M, Kristinsson SY, Turesson I, Landgren O. Highly increased familial risks for specific lymphoma subtypes. *Br J Haematol* 2009;146(01):91–94
- 20 Clarke CA, Morton LM, Lynch C, et al. Risk of lymphoma subtypes after solid organ transplantation in the United States. *Br J Cancer* 2013;109(01):280–288
- 21 Chiu BC, Dave BJ, Blair A, Gapstur SM, Zahm SH, Weisenburger DD. Agricultural pesticide use and risk of t(14;18)-defined subtypes of non-Hodgkin lymphoma. *Blood* 2006;108(04):1363–1369
- 22 Brennan P, Scélo G, Hemminki K, et al. Second primary cancers among 109 000 cases of non-Hodgkin's lymphoma. *Br J Cancer* 2005;93(01):159–166
- 23 Kandiel A, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005;54(08):1121–1125
- 24 Frumkin H. Agent Orange and cancer: an overview for clinicians. *CA Cancer J Clin* 2003;53(04):245–255
- 25 Ulickas Yood M, Quesenberry CP Jr, Guo D, et al. Incidence of non-Hodgkin's lymphoma among individuals with chronic hepatitis B virus infection. *Hepatology* 2007;46(01):107–112
- 26 Kaplan LD. HIV-associated lymphoma. *Best Pract Res Clin Haematol* 2012;25(01):101–117
- 27 Marcucci F, Mele A. Hepatitis viruses and non-Hodgkin lymphoma: epidemiology, mechanisms of tumorigenesis, and therapeutic opportunities. *Blood* 2011;117(06):1792–1798
- 28 Smith MR, Greene WC. Molecular biology of the type I human T-cell leukemia virus (HTLV-I) and adult T-cell leukemia. *J Clin Invest* 1991;87(03):761–766
- 29 Thorley-Lawson DA, Gross A. Persistence of the Epstein-Barr virus and the origins of associated lymphomas. *N Engl J Med* 2004;350(13):1328–1337
- 30 Ekström Smedby K, Vajdic CM, Falster M, et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. *Blood* 2008;111(08):4029–4038
- 31 Larsson SC, Wolk A. Body mass index and risk of non-Hodgkin's and Hodgkin's lymphoma: a meta-analysis of prospective studies. *Eur J Cancer* 2011;47(16):2422–2430
- 32 Saadoun D, Sellam J, Ghillani-Dalbin P, Crecel R, Piette JC, Cacoub P. Increased risks of lymphoma and death among patients with non-hepatitis C virus-related mixed cryoglobulinemia. *Arch Intern Med* 2006;166(19):2101–2108
- 33 Shapiro RS. Malignancies in the setting of primary immunodeficiency: Implications for hematologists/oncologists. *Am J Hematol* 2011;86(01):48–55
- 34 Larroche C, Cacoub P, Soulier J, et al. Castleman's disease and lymphoma: report of eight cases in HIV-negative patients and literature review. *Am J Hematol* 2002;69(02):119–126
- 35 Avilés A, Neri N, Huerta-Guzmán J. Large bowel lymphoma: an analysis of prognostic factors and therapy in 53 patients. *J Surg Oncol* 2002;80(02):111–115
- 36 Dawson IM, Cornes JS, Morson BC. Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. *Br J Surg* 1961;49:80–89
- 37 Glick DD, Soule EH. Primary malignant lymphoma of colon or appendix. Report of 27 cases. *Arch Surg* 1966;92(01):144–151
- 38 Perry PM, Cross RM, Morson BC. Primary malignant lymphoma of the rectum (22 cases). *Proc R Soc Med* 1972;65(01):72
- 39 Yu H, Wang Y, Peng L, Lia A, Zhang Y. Endoscopic manifestations of primary colorectal lymphoma. *Hepatogastroenterology* 2014;61(129):76–78
- 40 Zucca E, Roggero E, Berton F, Conconi A, Cavalli F. Primary extranodal non-Hodgkin's lymphomas. Part 2: head and neck, central nervous system and other less common sites. *Ann Oncol* 1999;10(09):1023–1033
- 41 Zucca E, Roggero E, Berton F, Cavalli F. Primary extranodal non-Hodgkin's lymphomas. Part 1: gastrointestinal, cutaneous and genitourinary lymphomas. *Ann Oncol* 1997;8(08):727–737
- 42 Economopoulos T, Asprou N, Stathakis N, et al. Primary extranodal non-Hodgkin's lymphoma in adults: clinicopathological and survival characteristics. *Leuk Lymphoma* 1996;21(1-2):131–136
- 43 Otter R, Gerrits WB, vd Sandt MM, Hermans J, Willemze R. Primary extranodal and nodal non-Hodgkin's lymphoma. A survey of a population-based registry. *Eur J Cancer Clin Oncol* 1989;25(08):1203–1210
- 44 d'Amore F, Christensen BE, Brincker H, et al; Danish LYFO Study Group. Clinicopathological features and prognostic factors in extranodal non-Hodgkin lymphomas. *Eur J Cancer* 1991;27(10):1201–1208
- 45 Myung SJ, Joo KR, Yang SK, et al. Clinicopathologic features of ileocolonic malignant lymphoma: analysis according to colonoscopic classification. *Gastrointest Endosc* 2003;57(03):343–347
- 46 Iwamuro M, Okada H, Takata K, et al. Colorectal manifestation of follicular lymphoma. *Intern Med* 2016;55(01):1–8
- 47 Mendelson RM, Fermoye S. Primary gastrointestinal lymphomas: a radiological-pathological review. Part 1: stomach, oesophagus and colon. *Australas Radiol* 2005;49(05):353–364
- 48 Ghai S, Pattison J, Ghai S, O'Malley ME, Khalili K, Stephens M. Primary gastrointestinal lymphoma: spectrum of imaging findings with pathologic correlation. *Radiographics* 2007;27(05):1371–1388
- 49 Devaney K, Jaffe ES. The surgical pathology of gastrointestinal Hodgkin's disease. *Am J Clin Pathol* 1991;95(06):794–801
- 50 Palli D, Trallori G, Bagnoli S, et al. Hodgkin's disease risk is increased in patients with ulcerative colitis. *Gastroenterology* 2000;119(03):647–653
- 51 Cai S, Cannizzo F Jr, Bullard Dunn KM, Gibbs JF, Czuczman M, Rajput A. The role of surgical intervention in non-Hodgkin's lymphoma of the colon and rectum. *Am J Surg* 2007;193(03):409–412, discussion 412
- 52 Kim YH, Lee JH, Yang SK, et al. Primary colon lymphoma in Korea: a KASID (Korean Association for the Study of Intestinal Diseases) Study. *Dig Dis Sci* 2005;50(12):2243–2247
- 53 Shepherd NA, Hall PA, Coates PJ, Levison DA. Primary malignant lymphoma of the colon and rectum. A histopathological and immunohistochemical analysis of 45 cases with clinicopathological correlations. *Histopathology* 1988;12(03):235–252

- 54 Doolabh N, Anthony T, Simmang C, et al. Primary colonic lymphoma. *J Surg Oncol* 2000;74(04):257–262
- 55 Hwang WS, Yao JC, Cheng SS, Tseng HH. Primary colorectal lymphoma in Taiwan. *Cancer* 1992;70(03):575–580
- 56 Son HJ, Rhee PL, Kim JJ, et al. Primary T-cell lymphoma of the colon. *Korean J Intern Med* 1997;12(02):238–241
- 57 Lee HJ, Han JK, Kim TK, Kim YH, Kim KW, Choi BI. Peripheral T-cell lymphoma of the colon: double-contrast barium enema examination findings in six patients. *Radiology* 2001;218(03):751–756
- 58 Wang MH, Wong JM, Lien HC, Lin CW, Wang CY. Colonoscopic manifestations of primary colorectal lymphoma. *Endoscopy* 2001;33(07):605–609
- 59 Rosenberg SA. Validity of the Ann Arbor staging classification for the non-Hodgkin's lymphomas. *Cancer Treat Rep* 1977;61(06):1023–1027
- 60 Moormeier JA, Williams SF, Golomb HM. The staging of non-Hodgkin's lymphomas. *Semin Oncol* 1990;17(01):43–50
- 61 Ruskoné-Fourmestreaux A, Dragosics B, Morgner A, Wotherspoon A, De Jong D. Paris staging system for primary gastrointestinal lymphomas. *Gut* 2003;52(06):912–913
- 62 Dana BW, Dahlberg S, Nathwani BN, et al. Long-term follow-up of patients with low-grade malignant lymphomas treated with doxorubicin-based chemotherapy or chemoimmunotherapy. *J Clin Oncol* 1993;11(04):644–651
- 63 Vaidya R, Habermann TM, Donohue JH, et al. Bowel perforation in intestinal lymphoma: incidence and clinical features. *Ann Oncol* 2013;24(09):2439–2443
- 64 Kim SJ, Kang HJ, Kim JS, et al. Comparison of treatment strategies for patients with intestinal diffuse large B-cell lymphoma: surgical resection followed by chemotherapy versus chemotherapy alone. *Blood* 2011;117(06):1958–1965
- 65 Lee J, Kim WS, Kim K, et al. Prospective clinical study of surgical resection followed by CHOP in localized intestinal diffuse large B cell lymphoma. *Leuk Res* 2007;31(03):359–364
- 66 Phan J, Mazloom A, Medeiros LJ, et al. Benefit of consolidative radiation therapy in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy. *J Clin Oncol* 2010;28(27):4170–4176
- 67 Hong J, Kim AJ, Park JS, et al. Additional rituximab-CHOP (R-CHOP) versus involved-field radiotherapy after a brief course of R-CHOP in limited, non-bulky diffuse large B-cell lymphoma: a retrospective analysis. *Korean J Hematol* 2010;45(04):253–259
- 68 Persky DO, Unger JM, Spier CM, et al; Southwest Oncology Group. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group study 0014. *J Clin Oncol* 2008;26(14):2258–2263
- 69 Reyes F, Lepage E, Ganem G, et al; Groupe d'Etude des Lymphomes de l'Adulte (GELA). ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. *N Engl J Med* 2005;352(12):1197–1205
- 70 Bellesi G, Alterini R, Messori A, et al. Combined surgery and chemotherapy for the treatment of primary gastrointestinal intermediate- or high-grade non-Hodgkin's lymphomas. *Br J Cancer* 1989;60(02):244–248
- 71 Koh PK, Horsman JM, Radstone CR, Hancock H, Goepel JR, Hancock BW. Localised extranodal non-Hodgkin's lymphoma of the gastrointestinal tract: Sheffield Lymphoma Group experience (1989–1998). *Int J Oncol* 2001;18(04):743–748
- 72 Pfreundschuh M, Trümper L, Osterborg A, et al; MabThera International Trial Group. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol* 2006;7(05):379–391
- 73 Guadagnolo BA, Li S, Neuberg D, et al. Long-term outcome and mortality trends in early-stage, Grade 1–2 follicular lymphoma treated with radiation therapy. *Int J Radiat Oncol Biol Phys* 2006;64(03):928–934
- 74 Seymour JF, Pro B, Fuller LM, et al. Long-term follow-up of a prospective study of combined modality therapy for stage I–II indolent non-Hodgkin's lymphoma. *J Clin Oncol* 2003;21(11):2115–2122
- 75 Shia J, Teruya-Feldstein J, Pan D, et al. Primary follicular lymphoma of the gastrointestinal tract: a clinical and pathologic study of 26 cases. *Am J Surg Pathol* 2002;26(02):216–224
- 76 Leitch HA, Gascoyne RD, Chhanabhai M, Voss NJ, Klasa R, Connors JM. Limited-stage mantle-cell lymphoma. *Ann Oncol* 2003;14(10):1555–1561
- 77 Gill BS, Vargo JA, Pai SS, Balasubramani GK, Beriwal S. Management trends and outcomes for stage I to II mantle cell lymphoma using the National Cancer Data Base: ascertaining the ideal treatment paradigm. *Int J Radiat Oncol Biol Phys* 2015;93(03):668–676
- 78 Takenaka R, Tomoda J, Sakata T, et al. Mucosa-associated lymphoid tissue lymphoma of the rectum that regressed spontaneously. *J Gastroenterol Hepatol* 2000;15(03):331–335
- 79 Tsang RW, Gospodarowicz MK, Pintilie M, et al. Stage I and II MALT lymphoma: results of treatment with radiotherapy. *Int J Radiat Oncol Biol Phys* 2001;50(05):1258–1264
- 80 Kobayashi T, Takahashi N, Hagiwara Y, et al. Successful radiotherapy in a patient with primary rectal mucosa-associated lymphoid tissue lymphoma without the API2-MALT1 fusion gene: a case report and review of the literature. *Leuk Res* 2008;32(01):173–175
- 81 Kiesewetter B, Raderer M. Antibiotic therapy in nongastrointestinal MALT lymphoma: a review of the literature. *Blood* 2013;122(08):1350–1357
- 82 Akasaka R, Chiba T, Dutta AK, et al. Colonic mucosa-associated lymphoid tissue lymphoma. *Case Rep Gastroenterol* 2012;6(02):569–575
- 83 Tanaka S, Ohta T, Kaji E, Kosaka T, Murakami I. EMR of mucosa-associated lymphoid tissue lymphoma of the rectum. *Gastrointest Endosc* 2003;57(07):956–959
- 84 Orita M, Yamashita K, Okino M, et al. A case of MALT (mucosa-associated lymphoid tissue) lymphoma occurring in the rectum. *Hepatogastroenterology* 1999;46(28):2352–2354
- 85 Okamura T, Suga T, Iwaya Y, et al. *Helicobacter pylori*-negative primary rectal MALT lymphoma: complete remission after radiotherapy. *Case Rep Gastroenterol* 2012;6(02):319–327
- 86 Kiesewetter B, Ferreri AJ, Raderer M. Chemoimmunotherapy for mucosa-associated lymphoid tissue-type lymphoma: a review of the literature. *Oncologist* 2015;20(08):915–925