Incidence and Risk Factors of Bone Marrow Involvement by Non-Hodgkin Lymphoma

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***Background**: Since trephine bone marrow biopsy is an invasive procedure, the identification of a subgroup of patients with Non-Hodgkin lymphoma (NHL) who have a minimal risk of bone marrow involvement would be helpful. This study is aimed to determine the incidence of bone marrow involvement (BMI) by NHL and the predictors of no BMI to not only avoid this invasive procedure but also decrease the cost of investigation.*

***Material and Method:** Data from 320 patients with NHL at division of hematology between January 2008 and June 2009 were reviewed and analyzed.*

***Results:** The cell types of NHL were classified as B-cell in 283 patients (88.4%), T-cell in 37 patients (11.6%) and incidence of BMI is 24.4% and 18.9% in B- and T-cell, respectively. Factors significantly associated with BMI in univariate analysis were the hepatic and splenic involvement ($p = 0.03$ and < 0.01, respectively), significant weight loss ($p = 0.02$), presence of lymphadenopathy (LN) below diaphragm ($p = 0.02$), anemia ($p = 0.001$), low percent of blood neutrophil ($p < 0.001$), high percent of blood lymphocyte ($p < 0.001$), low absolute neutrophil count ($p = 0.002$), high absolute lymphocyte count ($p = 0.045$), low platelet count ($p < 0.001$), high LDH ($p = 0.026$), and high alkaline phosphatase ($p = 0.020$). On the multivariate analysis, factors associated with BMI included LN below diaphragm, anemia, low percent of blood neutrophil and low platelet count. Excluding Burkitt lymphoma and mantle cell lymphoma, NHL patients with no LN below diaphragm, no hepatic & splenic involvement, no significant weight loss, hemoglobin (Hb) >11 g/dL and platelet > 150,000/uL had BMI in 3/78 (3.8%).*

***Conclusion:** The incidence of bone marrow involvement in NHL is 23.8%. Excluding Burkitt lymphoma and mantle cell lymphoma, NHL patients with no LN below diaphragm, no hepatic & splenic involvement, no significant weight loss, Hb > 11 g/dL and platelet >150,000/uL had low risk of BMI.*

***Keywords:** Bone Marrow, Non-Hodgkin Lymphoma*

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The incidence of bone marrow involvement (BMI) in patients with Non-Hodgkin lymphoma (NHL) is varied among different types of NHL which range from 8% in diffuse large B-cell lymphoma to almost 100% in patients with lymphoplasmacytic lymphoma[1-3]. The evidence of BMI is important not only to document the advanced stage of disease, which may modify the plan of treatment and change the prognostic index but also to make the diagnosis in some patients. Nevertheless, it is an invasive and painful procedure. There are some reports of its serious complications-retroperitoneal bleeding and other complications such as infection and persistent pain[4-6]. Identification of a group of patients with NHL who have a minimal risk of bone marrow involvement would be helpful.

For Hodgkin lymphoma, there are some studies showing clinical and laboratory prediction factors for bone marrow involvement[7] including B symptoms, stage, iliac/inguinal node involvement, elevated serum lactate dehydrogenase (LDH) and peripheral cytopenias. Nevertheless, the report of factors enabling prediction of BMI in NHL is rare.

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Material and Method

A retrospective study was performed including 320 patients at division of hematology, faculty

of medicine Siriraj hospital with biopsy-proven NHL between January 2008 and June 2009. The recorded data were reviewed to assess the incidence of BMI in each subtype of NHL and analyse the predictors of BMI by either univariate or multivariate methods. The NHL patients with either B-cell or T-cell types were staged according to Ann Arbor staging system. A history taking and complete physical examination; complete blood count (CBC) and relevant biochemical profiles; chest x-rays; computed tomography of the chest (optional), abdomen and/or the affected part; and unilateral bone marrow biopsy were done in order to stage the disease.

The protocol was approved by Siriraj Institutional Review Board. The data to be analyzed were the definitive diagnosis, stage of disease, each character of B symptoms, location of lymphadenopathy, liver and splenic involvement, the number of extranodal site involvement (not include bone marrow) and the prognostic index for each subtype of NHL (*e.g.* International Prognostic Index (IPI), age-adjusted IPI (aaIPI) for aggressive NHL, Follicular Lymphoma International Prognostic Index (FLIPI) for follicular lymphoma, Mantle cell Lymphoma International Prognostic Index (MIPI) for mantle cell lymphoma) and the following laboratory factors: LDH, albumin, globulin, alkaline phosphatase (ALP).

Statistical Analysis

For continuous variable, *e.g.* age, hemoglobin, percentage of neutrophil, and albumin, unpaired t-test or Mann-Whitney U test were used to compare the means between BMI and No BMI groups. Mann-Whitney U test was performed when continuous variable is not normally distributed. Chi-square or Fisher's exact tests were used to assess the differences of proportion of categorical variables (*e.g.* sex, age group, and cell type), between BMI and No BMI groups. Crude odds ratios (OR) with 95% confidence interval (CI) were used to describe the strength of the relationship between the presence of BMI and factor predictive of BMI. Multiple logistic regression analysis, *i.e.*, binary logistic regression analysis was used to assess the relationship between the presence of BMI and factor predictive of BMI (*e.g.* lymph node below diaphragm, hemoglobin, and percentage of neutrophil). Statistical significance judged by a two-tailed p-value of less than 0.05 was considered statistically significant.

Results

Incidence of bone marrow involvement (BMI) in NHL patients

Among 320 patients the most common lymphoma subtype is DLBCL (60.93%) followed by MALT lymphoma and follicular lymphoma (7.81% and 7.5%) respectively. The overall incidence of BMI for NHL is 23.8%. The incidence of BMI for B-cell and T-cell NHL is 69/283 (24.38%) and 7/37 (18.91%), respectively. The incidence of BMI (Table 1) is highest in patients with mantle cell lymphoma (100%), followed by splenic marginal zone lymphoma (75%), lymphoplasmacytic lymphoma (66.7%) and 50%, similarly, among follicular lymphoma, small lymphocytic lymphoma, peripheral T-cell lymphoma and angio-immunoblastic T-cell lymphoma.

Patient demographic data

Table 2 and 3 demonstrate patient characteristics and predicted factors of BMI for continuous and categorical data, respectively. For categorical data, we compared each parameter between the patients with this parameter to those without, for

Table 1. Incidence of bone marrow involvement (BMI) in each subtype of NHL

Lymphoma subtype	BMI (%)
DLBCL	34/195 (17.4%)
Follicular lymphoma	12/24 (50.0%)
Lymphoblastic lymphoma	0/4 (0%)
Burkitt lymphoma	3/12 (25.0%)
LPL	2/3 (66.7%)
AITL	1/2 (50.0%)
SMZL	3/4 (75.0%)
MALT lymphoma	3/25 (12.0%)
PTCL	4/8 (50.0%)
Mantle cell lymphoma	6/6 (100.0%)
SLL	1/2 (50.0%)
Low grade lymphoma with large cell transformation	2/5 (40.0%)
Plasmablastic lymphoma	0/3 (0%)
SCPLT	1/7 (14.3%)
ALCL	0/5 (0%)
Extranodal NK-T cell lymphoma	1/9 (11.1%)

DLBCL-diffuse large B-cell lymphoma, LPL-lymphoplasmacytic lymphoma, SMZL – splenic marginal zone lymphoma, AITL – angioimmunoblastic T-cell lymphoma, PTCL – peripheral T-cell lymphoma, SLL – small lymphocytic lymphoma, SCPLT – subcutaneous panniculitis-like T-cell lymphoma, ALCL – anaplastic large cell lymphoma

Table 2. Comparison of continuous data between bone marrow involvement (BMI) group and no bone marrow involvement group

	BMI (mean ± SD)	No BMI (mean ± SD)	p-value*
Age (yr)	56.3 ± 15.5	56.3 ± 16.7	0.809
Hb (g/dl)	10.4 ± 2.6	11.6 ± 2.1	0.001
WBC (/mm^3)	8,986 ± 7,339	7,982 ± 3,987	0.679
% neutrophil	55.6 ± 18.4	66.8 ± 12.8	< 0.001
% lymphocyte	30.9 ± 18.3	22.4 ± 11.3	< 0.001
ANC (/mm^3)	4,680 ± 4,000	5,435 ± 3,399	0.002
ALC (/mm^3)	2,867 ± 4,072	1,649 ± 1,402	0.045
Platelet (x 10^9/L)	189 ± 120.89	286 ± 123.05	< 0.001
LDH (U/L)	1,563 ± 4,190	731 ± 848	0.026
Globulin (g/dl)	4.2 ± 1.7	3.9 ± 0.8	0.748
Albumin (g/dl)	3.6 ± 0.7	3.8 ± 0.7	0.055
ALP (U/L)	153 ± 141	115 ± 159	0.020

Hb, hemoglobin; WBC, white blood cell count; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; LDH, serum lactate dehydrogenase; ALP, serum alkaline phosphatase
*Only 'Hb' data have normal distribution

Table 3. Comparison of categorical data between bone marrow involvement (BMI) group and no bone marrow involvement group

	BMI (n = 76)		No BMI (n = 244)		OR (95%CI)	p-value
	n	%	n	%		
Sex (%M)	M 42/76	55.3	M 123/244	50.4	1.22 (0.72-2.04)	0.46
Age : < 60 yr	42/76	55.3	129/244	52.9		
≥ 60 yr	34/76	44.7	115/244	47.1	0.91 (0.54-1.52)	0.72
Cell type: B	69/76	90.8	214/244	87.7		
T	7/76	9.2	30/244	12.3	0.72 (0.30-1.72)	0.46
Fever	24/75	32.0	58/243	23.9	1.50 (0.85-2.65)	0.16
Weight loss	35/75	46.7	78/243	32.1	1.85 (1.09-3.14)	0.02
Night sweat	11/63	17.5	21/210	10.0	1.90 (0.86-4.20)	0.11
ECOG: 0-I	41/69	59.4	167/234	71.4		
II-IV	28/69	40.6	67/234	28.6	1.70 (0.97-2.97)	0.06
LN location						
above diaphragm	46/76	60.5	129/244	52.9	1.37 (0.81-2.30)	0.24
below diaphragm	47/76	61.8	114/244	46.7	1.85 (1.09-3.13)	0.02

OR, odds ratio; CI, confidence interval; LN, lymph node

example, the lymph node (LN) location between those who had the LN below diaphragm to those who did not, the positive night sweat history to the negative history and B-cell NHL to not B-cell type.

The patients who have BMI compared to those without BMI have significantly lower hemoglobin (Hb) level (10.4 vs. 11.6 g/dL), lower percentage of neutrophil (55.6 vs. 66.8%), higher percentage of lymphocyte (30.9 vs. 22.4%) correlated with lower absolute neutrophil count (4,680 vs. 5,435/mm^3) and higher absolute lymphocyte count (2,867 vs. 1,649/mm^3), lower platelet count (189 x 10^9 vs. 286 x 10^9/L),

higher serum lactate dehydrogenase (LDH) (1,563 vs. 731 U/L), and higher alkaline phosphatase (ALP) level (153 vs. 115 U/L). Other parameters including age, WBC count, globulin, and albumin do not show any significant difference between the two groups.

From the categorical characteristics of patient, the significant parameters predicting BMI are history of weight loss (loss $\geq$ 10% of the baseline weight) with OR 1.85 (95% CI 1.09-3.14) when compared to those without this history and the location of lymphadenopathy below diaphragm (*i.e.* inguinal, mesenteric, iliac LN) compared with those without LN below diaphragm has the OR 1.85 (95% CI 1.09-3.13). Sex, age less or more than 60 years, cell types, the other B symptoms, performance status and location of LN above diaphragm do not show the significant association with marrow invasion by NHL.

The extranodal site involvement prior to bone marrow study is also the important predictor for BMI (Table 4). The presence of extranodal site involvement seems to be the negative predictor of BMI with the OR less than 1 if compared to those without any extranodal involvement. The invasion of disease to liver and/or spleen increases the likelihood of BMI with OR 2.99 (95% CI 1.05-8.55) and 4.36 (95% CI 2.34-8.14), respectively. No other extranodal sites are significant predictors of BMI.

Predictive factors of bone marrow involvement

The following covariates were significantly associated with the presence of bone marrow invasion by NHL (Table 2, 3 and 4): history of significant weight loss ($p = 0.02$), LN below diaphragm ($p = 0.02$), splenic involvement ($p < 0.01$), liver involvement ($p = 0.03$), Hb < 11 g/dL ($p = 0.001$), percentage of neutrophil less than 80% ($p < 0.001$), percentage of lymphocyte more than 50% ($p < 0.001$), low absolute neutrophil count ($p = 0.002$), high absolute lymphocyte count ($p = 0.045$), platelet count less than 150 x 10^9/L ($p < 0.001$), high LDH ($p = 0.026$), and high ALP ($p = 0.020$). Other factors such as age above or below 60 years old, sex, lymphoma cell types (B or T cell),the others B symptoms, other sites of extranodal involvement besides hepatic and splenic involvement, performance status, LN above diaphragm, and other laboratories (serum albumin, globulin) do not associate with the risk of BMI. Thus, nine covariates were examined in a logistic regression model. Among them, four factors remained to be the independent predictors of BMI (Table 5) including LN below diaphragm ($p = 0.032$), Hb level ($p = 0.028$), percentage of neutrophil ($p < 0.001$) and platelet ($p = 0.001$).

Excluding mantle cell lymphoma (MCL) and Burkitt lymphoma (BL), which are defined as rarely to have limited stage disease, we try to find the simple negative predictors of BMI for Non-Hodgkin lymphoma calculating from the univariate factors, we found six parameters including no LN below diaphragm, no hepatic involvement, no splenic involvement, no significant weight loss, Hb > 11 g/dL and platelet count > 150 x 10^9/L.

With regard to our analysis, among patients diagnosed as NHL, except BL and MCL, who had all of these six parameters, the chance of BMI is only 3.8% (3/78).

Regarding each subgroup of NHL, DLBCL patients with all these six factors had BMI of 6% (3/50) whereas none of 12 cases of MALT lymphoma and none of 6 cases of follicular lymphoma who had all the negative predictors had BMI.

Discussion

From this study we found that the incidence of BMI in NHL is similar to previous published data[1-3] which varied by the subtype. In general, indolent small B-cell lymphoma involves bone marrow much more common than aggressive B-NHL. Splenic marginal zone lymphoma almost always involves bone marrow while in this study the incidence is 75%. For follicular lymphoma, the incidence of BMI from other studies varies from 40%-70% compared to 50% in this study, whereas diffuse large B-cell lymphoma involves marrow in only 10%-30% from other studies compared to 17.4% in this study. Regarding T-cell lymphoma, only a few reports of BMI were published owing to its rare incidence. Peripheral T-cell lymphoma involves marrow in 70% from the study of Cho et al[8]. From study of Tong et al[9], the incidence of BMI in PTCL is 46%, 64% in AITL, 29% in ALCL and 23% in extranodal NK/T-cell lymphoma. In this study, the incidence of BMI for T-cell lymphoma is 50% (4 of 8), 50% (1 of 2), 0% (0 of 5) and 11.1% (1 of 9) for PTCL, AITL, ALCL and extranodal NK/T-cell lymphoma, respectively, which is rather similar to other reports. Due to the few cases of T-cell type lymphoma, the incidence of BMI is not well published.

Regarding extranodal site involvement of NHL, the location of primary disease is important to determine whether it will have BMI or not. The common locations for those who have BMI are hepatic and splenic involvement, the incidence of BMI for which is 46.67% and 50%, respectively. In contrary, those with

Table 4. Extranodal site involvement (not included bone marrow) and the odd ratios of bone marrow involvement (BMI)

Extranodal site	Total n (n = 320)		BMI (n = 76)	No BMI (n = 244)	OR (95%CI)	p-value
	n	%				
No	115	35.9	46	69	1	
1 site	172	53.8	24	148	0.24 (0.14-0.43)	< 0.01
2 sites	29	9.1	6	23	0.39 (0.15-1.04)	0.05
3 sites	4	1.2	0	4	N/A	
Liver	15	4.7	7	8	2.99 (1.05-8.55)	0.03
Spleen	52	16.2	26	26	4.36 (2.34-8.14)	< 0.01
CNS	27	8.4	5	22	0.71 (0.26-1.95)	0.50
Bone	12	3.8	3	9	1.07 (0.28-4.07)	0.92
Skin	16	5.0	2	14	0.44 (0.10-2.00)	0.28
Thyroid	5	1.6	0	5	N/A	
Breast	7	2.2	0	7	N/A	
Lung	15	4.7	5	10	1.65 (0.55-4.98)	0.36
Pleura	17	5.3	4	13	0.99 (0.31-3.12)	0.98
Waldeyer ring	22	6.9	2	20	0.30 (0.07-1.33)	0.09
Gastric	22	6.9	2	20	0.30 (0.07-1.33)	0.09
Duodenum	2	0.6	0	2	N/A	
Jejunum	6	1.9	0	6	N/A	
Ileum	7	2.2	0	7	N/A	
Colorectum	7	2.2	1	6	0.53(0.06-4.46)	1.00
Pancreas	7	2.2	0	7	N/A	
Renal	2	0.6	0	2	N/A	
Adrenal gland	1	0.3	0	1	N/A	
Urinary tract	1	0.3	0	1	N/A	
Testis	5	1.6	0	5	N/A	
Ovary	0	-	-	-	-	
Uterus	1	0.3	0	1	N/A	
Pericardium	0	-	-	-	-	
Pharynx	10	3.1	0	10	N/A	
Sinonasal	14	4.4	3	11	0.87 (0.24-3.21)	1.00
Conjunctiva	10	3.1	0	10	N/A	
Others	12	3.8	2	10	0.63 (0.14-2.95)	0.74

N/A, not available; CNS, central nervous system

Table 5. Parameters predicting the BMI in multivariate analysis

Parameters	OR (95%CI)	p-value
LN below diaphragm	1.94 (1.06-3.57)	0.032
Hemoglobin	0.86 (0.76-0.98)	0.028
% neutrophil	0.96 (0.94-0.98)	< 0.001
Platelet ($x10^9$/L)	0.995 (0.992-0.998)	0.001

central nervous system (CNS), gastric, Waldeyer ring and testis involvement almost do not have BMI. The explanation is that for patients with primary extranodal site disease (*e.g.* primary CNS lymphoma, gastric MALT lymphoma, primary testicular lymphoma, etc.), patients' symptoms are usually presented early leading to early diagnosis and thus bone marrow involvement is uncommon at the initial diagnosis. However, liver involvement is almost always from lymphoma dissemination and very rarely from the primary disease at the liver. For splenic involvement, it could be the primary site (*e.g.* splenic marginal zone lymphoma which commonly involves bone marrow) or dissemination of disease.

We also identified 6 simple clinical and

laboratory parameters which were the negative predictors of BMI in NHL patients. Among NHL patients, excluding Burkitt lymphoma and mantle cell lymphoma, six negative predictors of BMI included no weight loss, no intraabdominal, inguinal and iliac lymphadenopathy, no hepatomegaly, no splenomegaly, Hb > 11 g/dL and platelet > 150 x 10^9/L. We may discuss with each patient with all six negative predictors about his or her condition in order to spare bone marrow trephine biopsy for the purpose of staging owing to the very low incidence of BMI (3.8%). Other studies of BMI for Hodgkin lymphoma patients[7] also demonstrated the reproducible and effectiveness of BMI predictors. However, there is no previous published data of BMI prediction for NHL to compare with our result and the validation of our predictors has not yet been performed. These findings intend only to predict BMI in subgroup of NHL patients, in order to decrease the rate of bone marrow trephine biopsy for the advantages of lowering the cost and reducing the suffering of the patients. These parameters cannot replace BM study for all purposes, such as for diagnosis or to evaluate marrow abnormalities (*e.g.* myelofibrosis, hemophagocytosis, etc).

Conclusion

The incidence of bone marrow involvement in NHL is 23.8%. Excluding Burkitt lymphoma and mantle cell lymphoma, NHL patients with no LN below diaphragm, no hepatic & splenic involvement, no significant weight loss, Hb > 11 g/dL and platelet >150,000/uL had a low risk of BMI. It is still needed to demonstrate reproducibility of these findings in validation groups of patients.

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Potential conflicts of interest

None.

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อุบัติการณ์และปัจจัยเสี่ยงของการแพร่กระจายเข้าไขกระดูกของโรคมะเร็งต่อมน้ำเหลืองชนิด non-Hodgkin

เจนจิรา กิตติวรภัทร, ยิ่งยง ชินธรรมมิตร์

***ภูมิหลัง**: การเจาะตัดไขกระดูกเป็นหัตถการที่ดูน่ากลัวสำหรับผู้ป่วยหลายๆ คน และต้องทำในผู้ป่วยมะเร็งต่อมน้ำเหลืองเพื่อประเมินระยะของโรคก่อนการรักษา ดังนั้นการตรวจหากลุ่มผู้ป่วยโรคมะเร็งต่อมน้ำเหลือง ที่มีโอกาสแพร่กระจาย เข้าไขกระดูกน้อยมากอาจมีประโยชน์ที่จะเลี่ยงการเจาะไขกระดูก และลดค่าใช้จ่ายแก่ผู้ป่วย*

***วัสดุและวิธีการ**: คณะผู้นิพนธ์ได้ทำการศึกษาย้อนหลังกลุ่มผู้ป่วย 320 ราย ที่เป็นโรคมะเร็งต่อมน้ำเหลือง ชนิด non-Hodgkin ที่เข้ารับการรักษาที่สาขาวิชาโลหิตวิทยา โรงพยาบาลศิริราช ระหว่าง มกราคม พ.ศ. 2551 ถึงมิถุนายน พ.ศ. 2552*

***ผลการศึกษา**: มีผู้ป่วยโรคมะเร็งต่อมน้ำเหลืองชนิดนอนฮอดจ์กินชนิดเซลล์บีจำนวน 283 คน (88.4%) และชนิดเซลล์ทีจำนวน 37 คน (11.6%) โดยอุบัติการณ์ของการแพร่กระจายเข้าไขกระดูกของชนิดเซลล์บี และเซลล์ทีเท่ากับ 24.4% และ 18.9% ตามลำดับ จากการวิเคราะห์ตัวแปรเดี่ยวพบปัจจัยที่สัมพันธ์กับ การแพร่กระจายเข้าไขกระดูกคือ การกระจายเข้าตับ ($p = 0.03$) การกระจายเข้าม้าม ($p < 0.01$) น้ำหนักลด ($p = 0.02$) ต่อมน้ำเหลืองโตใต้กะบังลม ($p = 0.02$) ซีด ($p = 0.001$) เปอร์เซ็นต์นิวโตรฟิลในเลือดต่ำ ($p < 0.001$) เปอร์เซ็นต์ลิมโฟไซต์ในเลือดสูง ($p < 0.001$) จำนวนนิวโตรฟิลในเลือดต่ำ ($p = 0.002$) จำนวนลิมโฟไซต์ในเลือดสูง ($p = 0.045$) จำนวนเกล็ดเลือดในเลือดต่ำ ($p < 0.001$) ระดับแอลดีเอชสูง ($p = 0.026$) และระดับอัลคาไลน์ฟอสฟาเทสสูง ($p = 0.020$) จากการวิเคราะห์พหุตัวแปรพบปัจจัยที่สัมพันธ์กับการแพร่กระจายเข้าไขกระดูกคือ ต่อมน้ำเหลืองโตใต้กะบังลม ซีด เปอร์เซ็นต์นิวโตรฟิลในเลือดต่ำ และจำนวนเกล็ดเลือดในเลือดต่ำ ถ้าไม่นับรวมมะเร็งต่อมน้ำเหลืองชนิด Burkitt และชนิดเซลล์ mantle ผู้ป่วยที่ไม่มีต่อมน้ำเหลืองโตใต้กะบังลม ไม่มีการแพร่กระจายเข้าตับม้าม ไม่มีน้ำหนักลด ระดับความเข้มข้นฮีโมโกลบินมากกว่า 11 กรัมต่อเดซิลิตร และระดับเกล็ดเลือดมากกว่า 150,000 ต่อไมโครลิตร พบการแพร่กระจายเข้าไขกระดูกเพียง 3 ใน 78 ราย (3.8%)*

***สรุป**: อุบัติการณ์การแพร่กระจายเข้าไขกระดูกของโรคมะเร็งต่อมน้ำเหลืองชนิด non-Hodgkin เท่ากับ 23.8% ถ้าไม่นับรวมมะเร็งต่อมน้ำเหลืองชนิด Burkitt และชนิดเซลล์ mantle ผู้ป่วยที่ไม่มีต่อมน้ำเหลืองโตใต้กะบังลม ไม่มีการแพร่กระจายเข้าตับม้าม ไม่มีน้ำหนักลด ระดับความเข้มข้นฮีโมโกลบินมากกว่า 11 กรัมต่อเดซิลิตร และระดับเกล็ดเลือดมากกว่า 150,000 ต่อไมโครลิตร พบการแพร่กระจายเข้าไขกระดูกต่ำ*