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Original Article

Clinicopathological features and prognosis of primary thyroid lymphoma: a retrospective study of 49 cases

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Abstract: Primary thyroid lymphoma (PTL) is a rare disease, accounting for approximately 2%-5% of all thyroid malignancies, 1%-2.5% of all malignant lymphomas, 1%-2% of all extranodal malignant lymphomas. Rapidly enlarging mass in the neck, hoarseness and dyspnoea is the most common present. B symptoms, such as fever, night sweats or weight loss are uncommon and often carrying a worse prognosis. The purpose of this study was to evaluate clinicopathological characteristics, therapy strategy and outcome of PTL patients. And the results of this study could have various therapeutic implications. 49 patients with stage IE and IIE and diagnosed with diffuse large B cell lymphoma (DLBCL), mucosa-associated lymphoid tissue lymphoma (MALT) or MIX (coexistence of DLBCL and MALT) type were include in this study. Our multivariate analysis of data from patients identified the following independent prognostic factors: stage, pathology, unilateral or bilatera for OS, stage, B symptom for PFS. The surgery may be suitable for early stage indolent patients. Limited to the small number of cases, we can not clearly identify the preponderance of combined method therapy (CMT) in aggressive patients. While we observed a very poor prognosis of aggressive patients who underwent surgery alone which suggested that surgery is insufficient and CMT may be a suitable choice.

Keywords: Primary thyroid lymphoma, clinical features, surgery, combined method therapy

Introduction

Primary thyroid lymphoma (PTL) is a rare disease, accounting for approximately 2%-5% of all thyroid malignancies, 1%-2.5% of all malignant lymphomas, 1%-2% of all extranodal malignant lymphomas [1-3]. With an estimated annual incidence of two cases per million, it is almost B-cell origin, which mainly include diffuse large B cell lymphoma (DLBCL), mucosa-associated lymphoid tissue lymphoma (MALT) (representing 50-70% and 15-30% of all primary non-Hodgkin PTL, respectively), and coexistence of DLBCL and MALT (MIX). Follicular lymphoma and classical Hodgkin lymphoma have rarely been reported. T-cell origin are hardly seen and may predict a poor prognosis. Rapidly enlarged mass in the neck, hoarseness and dyspnoeaare the most common present. B symptoms, such as fever, night sweats or weight loss are very rare and often indicate a poor prognosis [4]. The developing of MALT is regarded as a result of chronic inflammation and lymphoplasmacytic infiltration in Hashimoto's thyroiditis, which may occur in 90% patients of MALT [5]. Patients with a 20-30 years Hashimoto's disease history performe 40-80 times greater risk than normal people [6]. The histological characteristics of MIX provide evidence of the theory of transformation from MALT to DLBCL [6]. And because of the background of thyroiditis, PTL occurs more often in female than male with a ratio of 2-14:1 [7].

The therapy strategy of PTL still remains controversial in some region. Due to the difficulty of diagnosis, surgery with supplement of radiotherapy (RT) if resection was incomplete was considered as the first choice of PTL in the past 20 years [8]. Since the using of fine needle aspiration biopsy (FNAB) with immunophenotypic analysis has been accuracy [9], and the introduction of effective chemotherapeutic regi-

Table 1. Patient characteristics in primary thyroid lymphoma

Clinical features	Number (%)
Gender	
Female	30 (61.20)
Male	19 (38.80)
Clinical stage	
I	27 (55.10)
II	22 (44.90)
Age	
<60	20 (40.80)
≥60	29 (59.20)
Rapid thyroid mass enlargement	
Absent	39 (79.6)
Present	10 (20.40)
Diagnosis by pathological review	
DLBCL	25 (51.00)
MIX	4 (8.2)
MALT	20 (40.80)
Aerodigestive tract compression	
Absent	33 (67.30)
Present	16 (32.70)
B symptom	
Absent	48 (98.00)
Present	1 (2.00)
Thyroidist	
Absent	27 (55.10)
Present	22 (44.90)

DLBCL (diffuse large B cell lymphoma), MALT (mucosa-associated lymphoid tissue lymphoma), MIX (coexistence of DLBCL and MALT).

mens become widely accepted. RT alone or combined with chemotherapy (CT) were initial to be applied to malignant lymphomas without a diagnostic surgery. RT was recommended to local indolent cases and combined modality therapy (CMT) for aggressive PTL lymphomas. And now, a recent study from Rare Cancer Network focused on the treatment of PTL which recommended CMT for aggressive PTL, and suggested that the using of rituximab, advanced RT for high risk cases and limited using of surgery will improve the disease free survival (DFS). While the value of CMT for indolent cases are still uncertain.

The purpose of this study was to evaluate clinicopathological characteristics, as well as therapy strategy and outcome of PTL patients. The results of this study could have various therapeutic implications.

Materials and methods

Clinicopathological data

A total of 62 patients were underwent primary treatment for PTL in our hospital between January 2001 and January 2016. Of the 62 patients, only patient with stage IE and IIE and diagnosed with DLBCL, MALT or MIX type were include in this study. Thus, 49 patients with PTL were included.

Follow-up data information about the PTL patients enrolled was obtained by review of the patients' hospital records, the progression free survival (PFS) and overall survival (OS), defined as the time relapsed from diagnosis to the first progression or recurrence, and death from the disease respectively.

The diagnosis of PTL and evaluation of pathologic parameters were performed by two pathologists (specializing in thyroid lymphoma) who were blinded to the clinical characteristics of the patients. In this work, the pathology diagnosed of PTL was based on the WHO classification [10], and the immunohistochemical markers CD3, CD5, CD10, CD19, CD20, CD45, bcl-2, bcl-6, c-myc, Ki67 and cyclinD1 were used to further diagnosis of PTL when required. Besides, the patients with other types of malignancy were not enrolled in our study. Of all the patients, histopathological diagnosis was made by the total thyroidectomy, partial thyroidectomy, unilateral lobectomy or local mass resection in 46 patients, 2 were diagnosed by FNA, and only one patient underwent core needle biopsy. According to the Ann Arbor Classification [11], patients with localized involvement of the thyroid alone are defined as stage IE (n = 27), whereas patients with the thyroid gland involvement and associated regional lymph node involvement are defined as stage IIE (n = 22). The clinical stage was evaluated by computed tomography (n = 48), ultrasonography (n = 42), and bone marrow aspiration and biopsy (n = 7). Their medical, radiological and pathological reports were reviewed subsequently.

Statistical analysis

The basic characteristics of patients with aggressive and indolent lymphomas were compared by using Fisher's exact test. Survival curves were obtained by the Kaplan-Meier method. Cox's proportional hazards regression

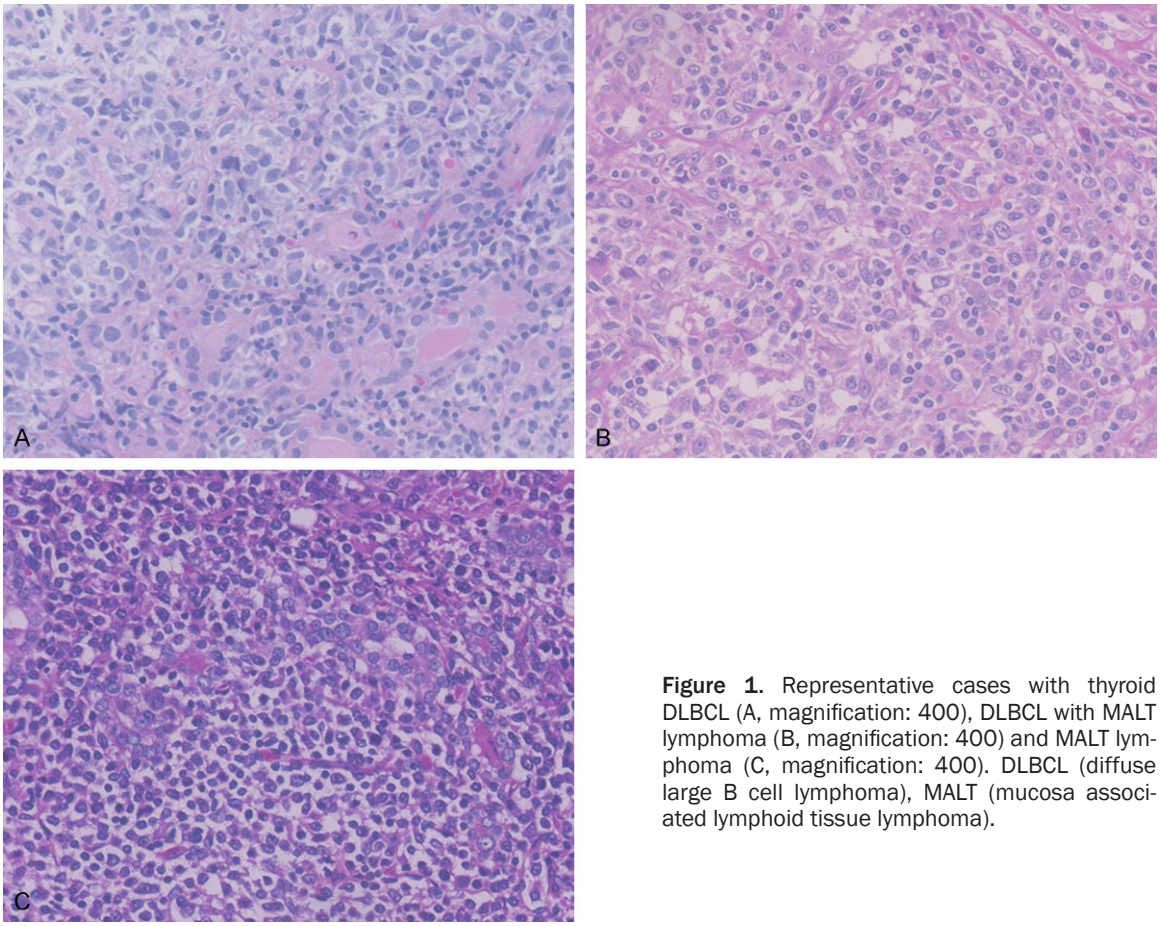

Figure 1. Representative cases with thyroid DLBCL (A, magnification: 400), DLBCL with MALT lymphoma (B, magnification: 400) and MALT lymphoma (C, magnification: 400). DLBCL (diffuse large B cell lymphoma), MALT (mucosa associated lymphoid tissue lymphoma).

models were using to evaluate the associations between treatment outcomes and potential prognostic factors that found to be significant by univariate analysis and were considered statistically significant when *P* values <0.05.

Results

Clinical features

Of all the patients, there were 30 female and 19 male (female: male = 1.5:1). The median age was 62 years with range of 23 to 81 year old. All of them were Chinese. The most common presenting feature was a enlarging, painless thyroid mass in 47 patients (96%) and compressive symptoms, beside dyspnea and dysphagia were rare (33%). 1 (2%) patients went to see a doctor because they feel uncomfortable in their neck without any other special symptom. 1 (2%) were diagnosed just because of thyroid nodule detected by medical examination. Only 1 (2%) patients got B symptoms. Thyroiditis were founded in 27 (55.1%) patients and rapid thyroid mass enlargement were seen in 10 patents (20%). Patient characteristics were shown on **Table 1**.

Histology characteristics

Diffuse Large B Cell Lymphoma (DLBCL) was diagnosed in 25 patients, MALT with DLBCL (MIX) in 4 patients and mucosa-associated lymphoid tissue (MALT) in 20 patients. **Figure 1** has showed the histological images of three representing cases in HE staining. Clinical and pathologic characteristics of patients with aggressive and indolent lymphomas have summarized in **Table 2**.

Treatment selection

The treatment methods of PTL include single therapy (no therapy after surgery, radiotherapy alone and chemotherapy alone), surgery followed by CT or RT alone and combined (combination treatment with chemotherapy and radiotherapy) methods. The choose of therapy

Table 2. Clinical and pathology characteristics of patients with aggressive and indolent lymphomas

		Indolent lymphoma	Aggressive lymphoma	*P* value
Treatment	Surgery	19	27	
	No surgery	1	2	
Stage	I	15	12	0.02
	II	5	17	
Tumor size (cm)	<5	14	22	0.22
	5-10	6	3	
	>10	0	4	
Age	<60	11	9	0.08
	≥60	9	20	
Gender	Male	12	11	0.56
	Female	8	18	
Rapid mass enlargement	Absent	17	22	0.34
	Present	3	7	
Compressive symptom	Absent	16	18	0.21
	Present	4	11	
B symptom	Absent	20	28	0.59
	Present	0	1	
Thyroiditis	Absent	10	17	0.38
	Present	10	12	
Rise-Lactate dehydrogenase	Absent	17	17	0.04
	Present	3	12	
Unilateral or bilatera	Unilateral	15	23	0.49
	Bilatera	5	6	

strategy is based on histology, stage, patient co-morbidities, performance status and patients' willing. And in this study, surgery was regarded as a based diagnosed method and a treatment selection for those patients with indolent local disease or a method to relieve the compressive symptoms or just refused to accept CT or RT. Surgery followed by CT or RT were performed in 22 and 7 patients respectively. The CMT were given to 3 stage I and 2 stage II patients. The summary of treatment method was shown on **Figure 2**.

Nearly all of the patients were underwent surgery treatment except three patients who diagnosed by FNA and core needle biopsy. One patient diagnosed by FNA with dysphagia got the CMT indications but only accepted CT therapy and still alive with OS of 51 months. Another patient underwent the CMT therapy and was still alive. The patient diagnosed by core needle biopsy refused to accept any possible therapy and died in 20 months.

Treatment outcome and prognosis factor

A total of 36 patients (73%) were still alive at last follow-up. The median survival time was 30.3 months (range 2-129). Surgery followed by CT was performed to 22 patients with a median survival of 55 months (range 4-129). RT followed Surgery was given to 7 patients with a median survival of 18 months (range 6-87). A total of 13 patients with surgery didn't accept the further treatment. 7 of them were because of their early stage, low-grade malignancy and the well response after surgery. 5 patients refused to accepted RT or CT after surgery and all of them underwent relapse. The last patient diagnosed with DLBCL died soon after accepted surgery. Of all the 5 patients who underwent CMT, 4 of them were still alive and 3 got 5-year survival. The last patient who was 77 year old died in 31 months after accepted first therapy. Their clinical features were listed on **Table 3**.

The prognostic factors in whole group, indolent and aggressive lymphomas for OS and PFS on univariate analysis of prognostic factors in analyses were summarized in **Table 4**. On multivariate analysis, stage (P = 0.05), unilateral or bilatera (P = 0.03) were the independent factors in whole group's overall survival. When considering the PFS independent factors, compressive symptoms (P = 0.04) were achieve the level of significance.

Discussion

PTL is a rare disease, published data often limited to the small number. It is commonly affects middle to older-aged females [12]. 5-year survival rate of PTL was approximate 71%-75% in aggressive patients and 96%-100% in indolent patients [5, 13]. Similar to the pathogenesis of

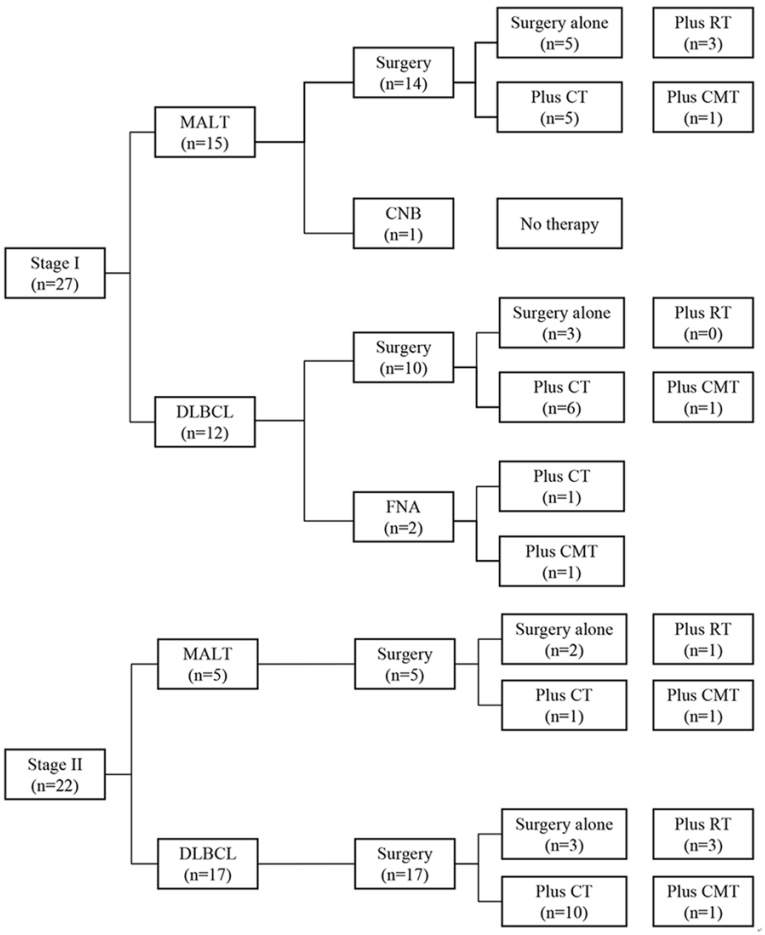

Figure 2. The summary of treatment method according to stage classification. DLBCL (diffuse large B cell lymphoma), MALT (mucosa associated lymphoid tissue lymphoma), FNA (fine-needle aspiration), CNB (core-needle biopsy), CT (chemotherapy), RT (radiotherapy), CMT (combined method therapy).

other primary extranodal NHL, the prolonged antigenic stimulation evidence suggested that autoimmune thyroiditis may lead to malignancy transformation [14]. A study from Japan [15] suggested that the background of Hashimoto's disease in old patients may have a higher risk of lymphoma, and it was inconsistent with Shigemasa et al. [16] and Kon & DeGroot et al. [17]. In our study, 27 of 49 presented thyroidist (55.1%), which seems to be lower than the report from Natsuko Watanabe et al. (90%) and Amanda Graff-Baker et al. (100%) [18]. The former explained the relationship between Hashimoto's and PTL and confirmed that the chronic thyroidist would progress to MALT lymphoma in some conditions. People with Hashimoto's thyroiditis are in the position of higher risk of PTL, especially at the median time with 18 months after diagnosed. Another study also suggested that patients with Hashimoto's thyroiditis have increased 67- to 80-fold risk of developing PTL [5]. While the evaluation from Hashimoto's thyroiditis to PTL was only observed in 0.5% patients [19].

Traditionally, surgery is the first choice for diagnosis and treatment of PTL patients. However, with advances of diagnose method, especially the development of immunophenotypic analysis, the accuracy of FNA has significantly improved to 80%-100% [20, 21]. Perhaps, in our cases, four patients underwent the FNA, but two of them only revealed the possible of malignancy and required core needle or surgery to make further diagnosis. The other two patients diagnosed with FNA is also confirmed by immunohistochemistry. This result is similar to Sarinah B [22], which reported a rate of 33% diagnosis with FNA without immunohistochemistry. Actually, due to the similar histological finding between thyroiditis and MALT and the exist of MIX type, the diagnosis depend on FNA is still remain problems in false-negative rates or false-lower classification from sampling error. Thus, surgery is still a better choice if necessary.

Previous studies confirmed the value of RT therapy in OS of localized, indolent diseases [23, 24]. However, some cases performed surgery alone also showed a well prognosis. Pyke et al. [23] observed no difference between RT or RT plus surgery, but noticed that 2 patients underwent surgery alone obtained a long disease free survival with a median time of 50.5 months. In the present study, all of MALT patients who underwent surgery alone are still alive with a median OS of 28 months (range 7-78). As is mentioned above, almost patients have underwent surgery, this is similar to the

Table 3. The clinical characteristics and outcome of patients who underwent surgery alone or CMT

Case	Gender	Age	LDH>UNL	Pathology	Thyroiditis	Stage	Compress symptoms	B symptoms	Therapy	OS (months)	Status
1	F	48	No	MALT	Present	I	Dysphagia	Absent	Surgery	28	Alive
2	F	62	No	MALT	Present	I	Absent	Absent	Surgery	70	Alive
3	M	63	No	MALT	Present	I	Absent	Absent	Surgery	7	Alive
4	F	72	No	MALT	Present	I	Absent	Absent	Surgery	26	Alive
5	F	65	No	MALT	Present	I	Dyspnoea	Absent	Surgery	73	Alive
6	M	81	Yes	DLBCL	Absent	I	Dysphagia Dyspnoea	Absent	Surgery	2	Death
7	F	71	No	DLBCL	Present	I	Absent	Absent	Surgery	42	Alive
8	F	72	Yes	DLBCL	Present	I	Absent	Absent	Surgery	40	Relapse
9	F	50	Yes	MALT	Absent	II	Absent	Absent	Surgery	35	Alive
10	F	66	No	MALT	Present	II	Absent	Absent	Surgery	19	Alive
11	F	65	Yes	DLBCL	Absent	II	Absent	Absent	Surgery	20	Death
12	F	66	No	DLBCL	Present	II	Dyspnoea	Absent	Surgery	24	Relapse
13	F	74	No	DLBCL	Present	II	Dysphagia Dyspnoea	Absent	Surgery	19	Relapse
14	F	43	No	MALT	Absent	I	Absent	Absent	CMT	105	Alive
15	M	23	Yes	DLBCL	Absent	I	Dyspnoea	Absent	CMT	80	Alive
16	M	52	No	DLBCL	Absent	I	Dyspnoea	Absent	CMT	64	Alive
17	M	77	No	MALT	Absent	II	Absent	Absent	CMT	6	Death
18	M	55	No	DLBCL	Absent	II	Absent	Absent	CMT	5	Alive

F (female), M (male), LDH (lactic dehydrogenase), UNL (upper normal limit), DLBCL (diffuse large B cell lymphoma), MALT (mucosa-associated lymphoid tissue lymphoma), CMT (combined method therapy), OS (overall survival).

Table 4. Prognostic factors in whole group, indolent and aggressive lymphomas for overall survival and disease free survival on univariate analysis by K-M method

	Whole Group		Aggressive lymphoma		Indolent lymphoma	
	OS *P* value	PFS *P* value	OS *P* value	PFS *P* value	OS *P* value	PFS *P* value
Age (<60 versus ≥60)	0.04	0.14	0.35	0.55	0.07	0.35
Stage (I versus II)	0.008	0.02	0.12	0.27	0.34	0.47
Tumor size (<5 versus 5-10 versus >10)	0.005	0.15	0.1	0.46	0.02	0.003
Sex (male versus female)	0.96	0.78	0.28	0.27	0.06	0.02
Rapid mass enlargement (absent versus present)	0.056	0.003	0.29	0.03	0.07	0.16
Compressive symptom (absent versus present)	0.007	0.001	0.02	0.008	0.31	0.07
B symptom (absent versus present)	<0.00001	<0.00001	0.006	0.02	-	-
Thyroiditis (absent versus present)	0.31	0.4	0.99	0.75	0.3	0.12
Indolent versus Aggressive	0.03	0.01	-	-	-	-
LDH	0.01	0.004	0.16	0.19	0.23	0.02
Unilateral or bilateral	0.13	0.43	0.1	0.24	0.63	0.42
Surgery alone versus surgery followed by CT and/or RT	0.565	0.949	0.821	0.17	0.564	0.275

OS (overall survival), PFS (progression free survival), LDH (lactic dehydrogenase), CT (chemotherapy), RT (radiotherapy).

study of Gregory and Harrington [5, 25]. In the study of Gregory, there was no died patient of MALT who underwent surgery alone as well. And we did not observe an obvious difference between surgery alone and surgery plus RT or CT (P = 0.565). These could be contributed to follow reasons: First, nearly all of our patients underwent surgery, the compare between each group were based on this background. And the cases of each group were also inequality. Thus, it is hardly to evaluate the actually effect of CT/RT alone. Second, this study included some newly diagnosed cases which made our median survival time shorter. At last, limited to the

small number, we can not conclude that the plus of CT or RT didn't perform any effect on PTL prognosis, especially in aggressive patients.

Recently, a study from Rare Cancer Network [26] analysed 87 patients of PTL from different countries and pointed out that CMT significantly improved DFS, OS, and LC for aggressive lymphoma and DFS and LC for other types of lymphoma. Other studies [27, 28] also suggested CMT therapy for PTL patients. We are agreed with these studies, because DLBCL always present the propensity for systemic recurrence and aggressive nature. In our study, three aggressive patients with stage II who accepted surgery alone didn't response well, (OS 19-24 months, one was relapse in 4 months with OS of 19 months, one was died with OS of 20 months, the last one was relapse with OS of 24 months). At the same time, five patients who underwent CMT present an excellent outcome. But limited to the small number, the actually effect of CMT can not be well evaluated. CMT may be a suitable therapy selection for aggressive PTL patients.

When considered the prognosis factor of PTL, we found that old age, high stage, huge tumor size, compressive symptom, B symptoms, the pathological type of DLBCL, evaluated LDH often indicated a bad prognosis, which was in agreement with the results from previous studies [12, 29]. Our multivariate analysis of data from patients identified the following independent prognostic factors: stage, pathology, unilateral or bilatera for OS, stage, B symptom for EFS.

Conclusion

In conclusion, we studied the clinical features, therapy strategies as well as pathological characteristics of PTL patients, and focus on the strategies of therapy under the background of surgery. The followed therapies after surgery seem to have no impact on prognosis in indolent cases. In our study, limited to the small case number of patients, we can not evaluate the actually effect of different therapy methods. While we were observed a poor prognosis of patient who underwent surgery alone in DLBCL stage II patients. Previous study focused on the CMT therapy and confirmed the well response in using CMT, especially for aggressive lymphoma. Therefore, CMT may be a suitable choice for these patients.

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Disclosure of conflict of interest

None.

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