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# Clinical and prognostic features of primary retroperitoneal diffuse large B-cell lymphoma: a single-center experience in China

**Xiao-Hong Liu[1], Hui Liu[2], Dong Ke[3], Xiao-Kang Ke[4], Ya-Dan Wang[5]**

[1]Department of Oncology, Wuhan University, Renmin Hospital, Wuhan, Hubei 430060, China;
[2]Department of Hematology, Wuhan University, Renmin Hospital, Wuhan, Hubei 430060, China;
[3]Department of Surgery, Wuhan University, Renmin Hospital, Wuhan, Hubei 430060, China;
[4]Department of Pathology, Wuhan University, Renmin Hospital, Wuhan, Hubei 430060, China;
[5]Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430022, China.

Due to a high degree of heterogeneity, different primary sites of diffuse large B-cell lymphoma (DLBCL) will have different clinical features and prognoses. The Revised European-American Lymphoma (REAL) classification emphasizes that knowledge of the primary site of the process is of high diagnostic value for unusual tumors. Diffuse large B-cell lymphoma primarily located in the retroperitoneum (PRLBCL) has been the subject of occasional reports.[1,2] The retroperitoneal space is large, embedded in a meshwork of loose connective tissue, allowing both primary and metastatic tumors to grow silently before clinical symptoms appear, therefore tumors in the retroperitoneum are often bulky. It is difficult to distinguish them from retroperitoneal lymphoma, and solid tumors such as gastrointestinal stromal ones and neurofibromas.[3] This study retrospectively analyzed PRLBCLs in our hospital to better understand this disease and summarize our experience.

Twenty patients with PRLBCL were admitted to Renmin Hospital of Wuhan University between January 2014 and September 2019, excluding patients with retroperitoneal lymph node involvement, secondary to malignant lymphoma. Clinical information of the patients included age, sex, staging, presence of symptoms, imaging, bulky mass size, pathological biopsy, lactate dehydrogenase (LDH) levels, hepatitis, treatment, and outcomes.

Pathological biopsy and immunohistochemistry confirmed the diagnosis. Based on the expression of CD10, MUM-1, and BCL-6 according to Han's classification, patients were classified as germinal center B cell (GCB) and non-germinal center B cell (n-GCB); double expression (DE) was defined as ≥40% MYC and ≥50% Bcl-2 expression. The National Comprehensive Cancer Network-International Prognostic Index (NCCN-IPI) was used to assess the risk of DLBCL.

Staging and response criteria were recommended by the Lugano classification in 2014;[4] staging included limited (stage I, II, II with bulky mass), and advanced (stage III or IV) diseases. Responses were classified as complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). Progression-free survival (PFS) was calculated from the date of diagnosis to the date of disease progression. The overall survival (OS) rate was measured from the time of diagnosis to the time of death or the last follow-up.

Between-group comparisons were performed using the chi-square and Fisher exact tests; the Kaplan–Meier method was used for survival analysis and the log-rank test was used for univariate analysis. All analyses were performed using IBM Statistics (version 25.0; SPSS Inc., Chicago, IL, USA).

The male-to-female ratio of patients with PRLBCL in our study was 1.86:1. The median age of all patients was 60 years (ranging from 26 years to 77 years). Although men were predominant, no gender differences were found between 20 patients with increased LDH levels at first diagnosis (85%), combined with hepatitis B (3.0%); imaging revealed that the maximum diameters of all retroperitoneal masses were > 7.5 cm (the largest mass measured 24.0 cm × 13.3 cm × 18.5 cm). Nine patients (45%) showed acute abdomen and received exploratory laparotomy; the other 11 patients (55%) suffered from

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**Correspondence to:** Prof. Ya-Dan Wang, Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430022, China
E-Mail: zys616@126.com



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chronic abdominal distension and underwent ultrasound-guided puncture biopsy.

In clinical staging, there were seven (35.0%)-stage II, nine (45.0%)-stage III, and four (2.0%)-stage IV patients. Han's classification was as follows: 8 cases (40%) were GCB and 12 cases (60%) were n-GCB. There were 6 cases (30%) with DE and 14 cases (70%) with non-DE. Patients with Ki-67% >60% accounted for the majority (85%). The NCCN-IPI score showed that 13 patients (65%) in the middle- and high-risk groups with a score of 4 or above, and seven patients (35%) in the low- and middle-risk groups with a score of 0–4; PRLBCLs were characterized by a bulky mass and high malignancy [Table 1].

Thirteen (65%) patients underwent radiotherapy (RT) or surgical resection; seven (35%) did not. Twelve patients (60%) were treated with rituximab (R), and eight (40%) were not treated with R; 13 cases (65%) were treated with combined modality therapy (CMT) and seven (35%) were treated with chemotherapy (CT) alone. After the first-line treatment, there were one case of CR, 13 cases of PR, and six cases of PD. The objective response rate (ORR) was statistically significant between patients who received first-line treatment plus RT and those who did not (8/8 *vs.* 6/12, $P = 0.042$). However, 10 patients (50%) received second- or third-line treatments. Treatment regimens and outcomes are presented in Supplementary Table 1, http://links.lww.com/CM9/A526.

The median follow-up time was 30.1 months; median progression-free survival (mPFS) was 24.0 months and the OS was 8–36 months. The 3-year cumulative survival rate was 55.0%. Univariate analysis showed that serum LDH level was a prognostic factor for OS ($\chi^2 = 6.535$, $P = 0.038$). According to Han's typing, patients with GCB had superior OS ($\chi^2 = 4.404$, $P = 0.036$) and PFS ($\chi^2 = 8.447$, $P = 0.004$) than those with nGCB. The effect of LDH level on prognosis has been widely recognized. The effect of Han's typing on prognosis remains to be explored.

**Table 1: Univariate analysis of OS and PFS in 20 patients with PRLBCL.**

| Variable | Value, *n* (%) | mOS (months) | $\chi^2$ | *P* | mPFS (months) | $\chi^2$ | *P* |
|---|---|---|---|---|---|---|---|
| Age | | | | | | | |
| ≤60 years | 11 (55) | – | 0.004 | 0.949 | 14.0 | 0.180 | 0.671 |
| >60 years | 9 (45) | 33.2 | | | 28.0 | | |
| Stage | | | | | | | |
| II | 7 (35) | 33.2 | 1.177 | 0.278 | 28.0 | 0.065 | 0.799 |
| III–IV | 13 (65) | 33.2 | | | 24.0 | | |
| LDH level | | | | | | | |
| Normal | 3 (15) | – | 6.535 | 0.038 | 10.0 | 2.849 | 0.241 |
| 1–3 times | 13 (65) | – | | | – | | |
| >3 times | 4 (20) | 25.1 | | | 8.0 | | |
| NCCN-IPI | | | | | | | |
| 0–3 | 7 (35) | 33.2 | 1.041 | 0.308 | 28.0 | 0.028 | 0.867 |
| ≥4 | 13 (65) | 33.2 | | | 24.0 | | |
| Han's | | | | | | | |
| GCB | 8 (40) | – | 4.404 | 0.036 | – | 8.447 | 0.004 |
| n-GCB | 12 (60) | 33.2 | | | 10.0 | | |
| DE | | | | | | | |
| Yes | 6 (30) | 33.2 | 0.603 | 0.437 | – | 3.172 | 0.075 |
| No | 14 (70) | – | | | 14.1 | | |
| Hepatitis | | | | | | | |
| No | 14 (70) | – | 2.568 | 0.109 | 14.1 | 0.155 | 0.693 |
| HBV | 6 (30) | 33.2 | | | 28.0 | | |
| KI-67, % | | | | | | | |
| ≤60 | 3 (15) | 33.2 | 0.001 | 0.980 | – | 1.187 | 0.276 |
| >60 | 17 (85) | – | | | 23.1 | | |
| RT or resection | | | | | | | |
| Yes | 13 (65) | – | 6.731 | 0.009 | – | 7.114 | 0.008 |
| No | 7 (35) | 33.2 | | | 10.1 | | |
| Rituximab | | | | | | | |
| Yes | 12 (60) | 33.2 | 0.594 | 0.441 | 11.0 | 2.856 | 0.091 |
| No | 8 (40) | – | | | – | | |
| Treatment | | | | | | | |
| CT alone | 7 (35) | 25.1 | 6.333 | 0.012 | 10.0 | 3.416 | 0.065 |
| CMT | 13 (65) | – | | | – | | |

–: Unreached; CMT: Combination therapy; CT: Chemotherapy; DE: Double expression; GCB: Germinal center B cell; LDH: lactate dehydrogenase; mOS: Median overall survival; mPFS: Median progression-free survival; n-GCB: Non-germinal center B cell; NCCN-IPI: National Comprehensive Cancer Network-International Prognostic Index; OS: Overall survival; PFS: Progression-free survival; PRLBCL: Diffuse large B-cell lymphoma primarily located in the retroperitoneum; RT: Radiotherapy.

Among the treatment options, patients who underwent RT or resection had longer OS ($\chi^2 = 6.731$, $P = 0.009$) and PFS ($\chi^2 = 7.114$, $P = 0.008$), and patients treated with CMT were superior to those who received CT alone for OS ($\chi^2 = 6.333$, $P = 0.012$); the rest parameters had no significance for prognosis ($P > 0.05$) [Table 1]. This may be related to the small number of cases and short follow-up time in our study.

Malignant lymphomas primarily arising in the retroperitoneum have rarely been reported in detail; PRLBCL may represent a more heterogeneous group of tumors than previously thought.[2] PRLBCLs do not easily perform lymph node biopsies in the anatomical position. Therefore, minimally invasive methods should be adopted to obtain deep biopsies for pathological diagnosis. In this study, four patients survived after surgical resection; pathological and bulk surrounding tissues were obtained from the five non-resected patients who underwent exploratory laparotomy. For patients with retroperitoneal disorders and abdominal diseases such as intestinal obstruction, exploratory laparotomy, or laparoscopy may be advisable to avoid death due to serious complications. Currently, there is no unified staging model for retroperitoneal lymphoma. Though most retroperitoneal lymphomas on the side of the diaphragm, the mass is bigger, and infiltration of more adjacent organs is observed; therefore, the prognosis for stage II is poor. The Lugano staging classification proposed a stage II mass with a similar prognosis to stages III–IV.[4] Our research revealed that the OS and PFS showed no obvious differences between stages II and III–IV ($P > 0.05$). Therefore, a new staging method that can effectively distinguish prognoses is worth further discussion.

Currently, there is no standard protocol for treating PRLBCL; treatment approaches are based on DLBCL-non-specific guidelines. In the R era, combined CT has significantly improved the OS and PFS. Among our 20 patients, 12 cases (60%) were treated with R, and eight cases (40%) were not treated with R, but there was no statistical significance on OS and PFS. The stratified studies suggest that the improvement of OS under the R-CHOP regimen was mainly observed in the IPI low-risk group; using R before salvage treatment suggests a poor prognostic factor. In our study, 13 patients (65.0%) were in the high-risk group. After the first-line treatment, they were found to have a higher PR. By the end of the last follow-up, patients mainly responded to PR (60%); CR was difficult to achieve. There were six deaths (30%) and the 3-year cumulative survival rate was 55.0%. At present, the efficiency of salvage treatment is poor in relapsed/refractory DLBCL. Our study suggests that the response rate to second-line treatment was similar. In our cases, one patient progressed, then received chimeric antigen receptor T-cell immunotherapy (CART) cell therapy, has lived for 32 months and is still undergoing maintenance treatment. Another was treated with PD-1 inhibitors; however, their efficacy was poor and he died. At present, there is a lack of prospective studies on new treatment options.

Surgical resection at the initial diagnosis was significant to OS. Prompt treatment of the intestinal obstruction caused by the bulky mass was effective. Bulky tumors treated with RT or resection obviously shrunk and patients had longer OS. A retrospective study by Tokola *et al*[5] has suggested that RT was effective for the treatment of positive areas of positron emission tomography (PET) metabolic activity in relapsed DLBCLs with bulky masses and residual tumors. Contrariwise, CT alone caused the mass to retreat slowly. The combination of RT or surgical resection for acute abdomen was beneficial for the prognosis of PRLBCLs. However, it is worth emphasizing that surgical resection is generally not recommended for confirmed patients without acute abdomen.

In summary, the 20 cases with PRLBCL showed heterogeneity in terms of characteristics, treatment, and outcome; PRLBCLs should be detected and diagnosed early, to avoid life-threatening situations caused by mass compression or invasion. When there is no obvious regression of masses after CT, other treatment approaches, such as RT, immunotherapy, CART, and new drugs, could be considered to extend the OS. It is necessary to stimulate international cooperation to collect a larger series of patients in the future.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s)/or his/her guardian has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients or his/her guardian understand that his/her/their name(s) and initials will not be published and due efforts will be made to conceal his/her/their identity, but anonymity cannot be guaranteed.

### Conflicts of interest

None.

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