Exploring The Prognostic Significance of Lymphoma in Colon and Rectum, National Cancer Institute Experience, Egypt

Mohamed Atef ElKordy[1]*, Anthony Nozhy Abd ElMesseh[1], Ahmed Hussein ElGammal[2], Rasha Mahmoud Allam[3], Mohammed Fouad Taher[1]

Surgical Oncology Department[1], Pediatric Oncology Department[2], Statistics Department[3], National Cancer Institute, Cairo University, Egypt

Corresponding author: Mohamed Atef ElKordy, **Telephone:** 002-01554090340, **Email:** malkordy2001@gmail.com

ABSTRACT

Background: Colorectal cancer is one of the commonest types of malignancies. Lymphoma is a rare occurrence in this population, with adenocarcinoma constituting the majority of cases. Few publications have analysed the clinico-pathological behaviour of colorectal lymphoma (CL). Both the effect of systemic therapy in these cases and the significance of surgical resection of these tumours remain unclear. **Objective:** The aim of the current study is to address CL from the perspectives of demographic, clinical characteristics, diagnosis and treatment, as well as studying prognosis. **Patients and methods:** The current retrospective cohort study included all cases diagnosed with CL and managed at the National Cancer Institute, Cairo University, during the period from 2010 to 2021. The data included demographic, clinical presentation, investigation used and their results, treatment modalities used, and prognosis.

Results: Throughout the duration of the study, 49 patients were diagnosed with CL and treated in the National Cancer Institute. Patients' ages ranged between 2 and 70 years, with a median of 5 years. Burkitt lymphoma was the most common type (71%). Most of the cases (63.3%) were aroused in ascending colon. Early stages (Stages I and II) accounted for 81.6% of the cases. Before chemotherapy, 32 cases (65.3%) underwent surgical resection. The absence of B symptoms, Hg ≥10 gm/dl, and surgically treated cases were associated with a favourable prognosis.

Conclusion: The incidence of lymphoma affecting the colon and rectum is uncommon. Patients' ages upon presentation vary, and it typically originates in the right colon. In combination with systemic therapy, surgical excision of the tumour appears to improve survival in the early stages.

Keywords: Colorectal, Lymphoma, Solid organs, Haematological malignancy, Retrospective study, Cairo University.

INTRODUCTION

Colorectal cancer is the third most common cancer in the world. The WHO reported about 1.93 million new cases in 2020 [(1)]. Most of these cases were adenocarcinoma, while lymphoma accounts for about 0.2-1% of malignancies that affected the colon and rectum. Extranodal lymphoma, defined as lymphomas that originated or infiltrated solid organs [(2)], occurs in approximately one-third of cases with Non-Hodgkin Lymphoma (NHL) [(3)]. Even though GIT is the commonest site of extranodal lymphoma, the colon and rectum are rarely affected compared to the stomach and small bowel [(4)], representing only 10-20% of GIT lymphomas [(5-7)]. In literature, the cecum and ascending colon represent the most common sites of CLs, accounting for 67-87% of CLs [(2)].

Due to the rarity of cases, a few published articles discussed the demographic and clinicopathological characteristics of CL. This study aimed to address CL at National Cancer Institute, Cairo University from the following perspectives: demographic, clinical characteristics, diagnosis and treatment, as well as determining the effects of systemic therapy and the role of surgical resection of the tumour in these cases.

PATIENTS AND METHODS

The current retrospective cohort study included all cases of CL presented and managed at the National Cancer Institute (NCI), Cairo University in the period 2010-2021. These cases were diagnosed through either colonoscopic biopsies from the colorectal lesion or definitive specimen pathology for cases that underwent resection. The patients' data were retrieved from archived medical records obtained from the Cancer Epidemiology and Biostatistics Department of NCI, Cairo University. The data included demographic (age, gender), clinical presentation, investigation used and their results, treatment modalities used, and prognosis of these cases in terms of overall survival.

Ethical approval: This study was approved by Institutional Review Board (IRB) of National Cancer Institute, Cairo University, with approval No: 2211-510-023. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

IBM SPSS® Statistics version 26 was used for the statistical analysis. The median and range were used to express numerical data. Frequency and percentage were used to express qualitative data. A Kaplan-Meier survival analysis was performed, and a log-rank test was used to compare two survival curves. To assess independent prognostic factors influencing survival, Cox regression analysis was used. All tests were two-tailed. P value ≤ 0.05 was considered significant.

RESULTS

During the study period, 49 patients were diagnosed with CL and treated at the NCI. The number of male patients outperformed females, accounting for 61% of cases. Patients' ages ranged between 2-70 years, with a median of 5 years. Patients' characteristics are illustrated in **Table 1.**

Received: 20/11/2022
Accepted: 15/01/2023

Table 1: Patients' characteristics and presentation.

Variable	Frequency (N)	Percent (%)
Gender		
Male	30	61.2 %
Female	19	38.8 %
Age (Year)		
≤18	34	69.4 %
>18	15	30.6 %
Presenting symptom		
Abdominal pain	20	40.8 %
Constipation	10	20.4 %
Diarrhea	2	4.1 %
Bleeding per rectum	8	16.3 %
Vomiting	3	6.1 %
Abdominal Mass	1	2 %
Abdominal distension	5	10.2 %
B symptoms		
Yes	7	14.3 %
No	42	85.7 %

Burkitt Lymphoma is the most common type (71.4%). Most cases were presented in the early stages, as stages I and II represented 81.6% of the cases. Tumours' characteristics are depicted in **Table 2**.

Table 2: Tumours' sites and characteristics:

	Variable	Frequency (N)	Percent (%)
Pathology	Burkitt lymphoma	35	71.40%
	Large B cell lymphoma	12	24.50%
	MALT	2	4.10%
Stage	I	28	57.10%
	II	12	24.50%
	III	7	14.30%
	IV	2	4.10%
Colorectal site	Ascending colon	31	63.30%
	Transverse Colon	6	12.20%
	Descending Colon	1	2%
	Sigmoid Colon	1	2%
	Rectum	7	14.30%
	Anal Canal	3	6.10%
Cervical LNs affection	Yes	8	16.30%
	No	41	83.70%
Mediastinal or axillary LNs affection	Yes	3	6.10%
	No	46	93.90%
Abdomino-pelvic LNs affection	Yes	12	24.50%
	No	37	75.50%
Inguinal LNs affection	Yes	3	6.10%
	No	46	93.90%
Liver affection	Yes	3	6.10%
	No	46	93.90%
Splenic affection	Yes	2	4.10%
	No	47	95.90%
Bone marrow affection (BMB)	Yes	2	4.10%
	No	47	95.90%

Laboratory findings showed that lymphocytic count ranged between 270-4870 cells/mm^3. Other laboratory findings are illustrated in **Table 3.**

Table 3: Laboratory investigation before treatment

Variable	Median	Minimum	Maximum
Hb	10.7	6.9	14.3
TLC	7.04	1.41	15.2
Neutrophils	3.8	0.10	9.3
Lymphocytes	2.1	0.26	4.87
LDH	294	170	3005

Even though the primary treatment for lymphoma is chemotherapy, most of the cases (32 [65.3%]) in the conducting study presented symptoms suggestive of intestinal obstruction or impending obstruction and underwent surgical resection before receiving systemic therapy.

A total 23 (71.9%) cases underwent right hemicolectomy. Anterior resection of rectal tumours has been done in 7 (21.9%) cases, one case underwent left hemicolectomy and one case underwent transverse colectomy.

The study included 34 paediatric cases; 13 cases received COPAD (Cyclophosphamide, Oncovin, Prednisolone, and Adriamycin), and 21 received COPADM (COPAD and Methotrexate) and CYM (Cytarabine and Methotrexate). Complete response was achieved in 27 cases, 3 cases progressed, and 4 cases died during the period of treatment.

In addition, the study included 15 adult cases; 9 cases received CHOP (Cyclophosphamide, Doxorubcin, Oncovin, Prednisolone), and 6 received the R-CHOP (Rituximab and CHOP) protocol. Complete response (CR) was achieved in 13 cases, while two died before completing the treatment protocol.

In the current study, follow-up of the cases ranged from 0.5 to 107 months, with a median of 31.74 months. Only 6 (12.2%) cases have experienced recurrence, and 9 (18.4%) cases died. Different factors that affected cumulative survival are displayed in **Table 4**.

Table 4: Overall survival and relations with different factors.

Variable	Number	Cumulative survival estimate at 5 years	P value
Gender			
Male	30	86.4 %	0.202
Female	19	73.7 %	
Age (year)			
≤18	34	79.4 %	0.572
>18	15	NR	
B Symptoms			
Yes	7	NR	**<0.001**
No	42	90.5 %	
Site of tumour			
Right colon	32	81.3 %	0.286
Transverse colon	5	60 %	
Left colon, rectum and anal cancal	12	91.7 %	
Stage of tumour			
I	28	89.3 %	0.45
II	12	50 %	
III, IV	9	100 %	
Hg (gm/dl)			
<10	27	50 %	**0.003**
≥10	22	51 %	
TLC (cells/mm^3)			
<4000	10	100 %	0.37
4000 -11000	34	82.4 %	
>11000	5	40 %	
Lymphocytic count (cell/mm^3)			
<2000	23	100 %	0.2
≥2000	26	65.4 %	
Pathology			
Burkitt	35	80 %	0.79
Large B cell	12	83.3 %	
MALT	2	NR	
Surgery done			
Yes	32	90.6 %	**0.013**
No	17	64.7 %	

In univariate analysis, the absence of B symptoms, Hg ≥10 gm/dl, and and surgically treated cases indicated a favourable prognosis while multivariate analysis showed that only B symptoms and Hg were independent factors **(Table 5).**

Table 5: Multivariate analyses for factors affects overall survival.

Independent prognostic factors	Beta coefficient	Standard error	P value	Hazard Ratio	95.% CI for HR Lower – Upper	
B symptom	2.102	0.64	0.006	8.186	1.830	36.622
Hb	2.632	0.084	0.015	13.900	1.660	116.418

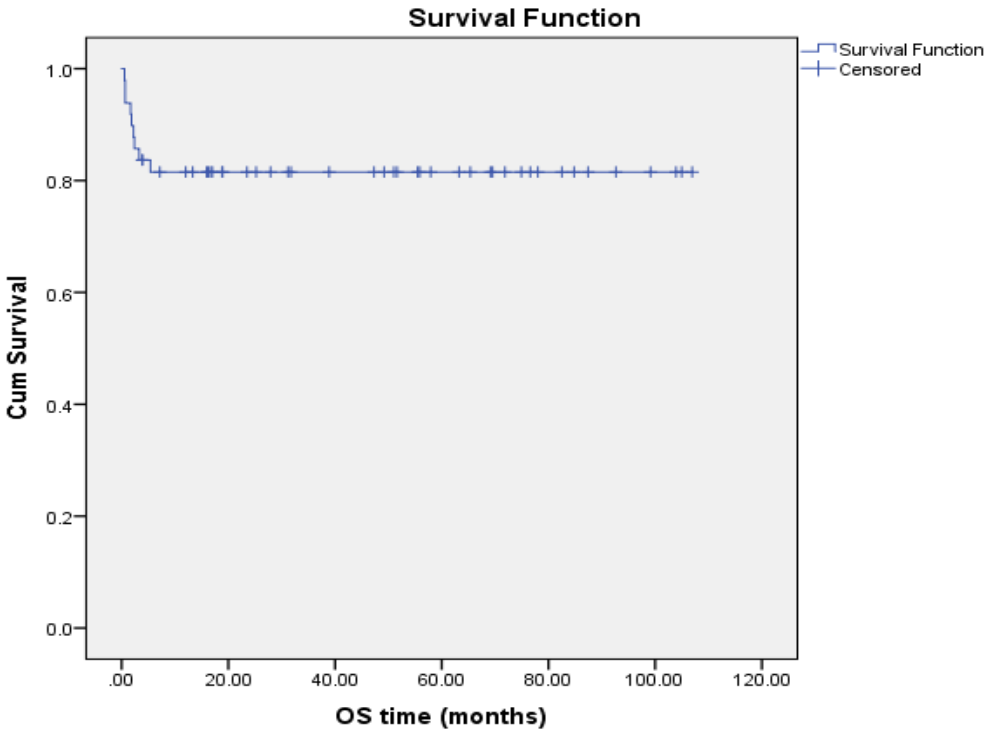

Figure 1: Cumulative survival of the cases of colorectal lymphoma.

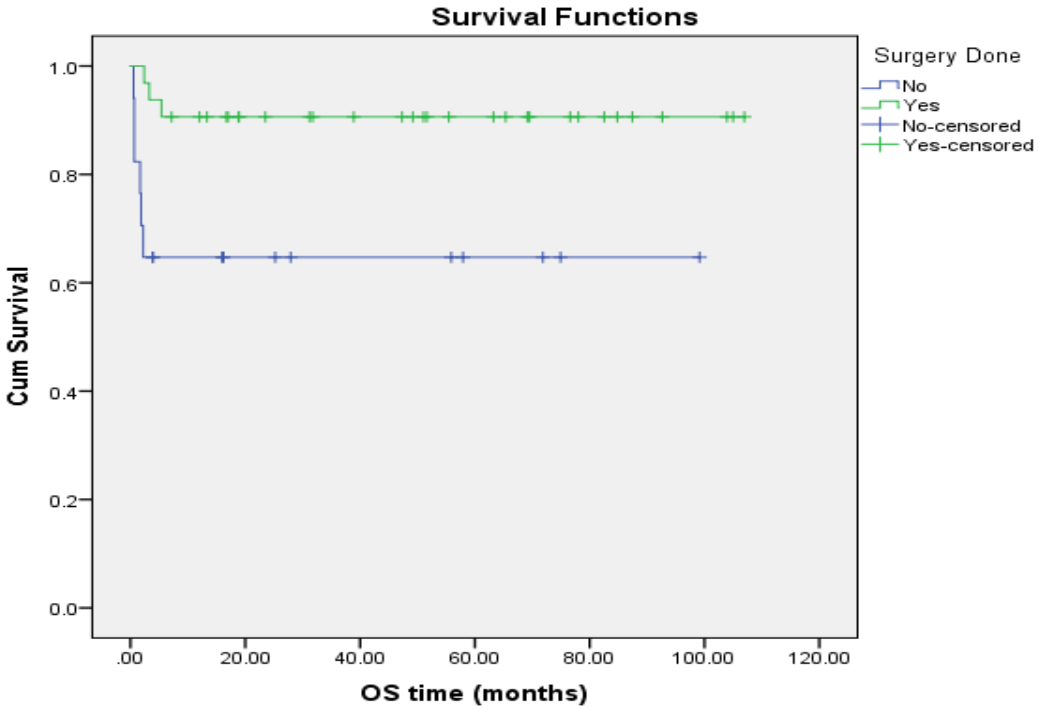

Figure 2: Relation of cumulative survival and surgery (P value= 0.013).

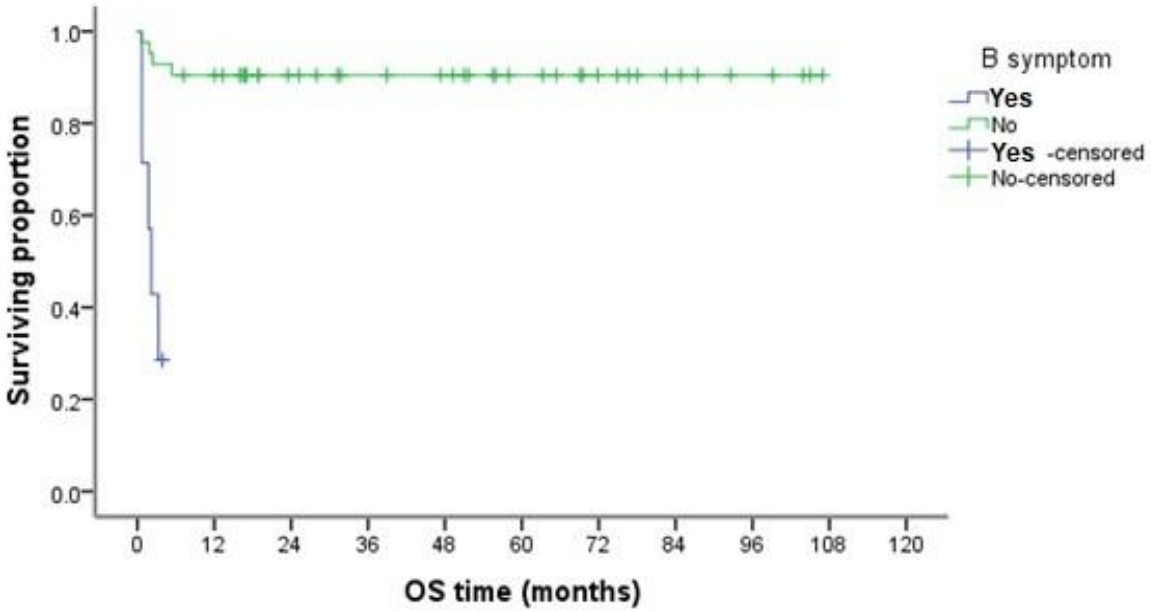

Figure 3: Relation of cumulative survival and B Symptoms (P value <0.001)

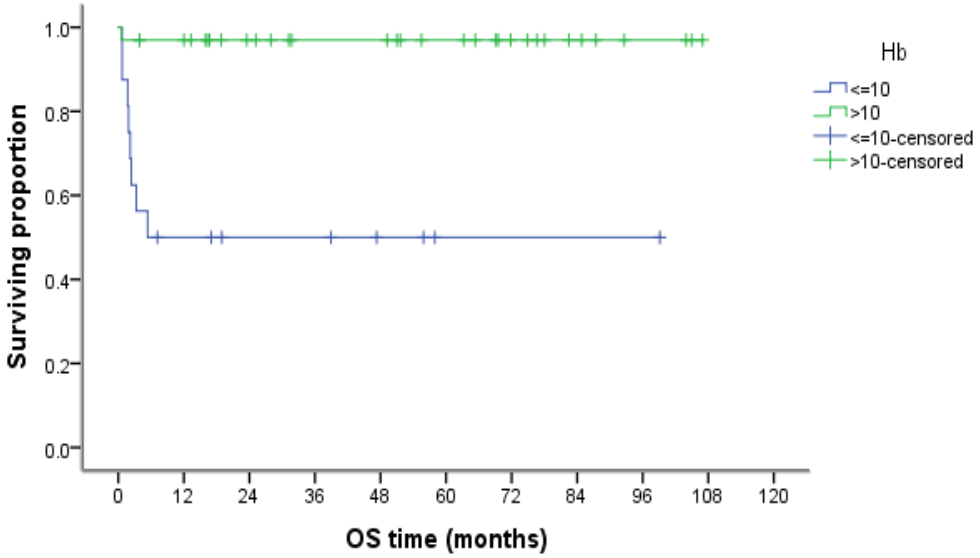

Figure 4: Relation of cumulative survival and HB level (P value= 0.003).

DISCUSSION

NHL, the most prevalent haematological malignancy in the world, accounts for approximately 3% of cancer diagnoses and mortality [(8)]. Approximately 40% of extranodal involvement (defined as lymphoma involving solid organs other than lymph nodes, spleen, and thymus) occurs in the gastrointestinal tract [(9)]. CL is the third most prevalent large intestinal cancer after adenocarcinoma and carcinoid, accounting for only 0.2% to 0.6% of colorectal malignancies and 10-20 % of GIT lymphomas [(10)].

The definition of primary CL changed over time. In 1961, **Dawson *et al.*** [(11)] established the diagnostic standards and criteria for primary CL. They defined it as lymphomas that affected only colorectal with or without the involvement of regional lymph nodes, no involvement of superficial lymph nodes, negative chest radiology to mediastinal lymph nodes involvement, and no affection of either liver or spleen. In 2003, **Krol *et al.*** [(3)] offered a more inclusive definition of primary extranodal NHL that encompasses all patients who present with NHL that appears to have originated from an extranodal site, even if there was a disseminated disease, as long as the extranodal component is clinically dominant.

In the current study, the number of male patients outperformed females, accounting for 61.2% of cases. The same results were reported by **Stanojevic *et al.*** [(4)] as they found that the incidence of CL in males was twice higher than that in females. Nevertheless, the majority of previous studies reported that CLs primarily

manifest in the sixth and seventh decades of life [4,12]. In the current cohort, the majority of cases were children (about 70% were younger than 18 years).

CL manifests differently based on the site of the lesion, degree of luminal obstruction of the colon, and ulceration on the mucosa, which may cause bleeding. According to **Bairey *et al*.** [5] the majority of cases presented with abdominal pain and weight loss (56% and 29%, respectively). This finding concurs with our results, as abdominal pain was the main presenting symptom (40% of patients). Primarily due to greater lymphoid tissue in the ileocecal region, 63% of the cases in the present study originated from ascending colon. In the literature, **Times** [2] reported that 67-87% of CLs arise in ascending colon. In their systematic review, **Lightner *et al.*** [13] reported comparable results involving 1524 patients with intestinal lymphoma (small and large intestine) as 37% of cases had lesions in the ileocecal region.

GIT lymphomas are classified according to the WHO criteria as large diffuse cells, MALT, mucosa-associated lymphoid tissue, Burkitt, and other types [14]. In the current study, Burkitt lymphoma was the most common type (71%), in contrast to the majority of previous findings, which demonstrated that diffuse large B cell lymphoma is the most common type arising in the colon [5,15,16]**.** This finding was mainly due to the difference in ages of patients as most of the cases in the current study were children younger than 18 years, while most of the studies reported cases with older ages (in the sixth and seventh decade) and Burkitt lymphoma usually developed in younger age than diffuse B cell lymphoma [17].

Kim *et al*. [9], in a retrospective cohort study involving 327 patients (both small and large intestine) and comparing the outcomes of two strategies for the treatment of CL, examined this topic by comparing the outcomes of the following: Surgical resection followed by systemic therapy (either CHOP or R-CHOP protocol) as compared to systemic therapy alone. In the early stages of CL (stages I and II), higher complete remission (CR) and three years overall survival (OS) rates in cases who underwent surgery followed by systemic therapy in comparison to those who received only systemic therapy [(CR 85.3% versus 64.4%) P-value <0.001] and [(3 years OS 91% versus 62%) P-value <0.001], respectively. In contrast, in advanced disseminated disease (Stage IV), there was no significant difference in progression-free survival (PFS) or OS between the two strategies [P-value >0.05]. Comparable results were reported by **Jaime-Andrade *et al.*** [18] as their study showed improved survival in cases that underwent surgery followed by chemotherapy. These results are consistent with those of the current study, as the 5-years OS improved in cases that underwent surgery compared to those that did not [(90.6% vs. 64.7%, respectively) P-value= 0.013].

The current study revealed that the absence of B symptoms, Hg ≥10 gm/dl, and surgery cases had a favourable prognosis. In order to help predict the prognosis of patients with non-Hodgkin lymphoma, an oncologist developed the International Prognostic Index (IPI), a clinical tool to estimate the prognosis of the cases diagnosed with NHL. In IPI, five prognostic factors (performance status ≥2, Age 60 years or older, advanced stage (III or IV), presence of more than one extranodal site, and high LDH) were included. Patients were categorised according to the total score as follows: low risk (0-1 points), low-intermediate risk (2 points), high-intermediate risk (3 points), and high risk (4-5 points). The five-year OS were 73%, 51%, 43%, and 26% for low-risk, low- intermediate-risk, high-intermediate-risk, and high-risk groups, respectively [17].

Olszewski *et al.* [19] attempted to modulate IPI to be more suitable for Burkitt lymphoma. Burkitt Lymphoma- International Prognostic Index was calculated using four prognostic factors (Performance score ≥ 2, age ≥ 40, CNS involvement, and LDH >3 times the upper limit). Each factor is assigned one point, and patients are categorised as follows: low risk (0 points), intermediate risk (1 point), and high risk (≥2 points) with estimated three years OS 96%, 75.9%, and 58.7%, respectively. Despite the limitations of the current study regarding the retrospective design and a small number of patients, it highlighted the characteristics of CL, particularly the majority of paediatric patients, in contrast to previous studies, and its results showed that surgical resection of CL improved the overall survival. Multi-centric clinical randomised clinical trials are required to determine which patients with CL can benefit from surgery.

CONCLUSION

CL is an extremely rare disease. Varying ages of patients are typically present at the time of diagnosis. The right colon is the most common site of occurrence. In conjunction with systemic therapy, surgical resection of CL appears to improve overall survival in early cases.

DECLARATIONS

- **Consent for publication:** I attest that all authors have agreed to submit the work.
- **Availability of data and material:** Available
- **Competing interests:** None
- **Funding:** No fund
- **Conflicts of interest:** No conflicts of interest.

REFERENCES

1. **Ferlay J, Ervik M, Lam F *et al*. (2020):** Global Cancer Observatory: Cancer Today. https://gco.iarc.fr/today
2. **Times M (2011):** Colorectal lymphoma. Clinics in colon and rectal surgery, 24(03):135-141.
3. **Krol A, Le Cessie S, Snijder S *et al*. (2003):** Primary extranodal non-Hodgkin's lymphoma (NHL): the impact

of alternative definitions tested in the Comprehensive Cancer Centre West population-based NHL registry. Annals of Oncology, 14(1):131-139.

4. **Stanojevic G, Nestorovic M, Brankovic B *et al*. (2011):** Primary colorectal lymphoma: an overview. World journal of Gastrointestinal Oncology, 3(1):14.
5. **Bairey O, Ruchlemer R, Shpilberg O (2006):** Non-Hodgkin's lymphomas of the colon. Isr Med Assoc J., 8(12):832-835.
6. **Sanchez-Bueno F, Garcia-Marcilla J, Alonso J *et al*. (1998):** Prognostic factors in primary gastrointestinal non-Hodgkin's lymphoma: a multivariate analysis of 76 cases. The European Journal of Surgery, 164(5):385-392.
7. **Andrews C, Gill M, Urbanski S *et al*. (2008):** Changing epidemiology and risk factors for gastrointestinal non-Hodgkin's lymphoma in a North American population: population-based study. Official Journal of the American College of Gastroenterology, 103(7):1762-1769.
8. **Thandra K, Barsouk A, Saginala K *et al*. (2021):** Epidemiology of non-Hodgkin's lymphoma. Medical Sciences, 9(1):5.
9. **Kim S, Kang H, Kim J *et al*. (2011):** Comparison of treatment strategies for patients with intestinal diffuse large B-cell lymphoma: surgical resection followed by chemotherapy versus chemotherapy alone. Blood, 117(6):1958-1965.
10. **Boot H (2010):** Diagnosis and staging in gastrointestinal lymphoma. Best Practice & Research Clinical Gastroenterology, 24(1):3-12.
11. **IMP D, JS C, BC M (1961):** Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. British Journal of Surgery, 49(213):80-89.
12. **Gonzalez Q, Heslin M, DÁVila-Cervantes A *et al*. (2008):** Primary colonic lymphoma. The American Surgeon, 74(3):214-216.
13. **Lightner A, Shannon E, Gibbons M *et al*. (2016):** Primary gastrointestinal non-Hodgkin's lymphoma of the small and large intestines: a systematic review. Journal of Gastrointestinal Surgery, 20(4):827-839.
14. **Swerdlow S, Campo E, Harris N *et al*. (2008):** WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues (4th Ed.). Lyon, France: IARC Press.
15. **Koniaris L, Drugas G, Katzman P *et al*. (2003):** Management of gastrointestinal lymphoma. Journal of the American College of Surgeons, 197(1):127-141.
16. **Musallam K, Hatoum H, Barada K *et al*. (2010):** Primary colorectal lymphoma. Medical oncology, 27(2):249-254.
17. **Shipp M (1993):** A predictive model for aggressive non-Hodgkin's lymphoma. The international non-Hodgkin's lymphoma prognostic factors project. N Engl J Med., 329:987-994.
18. **Jaime-Andrade E, Lino-Silva L, Salcedo-Hernández R *et al*. (2018):** Colorectal lymphoma in Mexico: clinico-pathological and survival analysis. Journal of Gastrointestinal Oncology, 9(1):90.
19. **Olszewski A, Jakobsen L, Collins G *et al*. (2021):** Burkitt lymphoma international prognostic index. Journal of Clinical Oncology, 39(10):1129-1138.