Original Article

Bone marrow evaluation for diffuse large B-cell lymphoma: Prevalence and histologic findings

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Abstract

Introduction: Diffuse large B-cell lymphoma (DLBCL) with bone marrow involvement (BMI) indicates poor prognosis. BMI can be assessed by morphology in H&E slide and/or CD20 immunohistochemistry (IHC). This study aims to 1) evaluate the prevalence of BMI in Thammasat university hospital, 2) comparing morphology and CD20 in detection yield of BMI, and 3) correlate tumor volume to IPI score.

Method: Retrospective study, 117 bone marrow tissues (staging 111 cases and primary diagnosis 6 cases) from Pathology Laboratory of Thammasat University Hospital from 1 January 2012 to 31 December 2016.

Result: BMI was found in 10.8% (12/111 cases) of staging cases and 6 cases of primary diagnosis. H&E had sensitivity 83.3%, specificity 100%, positive predictive value (PPV) 100%, negative predictive value (NPV) 98.0% and receiver operating curve (ROC) area 92.0%. Bone marrow tumor volume correlated with IPI-high as 51 - 100% tumor volume had IPI-high in 3/4 cases (75%), 11 - 50% tumor volume had IPI-high in 3/5 cases (60%), and tumor volume 1-10% had IPI-high in 4/8 cases (50%).

Conclusions: Prevalence of BMI in DLBCL staging in Thammasat university hospital is slightly lower than previous studies. The detection of tumor cells by morphology in H&E is reliable and maybe unnecessary to stain CD20 in all cases upfront. There is a trend that increasing tumor volume has IPI-high score.

Key word: Bone marrow involvement, DLBCL, Bone marrow staging

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common malignant lymphoma in Thailand.[1] The five years overall survival is 35% - 80%[2] and without treatment, the patients will die within two years.[3] All patients with DLBCL should undergo bone marrow biopsy (BMBx) for staging. The evidence of bone marrow involvement (BMI) indicates advance stage disease (stage 4). The prevalence of BMI in DLBCL varied from 11[4] - 25[5] worldwide, and 12.7%[6] in Thailand. The BMBx staging can be assessed morphologically by routine H&E with or without CD20 immunohistochemistry (IHC). By morphology, DLBCL tumor cell has nuclear size equal to or exceeding normal macrophage nuclei or more than twice the size of a normal lymphocyte and has prominent nucleolus.[7] The tumor cells involve bone marrow (BM) in 6 patterns as focal nodular, paratrabecular, interstitial, diffuse, intrasinusoidal and mixed. Focal nodular and mixed are the most common pattern.[8] The CD20 is a B-cell lineage marker which stains almost all DLBCL tumor cell. The previous study recommended additional IHC should be performed in all staging BMBx specimens of patients with DLBCL. A panel of antibodies including CD3, CD20 and other B-cell markers such as CD79a and /or PAX-5 was suggested for initial evaluation of BMI by DLBCL.[9] A CD20 IHC for the purpose of detecting BMI of DLBCL was not advocated because it did not detect additional cases of DLBCL with BMI that were not identified by morphologic evaluation.[10] In addition to tumor staging, the International Prognostic Index (IPI) is also used for prognosis assessment. IPI is a scoring system based on 5 risk factors (age, stage, performance status, serum lactate dehydrogenase (LDH) level and number of extranodal sites) to stratify patients into 4 risk groups.[11]

This study aims to 1) evaluate the prevalence of BMI in Thammasat university hospital, 2) comparing morphology and CD20 in detection yield of BMI and 3) correlate tumor volume to IPI score.

Methods

This retrospective descriptive study reviewed BMBx from patients with DLBCL diagnosed at pathology laboratory of Thammasat university hospital during January 1, 2012 to December 31, 2016. The eligible criteria were 1) BM staging after diagnosis DLBCL within 3 months, 2) no prior chemotherapy, 3) primary diagnosed DLBCL from BM, 4) not associated with small B-cell non-Hodgkin lymphoma (NHL), and 5) available paraffin block and slide H&E. The cases were divided into two groups as staging DLBCL and DLBCL primarily diagnosed from BM. The primary DLBCL of BM was defined as no evidence of leukemia or lymphoma in lymph node, spleen, liver or others extra BM involvement from physical examination and imaging.

The patient data were collected from medical record files and electronic database. The data consisted of gender, age, tumor location, Ann Arbor staging, serum LDH, Eastern Cooperative Oncology Group (ECOG), IPI, and BMI. The tumor location was divided in nodal organs, including lymph node, tonsil, Waldeyer's ring, spleen and thymus and extranodal organs, including BM, central nervous system (CNS), liver, gastrointestinal tract (GI) lung, soft tissue, sinonasal/nasopharynx, mediastinum, endocrine organs, reproductive organ and pleural cavities. For primary diagnosed DLBCL from BM cases, additional data included fever of unknown origin (FUO) and CBC. Calculation of IPI for all patients was based on presence of these factors: age > 60 years, Ann Arbor stage 3 or 4, high serum LDH, ECOG status ≥ 2 and extranodal involvement ≥ 2 sites, one score for each. The risk groups were classified into low score 0 or 1, low intermediate score 2, high intermediate score 3 and high score 4 or 5 for patients age > 60 years old. If patients age ≤ 60, the risk group as low score 0, low intermediate score 1, high intermediate score 2 and high score 3.[11]

All slide labels were de-identified before histologic review by hematopathologist (NW). All BM morphology based on H&E slides were evaluated for BMI (index test), tumor volume (%) and pattern. We divided cases into 3 morphology groups of 1) H&E positive, 2) H&E suspicious and 3) H&E negative. All cases were stained with CD20 IHC (reference standard). The cases, based on H&E or CD20, containing at least one large lymphoid cell having nuclear size equal to or exceeding normal macrophage nuclei or more than twice the size of a normal lymphocyte based on were categorized as H&E positive or BMI positive. The H&E suspicious cases were those containing medium to large mononuclear cell, increased number of small lymphoid cells, lymphoid cell aggregate, and BM necrosis. H&E suspicious were included in BMI negative.

Prevalence of BMI in staging DLBCL group was based on detection by CD20 IHC.

Detection yield of BMI by morphology (H&E) comparing to CD20 IHC were reported in sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area ROC area.

BMI positive and primary diagnosed DLBCL of BM were assessed for tumor volume and pattern based on CD20. The pattern of BMI included focal nodular, paratrabecular, interstitial, diffuse, intrasinusoidal and mixed pattern. The focal nodular pattern had sharp border with spherical or oval shape of tumor cells group. The paratrabecular pattern had the tumor cells that arrange parallel to the trabecular bone. The interstitial pattern had tumor cells infiltrating the fat cells. The diffuse pattern had the tumor cells cluster measuring lager than 2 mm. The intrasinusoidal pattern had tumor cells confined in vascular spaces. The mixed pattern had more than two different patterns.[8] The tumor volume was divided into 3 levels as 1 - 10%, 11 - 50% and 51 - 100%. Each level of tumor volume was correlated with IPI score.

Results

One hundred seventeen patients with DLBCL met eligible criteria. Five cases were excluded because associated small B cell NHL (N = 1) and no paraffin blocks/slides (N = 4). The 111 cases of BM staging and 6 cases of primary diagnosed DLBCL from BM with corresponding demographic data (Table 1) have similar features in both group by age, gender, tumor location, LDH, and ECOG with difference in Ann Arbor staging and IPI score

Table 1 Demographic data of patients in staging groups and primary diagnosis

Factors	Staging (N = 111)	Primary diagnosis (N = 6)	p-value
Age Median (+/- SD)	60.0 (+/- 16.3)	59.7 (+/-19.0)	0.962
Gender			0.541
Female	45	2	
Male	66	4	
Tumor location			0.076
Nodal	40	0	
Extranodal	71	6	
Ann Arbor staging			0.007
I - II	64	0	
III - IV	47	6	

Table 1 Demographic data of patients in staging groups and primary diagnosis

Factors	Staging (N = 111)	Primary diagnosis (N = 6)	p-value
Serum LDH			0.808
Normal	4	0	
High	107	6	
ECOG			0.531
0 - 1	70	3	
2 - 4	31	2	
No data*	10	1	
IPI			0.008
Low-intermediate (2)	38	0	
High-intermediate (3)	50	2	
High (4 - 5)	13	4	
No data*	10	0	

LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index

*No data of ECOG in the hospital electronic record

Bone marrow involvement in 18 cases (12 staging and 6 primary diagnosis) with demographic data (Table 2) showed age > 60 years (61.1%), male:female 1:1, extranodal involvement more than 1 site 16.6%, high LDH 100%, ECOG performance status 2 - 4 47.1%, IPI high 55.6%. The most common primary sites of DLBCL with BMI positive was lymph node. Abnormal CBC were anemia 50%, low absolute neutrophil count 16.7%, thrombocytopenia 44.4%, and cytopenia 66.6%. BM length ranged from 0.3 to 2 cm with median of 1.0 cm; only one specimen (5.5%) measuring ≥ 1.6 cm.

Table 2 Demographic data of patient with BMI positive (N = 18)

Factors	Number	Percentage
Age (> 60 year)	11	61.1
Gender		
Female	9	50
Male	9	50
Extranodal involvement > 1 site	3	16.6
High LDH	18	100
ECOG 2-4	8	47.1
IPI		
Low-intermediate	1	5.5
High-intermediate	7	38.9
High	10	55.6
Anemia	9	50
ANC < 500/mm^3	3	16.7
Thrombocytopenia Plt < 140,000/uL	8	44.4
Cytopenia	12	66.6

LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; Hb, hemoglobin; Absolute neutrophil count, ANC; Plt, platelet

* No data of ECOG in the hospital electronic record

Morphology review of 111 BM staging cases detected 10 H&E positive, 5 H&E suspicious, and 96 H&E negative. In suspicious group, there were small lymphoid aggregate (N = 1), increased small lymphocytes (N = 1), medium to large cells (N = 2) and extensive necrosis (N = 1). CD20 IHC detected large atypical lymphoid cells in 12 cases, thus the prevalence of BMI positive in DLBCL staging is 10.8% (Figure 1).

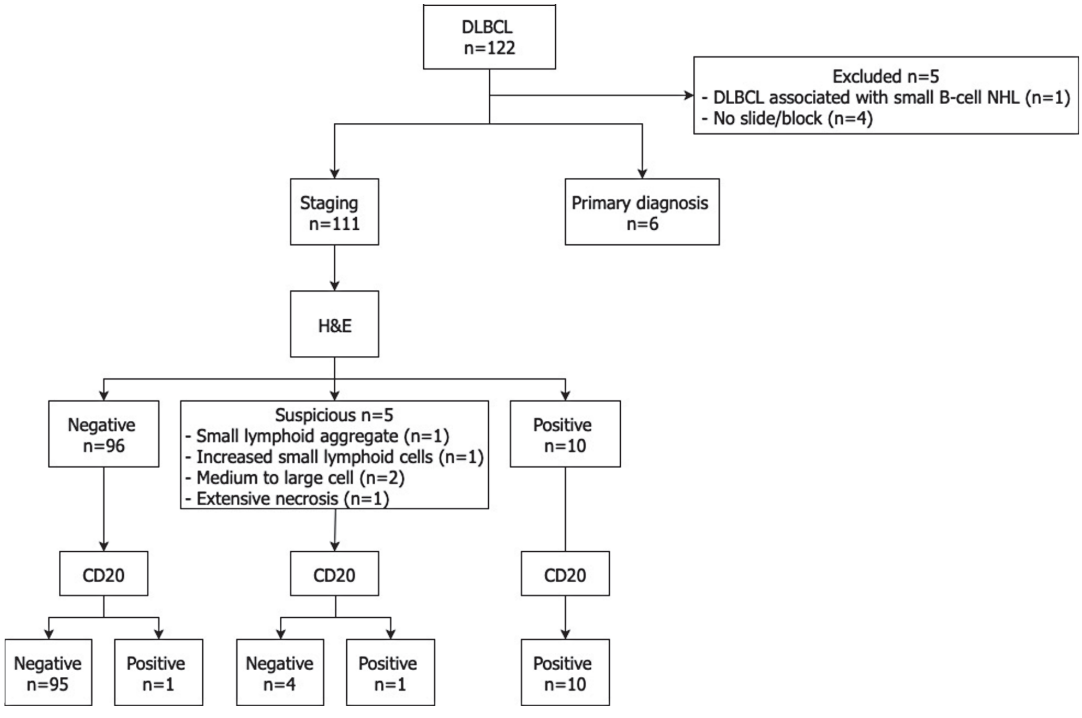

Figure 1 Study flow diagram

Comparing morphology and CD20 in detection yield of BMI (Table 3) revealed 1) all 10 cases of H&E positive (Figure 1A) were also positive in CD20 IHC (Figure 2B), 2) 1 case of H&E suspicious (Figure 2C) initially grouped as BMI negative with extensive necrosis was positive for CD20 IHC (Figure 2D), 3) 1 case of H&E negative (Figure 2E) was positive in CD20 IHC (BMI positive) in less than 1% of total nucleated cells (Figure 2F). Thus, there were 10 true positive cases, 99 true negative cases, 2 false negative cases and no false positive case. The diagnostic accuracy indexes of morphology by H&E in BMI detection were sensitivity 83.3%, specificity 100%, PPV 100%, NPV 98.0% and ROC area 92%. The patterns of BMI by CD20 were 7 diffuse, 6 interstitial, 2 focal nodular and 2 mixed (Table 4).

Table 3 Diagnostic accuracy of morphology by H&E for BMI detection compare to CD20 immumohistochemistry

CD20	H&E		Total
	BMI positive	BMI negative	
CD20-positive	10	2	12
CD20-negative	0	99	99
Total	10	101	111

Prevalence of bone marrow involvement = 10.8%

Sensitivity = 83.3%

Specificity = 100.0%

ROC area = 92%

Positive predictive value = 100%

Negative predictive value = 98.0%

Table 4 Correlation of International Prognostic Index (IPI) with tumor volume (%) and pattern

Case ID	IPI	Tumor volume (%)		Pattern	
		H&E	CD20	H&E	CD20
1	High	75	80	1	4
2	High	23	25	4	4
3	High	10	5	3	6
5	High-intermediate	5	4	4	6
6	High-intermediate	90	90	4	4
7	High	90	90	4	4
52	High	1	5	3	3
64	High-intermediate	Extensive necrosis	Extensive necrosis	Extensive necrosis	Extensive necrosis
67	High	3	3	3	3
71	High-intermediate	3	3	6	3
83	Low-intermediate	0	1	0	3
86	High-intermediate	35	30	4	4
96	High	5	2	1	3
98	High-intermediate	12	15	1	1
99	High-intermediate	8	2	1	3
105	High	95	95	4	4
113	High	6	11	1	1
116	High	3	15	6	4

Pattern 1 focal nodular, 2 paratrabecular, 3 interstitial, 4 diffuse, 5 intrasinusoidal and 6 mixed

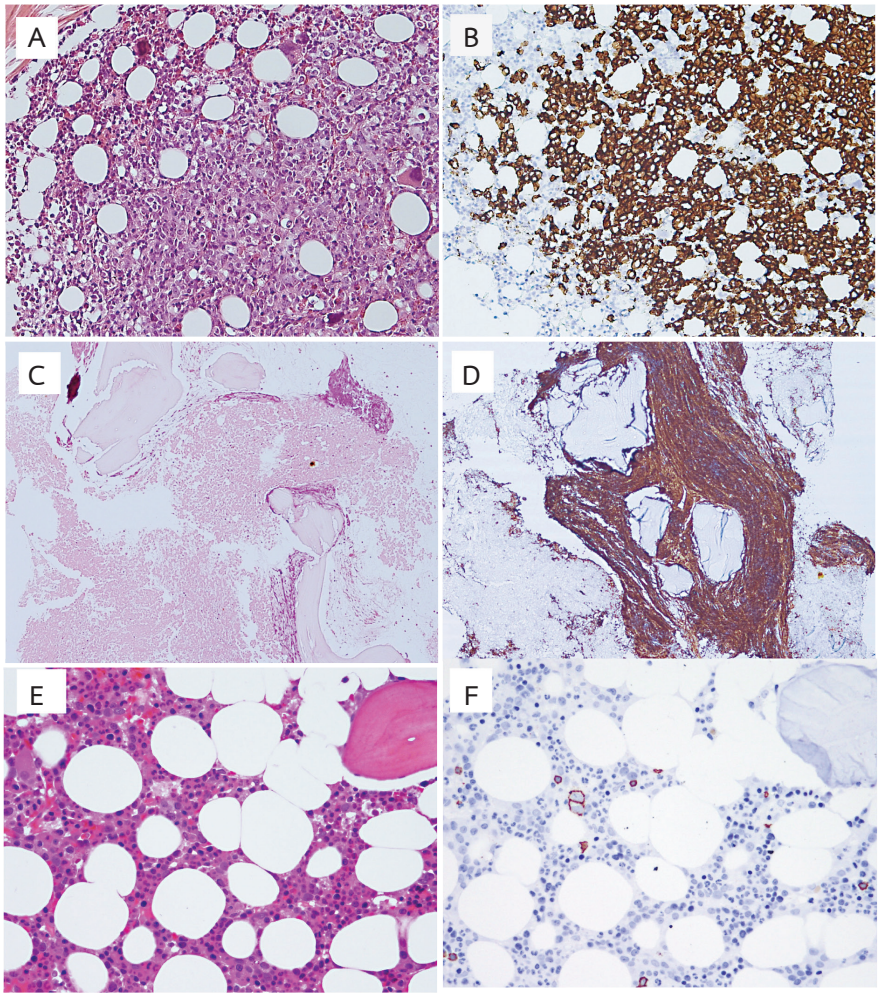

Figure 2 Three bone marrow cases with BMI positive. Case ID 86 (A) tumor volume by morphology 35% (H&E x 200) and (B) by immunohistochemistry 30% (CD20 x 200). Case ID 64 (C) extensive tumor necrosis (H&E x 40) and (D) CD20 IHC positive (CD20 x 40). Case ID 83 bone marrow biopsy (E) H&E negative (H&E x 400) but (F) CD20 positive for two large atypical lymphoid cells (CD20 x 400)

Correlating tumor volume to IPI-high score could be done in 17 from 18 cases. One case had extensive necrosis limiting evaluation of tumor volume and pattern. The correlation results were 4/8 cases with tumor volume 1 - 10% had IPI high (50%); 3/5 cases with tumor volume 11 - 50% (60%) had IPI high; and 3/4 cases (75%) with tumor volume 51 - 100% had IPI high (Tab. 5).

Table 5 Comparison tumor volume with high International Prognostic Index (IPI-high)

Tumor volume (%)	N (cases)	IPI-High %
1 - 10	8	4/8 (50%)
11 - 50	5	3/5 (60%)
51 - 100	4	¾ (75%)

Comparing prognosis assessment of the two false negative cases, by BMI as negative vs. BMI as negative are demonstrated. Case ID 64 with extensive necrosis was a 53 year-old tumor location at axillary soft tissue (extranodal site), multiple extranodal involvements (pleura, liver, peritoneum, and paravertebral soft tissue = stage IV), high LDH, ECOG 1; IPI score as age adjusted - false negative BMI by LDH (1) + ECOG (0) + stage (1) = 2 (high intermediate) vs. IPI score as age adjusted - positive BMI by LDH (1) + ECOG (0) + stage (1) = 2 (high intermediate); thus no difference in IPI score. Case ID 83 with 1% tumor volume was a 70 year-old tumor at lymph node, high LDH, stage I, no extranodal involvement, ECOG 1 thus IPI score - false negative as age (1) + LDH (1) + ECOG (0) + stage (0) + extranodal involvement (0) = 2 (low intermediate) vs. IPI - positive BMI by as age (1) + LDH (1) + ECOG (0) + stage (1) + extranodal involvement (0) = 3 (high intermediate); increased IPI risk from low-intermediate to high intermediate.

Discussion

The patients from staging (N = 111) and primary diagnosis (N = 6) were mostly elderly, slightly male predominant, more of extranodal primary site, stage I-II, high LDH and IPI high intermediate. The primary diagnosis group had more advanced stage (p-value 0.007) and higher IPI score (p-value 0.008).

The prevalence of BMI of DLBCL in Thammasat university hospital is 10.8%, which is slightly lower than previous studies, Thailand 12.7%[6] and worldwide 11%[4] - 25%[5], done at the larger hospitals and some used molecular technique to detect tumor cells.

The detection yield of BMI based on H&E by hematopathologist comparing to CD20 IHC is reliable (sensitivity 83.3%, specificity 100%, PPV 100%, NPV 98.0% and ROC area 92%). The ROC area 90% - 100% indicates excellent discrimination between positive and negative cases.[12] It maybe unnecessary to stain CD20 IHC in all cases upfront. However, there were 2 false negative cases by H&E (one as extensive necrosis and one case with 1% tumor volume). CD20 IHC should be considered in cases with 1) subtle interstitial involvement or occult involvement, 2) intravascular or intrasinusoidal pattern of involvement, 3) accompanying hemophagocytic syndrome, 4) T-cell/histiocyte-rich large B-cell lymphoma, 5) presence of large cells of undetermined lineage and 6) discordant morphology of the lymphomatous cells between nodal/extranodal extramedullary site and marrow.

The false negative BMI in two cases resulting in one patient with low tumor volume with change of IPI risk group from low intermediate to high mediate. Although treatment regimen is not different between IPI risk group but number of cycle may increase from 3 in stage I-II to 6-8 cycles in stage III-IV.[13] The prognosis of patient with DLBCL having BMI tumor volume less than 10% showed progressive free survival and overall survival near DLBCL patients without BMI. The BMI positive more than 50% had 5 years overall survival (OS) 30% and progression free survival (PFS) 15% but the BMI positive less than 50% had 5 years OS 45% and PFS 30%.[14]

An attempt to correlate tumor volume to IPI score, showed an increment trend, as patients with higher tumor volume tend to have more IPI-high. Since the IPI-high indicates poor clinical outcome, therefore, reporting tumor volume in all BMI cases could be helpful prognosis assessment.

Prevalence of BMI positive in staging DLBCL at Thammasat university is slightly lower than previous reports. Detection yield of BMI by H&E is reliable, thus CD20 IHC staining upfront may not be necessary in all cases. The BMI positive patients with increasing marrow tumor volume tend to have IPI-high score, therefore reporting tumor volume may have prognostic value.

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บทคัดย่อ

การตรวจชิ้นเนื้อไขกระดูกในผู้ป่วย Diffuse large B-cell lymphoma: ความชุกและลักษณะทางจุลพยาธิวิทยา

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บทนำ: ผู้ป่วย Diffuse large B-cell lymphoma (DLBCL) ที่มีรอยโรคที่ไขกระดูกมีการพยากรณ์ โรคที่ไม่ดี การประเมิน DLBCL ในไขกระดูกได้จากการดู morphology ในชิ้นเนื้อย้อมด้วย Hematoxilin & Eosin (H&E) และ/หรือ CD20 Immunohistochemistry (IHC) การศึกษานี้ มีวัตถุประสงค์เพื่อศึกษา 1) อัตราการพบ DLBCL ในไขกระดูกที่ รพ.ธรรมศาสตร์ 2) เปรียบเทียบความสามารถในการตรวจพบเซลล์มะเร็งในไขกระดูก (bone marrow involvement, BMI) ระหว่าง morphology (H&E) และ CD20 และ 3) แนวโน้มของปริมาณเซลล์มะเร็ง (tumor cell volume) ในไขกระดูกกับ International Prognostic index (IPI)

วิธีการศึกษา: การศึกษาย้อนหลังในผู้ป่วย diffuse large B-cell lymphoma 117 ราย ได้รับการวินิจฉัยจากโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ ระหว่างวันที่ 1 มกราคม 2555 ถึง 31 ธันวาคม 2559 และ

ผลการศึกษา: 1) อัตราการพบ DLBCL ในไขกระดูก 12/111 ราย (10.8%) ในกลุ่ม staging และ 6 รายในกลุ่มผู้ป่วยที่ วินิจฉัยครั้งแรกในไขกระดูก 2) ความสามารถในการตรวจพบ BMI ระหว่าง morphology (H&E) เปรียบเทียบกับ CD20 มี sensitivity 83.3%, specificity 100%, positive predictive value 100%, negative predictive value 98% และ receiver operating curve (ROC) area 92% 3) แนวโน้มของปริมาณเซลล์มะเร็งเทียบกับ IPI พบ 4/8 ราย (50%) ที่ tumor volume 1 - 10% พบ IPI-high, 3/5 ราย (60%) ที่ tumor volume 11 - 50% พบ IPI-high และ 3/4 ราย (75%) ที่ tumor volume > 50% พบ IPI-high.

สรุปผลการศึกษา: ผู้ป่วย DLBCL ที่กระจายไปไขกระดูกในโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติมี อัตราต่ำกว่ารายงานก่อนหน้านี้ Morphology (H&E) มีความน่าเชื่อถือสูงในการประเมินเซลล์มะเร็งในไขกระดูกใน จึงอาจไม่จำเป็นต้องย้อม CD20 ในผู้ป่วยทุกราย ผู้ป่วยที่มีปริมาณเซลล์มะเร็งในไขกระดูกสูงมีแนวโน้มที่จะมีคะแนน IPI-high

คำสำคัญ: รอยโรคในไขกระดูก, รอยโรค diffuse large B-cell lymphoma, ชิ้นเนื้อไขกระดูก