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Original Article

Lymphoma of the female genital tract: a clinicopatholngical analysis of 25 cases

Jingping Wang[1], Linggong Zeng[1], Shoukang Chen[2], Qiong Wu[1], Li Ma[1], Shiwu Wu[1], Z Peter Wang[3,4], Yisheng Tao[1], Damin Chai[1]

Departments of [1]Pathology, [2]Radiology, The First Affiliated Hospital of Bengbu Medical University, Bengbu Medical University, Bengbu, Anhui, China; [3]Department of Biochemistry and Molecular Biology, School of Laboratory Medicine, Bengbu Medical College, Bengbu 233030, Anhui, China; [4]Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

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Abstract: Occurrence of lymphoma of the female genital tract (FGT) is extremely rare, and cohort studies on survival rates of affected patients are sparse. The aim of this study was to retrospectively evaluate the clinicopathological characteristics of patients diagnosed with non-Hodgkin lymphoma of the FGT. This study included 25 women diagnosed with lymphoma of the FGT. Their data on presenting pathological subtype, International Federation of Gynecology and Obstetrics (FIGO) and Ann Arbor staging, International Prognostic Index (IPI) score, treatment, and survival time were collected. Among the 25 patients, the most prevalent histological subtype was diffuse large B-cell lymphoma (23/25). Tumors were most commonly located in the ovary (15/25), with the remainder located in the cervix (7/25) and uterine corpus (3/25). 76% of cases by Ann Arbor were stage III or IV, and 70% of cases by FIGO were stage III or IV. The overall median survival from diagnosis of lymphoma was estimated to be 71 months, with 3-year and 5-year survival rates of 92% and 80%, respectively. The FIGO and Ann Arbor staging and IPI score were significantly correlated with overall survival time.

Keywords: Lymphoma, FGT, ann arbor stage, FIGO, survival time

Introduction

Occurrence of non-Hodgkin lymphoma (NHL) in the FGT is extremely rare [1]. The genital tract is the most common site for extranodal lymphoma; other sites that may be affected are salivary gland, orbit and testis. Extranodal NHL involves the gastrointestinal tract and central nervous system under normal conditions, but it is also occasionally identified in the adrenal glands, breast, thyroid, bones, prostate, and FGT with lower rates of occurrence [2-6]. Primary genital tract lymphoma accounts for 0.2%-1.1% of all cases of extra-nodal lymphoma [1].

In the early stages of lymphoma of the genital tract, patients tend to be asymptomatic; by the time patients visit physicians, they develop abdominal symptoms including abnormal vaginal discharge, abnormal vaginal bleeding, bloating, abdominal pressure, and discomfort [7, 8]. Because in the majority of patients, gynecological symptoms are initially observed, they tend to first visit the department of oncology meant for females rather than that of hematology, resulting in most lymphoma of the FGT being initially treated as any other common gynecologic malignancy [1, 8]. The International Federation of Gynecology and Obstetrics (FIGO) staging system is usually used for tumor staging prior to surgery [9]. It is generally difficult to confirm the presence of lymphoma of female genital preoperatively; thus, many cases are diagnosed as lymphoma after tumor debunking is performed [10]. The definitive diagnosis is obtained postoperatively during pathological examination of surgical specimens [4]. However, the staging standard used by most hematologists in extranodal lymphoma cases is the Ann Arbor staging system [11], whereas gynecologists prefer the FIGO staging system. The aim of this study was to compare the FIGO and Ann Arbor staging systems in terms of survival time and to determine the more effective system between them.

We present 25 cases of lymphoma of FGT in which diagnosis was confirmed using immunohistochemical analysis. The histological classification of all species was based on World Health Organization (WHO) standards [12], whereas staging was in accordance with the Ann Arbor and FIGO staging systems [11, 13-17]. Diffuse large B-cell lymphoma (DLBCL), the most common histological classification of lymphoma of female tract, has a number of distinctive pathological features, with poor prognosis and preferential dissemination in the central nervous system [18, 19]. Nasioudis *et al.* performed a large multi-institutional study including 697 cases in their cohort and clarified clinicopathological characteristics, demographics, and survival rates for primary lymphoma of FGT [10]. We believe that the present study, as a representative sample from eastern China, can remedy deficiencies in staging, clinical pathology, and imaging. In addition, we determined the correlation between the survival time of patients who underwent and those who did not undergo surgery.

Methods

Case selection

A review chart study was retrospectively performed on patients diagnosed with genital tract NHL between January 2008 and January 2013. The information recorded from each patient included information on age, complaints, clinical presentation, pathologic subtype of NHL, International Prognostic Index (IPI) score, surgical technique, chemotherapy regimens, and follow-up of at least 5 years. Cases lacking histological and/or cytological confirmation and those without active follow-up were excluded. Because most patients' initial diagnosis was determined in the gynecological department and was only confirmed as NHL postoperatively, we reclassified their clinical stage lymphoma using the FIGO and Ann Arbor staging systems. The IPI is a standard approach to assess prognosis of patients with lymphoma [20], and we calculated the IPI score based on age, clinical staging, extranodal sites, physical condition, and serum lactate dehydrogenase levels at four levels: low risk (0-1 point), low-intermediate risk (2 points), high-intermediate risk (3 points), and high risk (4-5 points). Overall survival (OS) was calculated as the period between pathological diagnosis and the date of death or last follow-up (months).

We included 25 patients (median age, 60 years; range, 20-77 years) diagnosed with lymphoma of the FGT, as confirmed by immunohistochemical diagnosis of markers such as CD19, CD20, CD79a, vimentin, Bcl-6, and Ki-67 (Supplementary Table 1). All 25 cases were reclassified according to the recent WHO classification [3] on the basis of extensive histopathological investigations by two senior pathology experts and conventionally stained paraffin sections with immunohistochemical analysis. The methods of collection of database information were all in accordance with the guidelines of the Declaration of Helsinki.

Immunohistochemical analysis

Immunohistochemical analysis was performed with the Elivision™ Plus detection kit (Lab Vision, USA) according to the manufacturer's instructions to examine the expression of CD19, CD20, CD79a, vimentin, Bcl-6, and Ki-67 (their concentrations are listed in Supplementary Table 2). Immunohistochemical staining can usually efficiently distinguish lymphoma from endometrial stromal sarcoma, lymphoma-like lesion, carcinoma, carcinosarcoma, melanoma, and primitive neuroectodermal tumor [1].

Evaluation of staining

The staining results were interpreted by two independent pathologists who were blinded to the clinical data and were judged by semi-quantitative points. To overcome the intratumoral heterogeneity of antigen expression, 10 visual fields from different areas of each tumor were examined. In cases of disagreement between the observers, consensus was achieved by re-examining the sections. Staining was scored according to the intensity and extent, ≤3 as negative, >3 as positive. The staining intensity score was graded for four stages as follows: 0, none; 1, weak; 2, moderate; and 3, strong. The extent of positive staining was graded as follows: 1, ≤10%; 2, 11%-50%; 3, 51%-75%; and 4, >75%.

Statistical analysis

To determine median and 3-year OS, the Kaplan-Meier curves were generated and the log-rank test was employed for comparisons between the groups. Statistical analysis was performed with the SPSS (v.24; New York, IBM)

statistical package. Statistical significance was set at $P<0.05$.

Results

Clinicopathological features

In total, 25 women with lymphoma of FGT who met the diagnosis were identified. The primary clinicopathological features of the 25 cases are summarized in Supplementary Table 3. The symptoms include abnormal uterine bleeding, pelvic pain, abdominal distension, and bloating. Among the study patients, the most prevalent histological subtype was DBLCL (23/25), with the remaining one case having small lymphocytic lymphoma (1/25) and another having follicular lymphoma (1/25). Tumors were most commonly located in the ovary (15/25), with the remaining tumors located in the cervix (7/25) and uterine corpus (3/25). According to the Ann Arbor and FIGO staging systems, by Ann Arbor 76% of cases were stage III or IV, and by FIGO 70% of cases were stage III or IV, and the results were confirmed via literature research [10, 21]. The overall median survival time from diagnosis of lymphoma was 71 months (range, 35-96 months), with 3- and 5-year survival of 92% and 80%, respectively. A total of 17 patients underwent total abdominal hysterectomy debulking, and their median survival time was 67 months (range, 35-96 months); the remaining eight patients who did not undergo surgery had a median survival time of 71 months (range, 36-90 months). The Ann Arbor and FIGO staging systems showed statistical significance with respect to OS with P=0.048 and P=0.032 respectively (**Figure 1A**, **1B**). However, surgery was not statistically significant in this cohort (**Figure 1C**). The IPI score evaluating prognosis was statistically significant for lymphoma of FGT as P=0.006 (**Figure 1D**).

Based on physical conditions, family conditions, and expected prognosis, the patients selected different treatment options. A total of 17 patients underwent surgery, with surgeries including total hysterectomy, pelvic and paraaortic lymph node dissection, and omentectomy. Diagnosis of the remaining eight patients was performed using immunohistochemical analysis of biopsy or puncture specimens. NHL is often only diagnosed definitively postoperatively because confirmation requires immunohistochemical analysis, flow cytometry, cytogenetics, and molecular diagnostic evaluation to be performed. Flow cytometry detects monoclonality in B-cells [4, 22]. Immunohistochemical analysis facilitates the determination of whether a tumor is a B-cell lymphoma (CD20+), T-cell lymphoma (CD3+), or carcinoma (keratin+) [23, 24].

Morphological features

Representative micrographs showing lymphoma of FGT using hematoxylin-eosin (HE) stain and immunohistochemical analysis were generated, demonstrating three different subtypes: DBLCL (**Figure 2**), follicular lymphoma (**Figure 3**), and small lymphocytic lymphoma (**Figure 4**).

Treatments and outcomes

Currently, there is no recognized standard treatment for lymphoma of FGT, and treatments for NHL only referring to small-sized samples [25]. Upon confirmed diagnosis of lymphoma of FGT, a standard NHL chemotherapy regimen, such as rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (R-CHOP), is usually administered [26, 27]. Radiation therapy may or may not be administered depending on tumor histological subtype, extent of disease, and patient-related factors [25]. The paradigm of primary surgical debulking is in direct contradiction with the current standard treatment for DLBCL, which is R-CHOP chemotherapy without surgery [26, 28]. The patients in our cohort were administered chemotherapy with different chemotherapeutics: six cycles of R-CHOP; cyclophosphamide, adriamycin, vincristine, and prednisone; rituximab, ifosfamide, carboplatin, etoposide; rituximab, gemcitabine, cisplatin, and dexamethasone; rituximab, bleomycin, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; and paclitaxel and cisplatin.

In our cohort, two patients developed brain metastasis following systemic treatment and died 3 and 11 months after recurrence, respectively; one developed kidney metastasis and died 6 months later; and another developed recurrence in the skin and died 3 months later. However, we noted that lymphoma of FGT tended to recur in the central nervous system, consistent with the results reported by Ollila [29]. Remarkably, in the current study, we did not find any preventive treatment for recurrence in

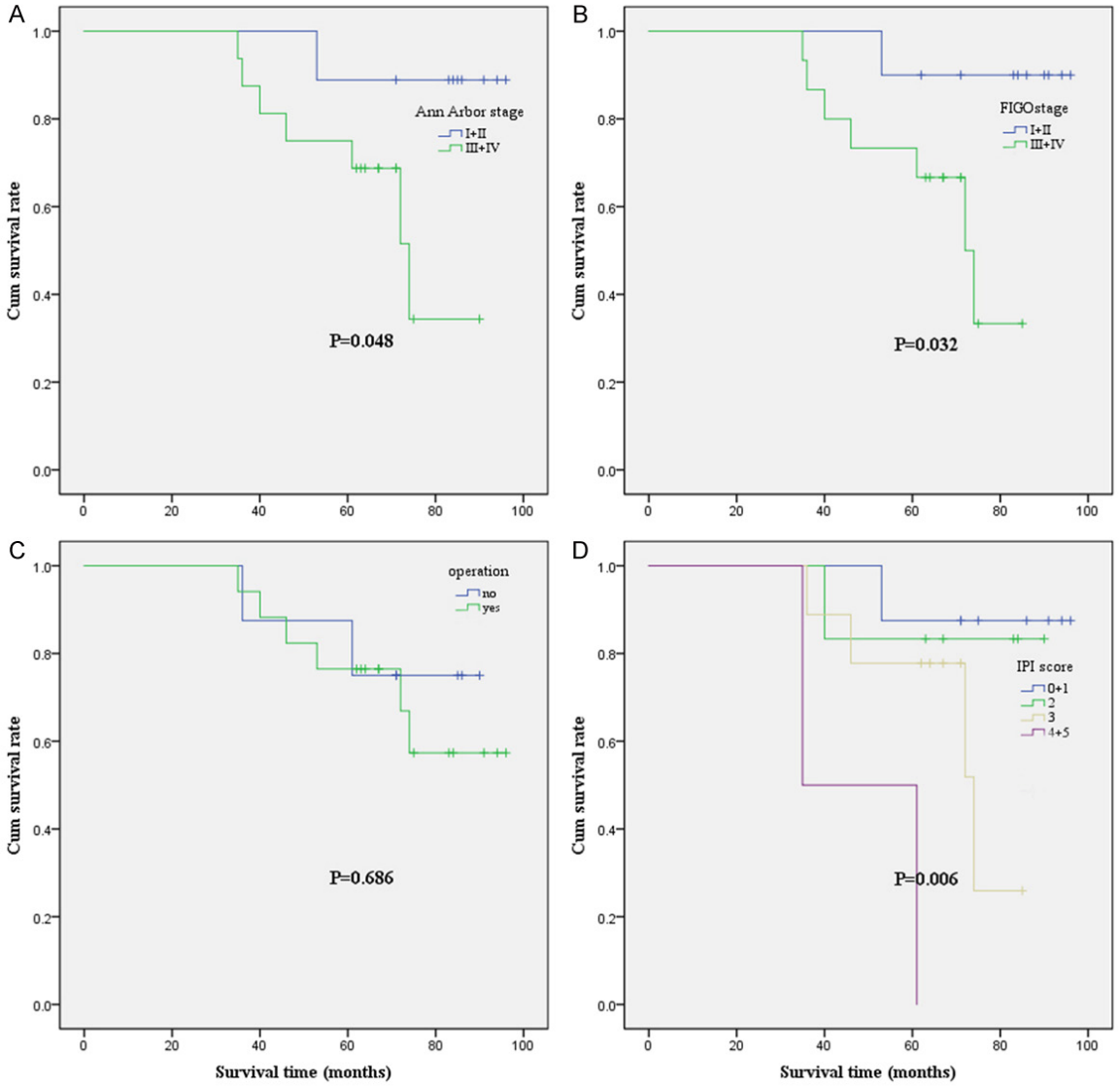

Figure 1. Kaplan-Meier survival analysis by Ann Arbor stage, FIGO stage, IPI score and surgery status (n=25). The y-axis represents the percentage of patient; the x-axis, their survival in months. A. The blue line represents patients with Ann Arbor I + II with a trend of better survival time than the green line representing Ann Arbor III + IV group (P=0.048). B. The blue line represents patients with FIGO I + II with a trend of better survival time than the green line representing FIGO III + IV group (P=0.032). C. The blue line represents patients who had not perform surgery, the green line represents patients who got surgery, these two lines has no statistical significance (P=0.686). D. The blue line represents patients with IPI score range 0 and 1, the green line represents patients with IPI score 2, the yellow line represents patients with IPI score 3, and the purple line represents patients with IPI score 4 and 5. The purple line with a trend of worse survival time than the yellow line; the yellow line with a trend of worse survival time than the green line; the green line with a trend of worse survival time than the blue line (P=0.006).

the central nervous system. Further, four other patients died of lymphoma of FGT. The International Extra-nodal Lymphoma Study Group (IELSG) clarified that the need for management of extra-nodal lymphoma at sites such as bones, thyroid, and breast is rare [2, 30]. We hypothesize that the development of an international multi-institutional registry would aid in further elucidation of the optimal management of women with lymphoma of FGT.

Radiological features

Preoperative pelvic ultrasound images of the ovary and uterus are shown in A and B of **Figure 5**. Ultrasound, computed tomography (CT),

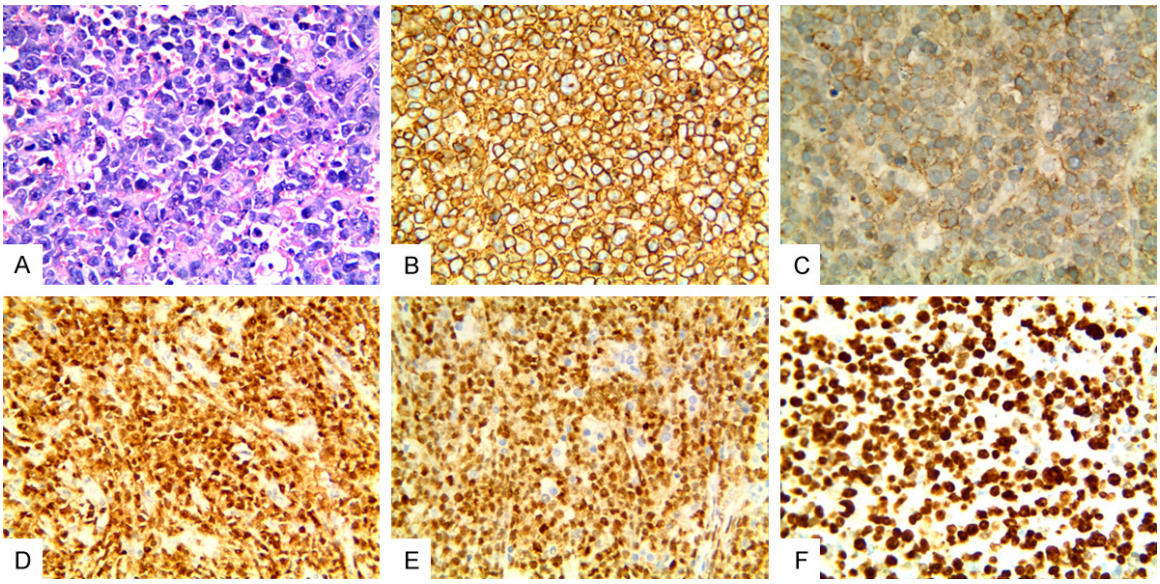

Figure 2. The representation micrographs showing of Diffuse large B cell type (DLBCL) extra-nodal lymphoma (hematoxylin eosin stain for A, ×400; immumohistochemical stain, ×400 for B-F). (A) Postoperative specimen of ovary tumor reduction. (B) CD20 staining. B lymphoid cells population showing CD20 membrane expression is positive. (C) CD30 staining. CD30 membrane expression is positive. (D) PAX-5 staining. PAX-5 medial gigantocellular nuclei expression is positive. (E) MUM1 staining. MUM1 nuclei expression is positive. (F) Ki-67 staining. Ki-67 is expressed positivity in 80% tumor cells.

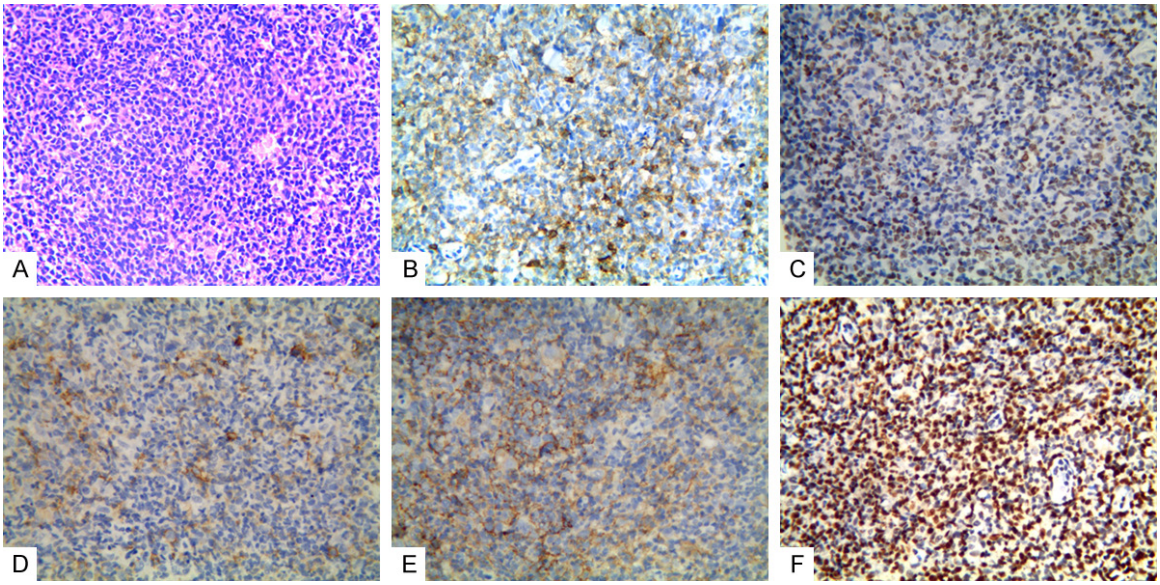

Figure 3. The representation micrographs showing of follicular lymphoma (hematoxylin eosin stain for A, ×400; immumohistochemical stain, ×400 for B-F). (A) Specimen of ovarian puncture biopsy. (B) CD20 staining. B lymphoid cells population showing CD20 membrane expression is positive. (C) Bcl-6 staining. Nuclei expression is positive. (D) CD23 staining. Membrane expression is positive. (E) CD35 staining. Membrane expression is positive. (F) PAX-5 staining. Medial gigantocellular nuclei expression is positive.

and positron emission tomography-CT (PET-CT) images for distant metastatic invasion to the kidney and pericardium are shown in C-F of **Figure 5**, whereas CT and magnetic resonance imaging images of intracranial lymphoma infiltration are shown in **Figure 6**. Among these, lymphoma metastasized to the kidney was diagnosed by puncture and intracranial lymphoma was diagnosed by a combination of medical history and imaging data.

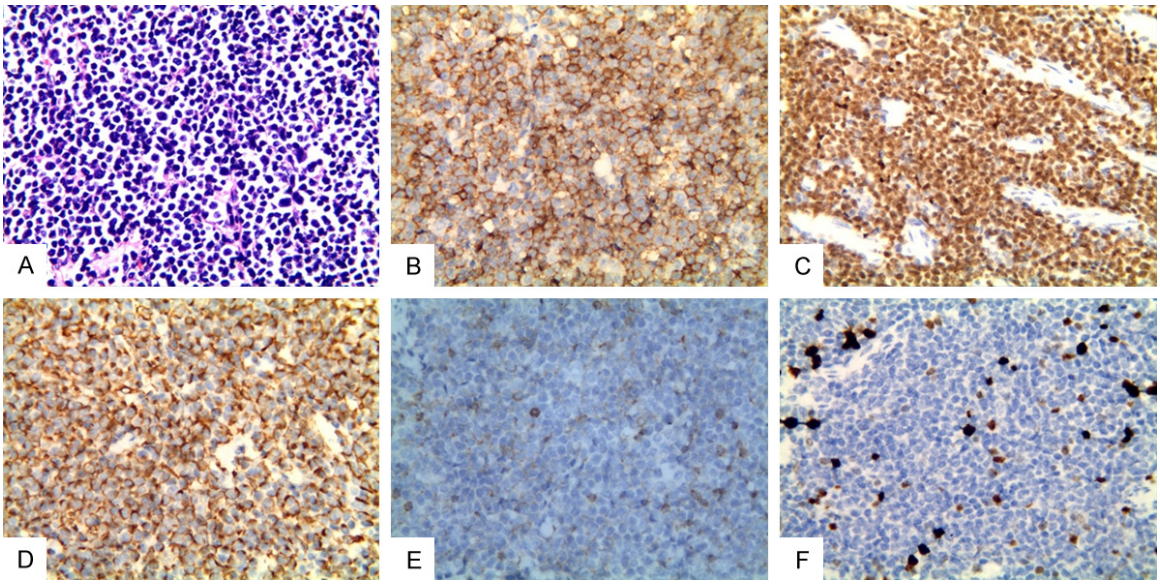

Figure 4. The representation micrographs showing of small lymphocytic lymphoma (hematoxylin eosin stain for A, ×400; immumohistochemical stain, ×400 for B-F). (A) Postoperative specimen of cervix tumor reduction. (B) CD20 staining. Membrane expression is positive. (C) PAX-5 staining. Nuclei expression is positive. (D) Vimentin staining. Cytoplasm expression is positive. (E) CD99 staining. Cell membrane and cytoplasm expression is positive. (F) Ki-67 staining. Ki-67 in nuclear is expressed positivity in 20% tumor cells.

Discussion

Considering the extremely low incidence of lymphoma of FGT, symptomatic patients usually visit the department of gynecology, where most lymphoma of FGT cases are initially treated as any other common gynecologic malignancy [7]. Definitive diagnosis is made postoperatively during pathological examination of surgical specimens. Preoperative differentiation of lymphoma from other primary diseases of the FGT is complicated; thus, tumor debulking is often performed. For the majority of FGT lymphoma cases, panhysterectomy has possibly been implemented for diagnostic rather than therapeutic purposes [10].

Immunohistochemical studies prove to be useful in achieving a correct diagnosis and are suitable in diagnosing endometrial stromal sarcoma, melanoma, and primitive neuroectodermal tumor because some follicular lymphomas are difficult to distinguish from benign reactive diseases such as severe chronic cervicitis or follicular cervicitis [5, 31]. At the first time of diagnosis, we meet kinds of suspension diagnosis, here we list immunohistochemical list of differential diagnosis which present our experience of diagnosis of lymphoma of FGT. Immunohistochemistry staining in carcinoma CK is positive; in malignant melanoma S-100 and HMB-45 is positive; in endometrial stromal sarcoma CD10 is positive; in granulosa cell tumor inbibin-α and Calretinin are positive; in peripheral primitive neuroectodermal tumor CD99, MPO and Syn are positive; in connective tissue proliferative small round cell tumor CK pan, desmin are positive. And all of these tumor did not positive in B-cell immunohistochemistry staining such as CD20, CD79, CD21, CD23, CD45RA, or T-cell immunohistochemistry staining such as CD3, CD43, CD45RO. Consistent with our report, previous literature reports state that DLBCL is the most common histological type of lymphoma of FGT [8], whereas lymphocytic lymphoma and follicular lymphoma occasionally occur [32]. Prognosis is usually assessed in accordance with the Ann Arbor staging system, including size and extent of the disease, age, IPI score, and pathological subtype [8, 10]. Study report that a low Ki-67 proliferation index (<10%) tended to be related to a shorter survival compared with high proliferation activity, but this relationship was not found to be statistically significant [20]. However, it has been shown that a high Ki-67 proliferation index is also a poor prognostic marker for DLBCL [33]. According to a study by the IELSG,

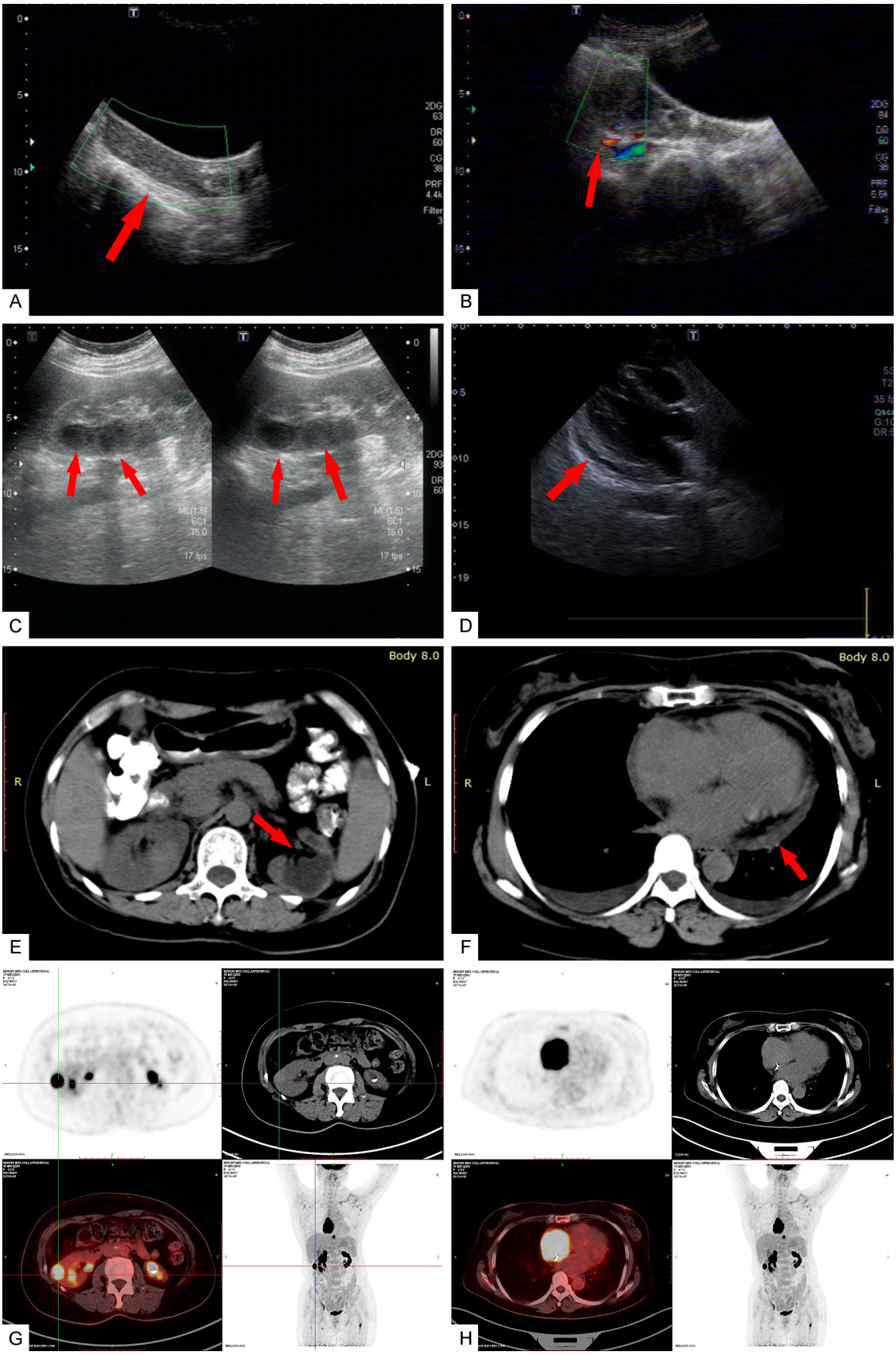
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Figure 5. Ultrasound image. A. Ultrasonic probing there was a substantial low echo sized 23 mm*83 mm*85 mm at the back of the bladder, cling to the top of the uterine corpus, the boundary of the irregular shape is not clear, the color shows no blood flow signal (case 10). B. In the left ovary, see the 32 mm*41 mm*53 mm low echo mass, the shape is still regular, the boundary is not clear, the local protrusion, the echo is uneven, and the strip shows blood flow signal around the color display (case 12). C-H. Are different imaging of distant metastasis to double kidneys and pericardium of case 9 which including ultrasound, CT and PET-CT. C. Ultrasound image: In the dorsal parenchyma of the right kidney, there are several low echoes of 20 mm*25 mm, the shape is still regular, and the boundary is clear. D. Ultrasound image: In the diastolic phase, the left ventricular posterior wall of the pericardial cavity has a liquid component, and the internal fluid is clear, with a maximum depth of 10 mm. E. CT image: The horizontal axis scans the abdominal cavity window sees a low-density shadow in the center of the left kidney which Puncture confirmed as diffuse large B-cell lymphoma. F. CT image: The horizontal axis of the CT scan window in the posterior wall of the left ventricle is obviously thickened in the pericardium, and the effusion is seen in the pericardial cavity. G. PET-CT image: In the right kidney, a number of round-like slightly high-density shadows were seen, some of which were nodular-like protrusions, and the fluorodeoxyglucose (FDG) metabolism was significantly increased. The left kidney was significantly smaller than the contralateral side, and the inner circular sac-like low-density shadow was seen. H. PET-CT image: A large mass of soft tissue mass can be seen in the pericardial cavity, the size is about 57 mm*62 mm*68 mm, the density of the mass is acceptable, and the boundary between the right pericardium is unclear, and the FDG metabolism is significantly increased.

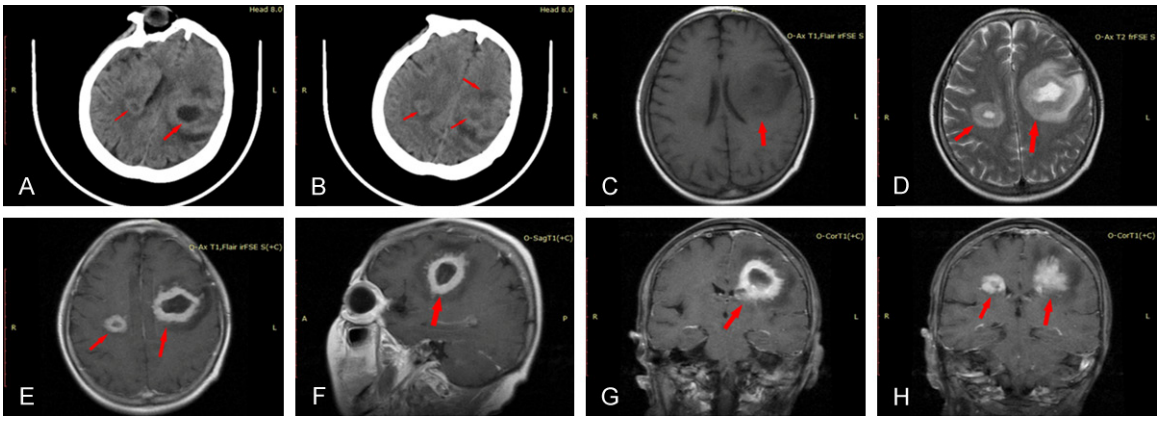

Figure 6. This is the CT and MRI images of brain metastases of case 5. A and B. CT scan horizontal axis: A mass of soft tissue density in the left frontal white matter, showing a high density of mixed density, which can be seen in low density. The same image of the smaller mass was seen in the brain parenchyma of the right parietal lobe. C-E. Are MRI T1 weighting, T2 weighting, and T1 enhancement, respectively. The horizontal axis: In the left frontal white matter, a blocky medium-high signal region was seen, which was equal-length T1 and T2 signals. The tumor was obviously strengthened, and a longer T1, longer T2 signal, no enhancement was observed, and the surrounding abnormal signals were flaky-long T1T2 signal with no enhancement. The image named “Clenched fist signs”. F. MRI T1 enhances sagittal position: Similar to the E-like signal in the brain parenchyma of the corpus callosum, showing a mass reinforcement. G and H. MRI T1 enhances coronal position: Lighter edema around the tumor.

a favorable IPI score, anthracycline chemotherapy, and radiotherapy (RT) were significantly associated with longer OS; the combination of limited surgery, anthracycline chemotherapy, and involved-field RT produced the best outcome in the pre-rituximab era [34].

As per our literature search, standard chemotherapy for NHL has been R-CHOP [27, 35], whereas surgery has markedly contributed to the diagnosis of lymphoma of FGT. However, whether do a surgery can improvement overall survival was still unknown [10]. The Hans classifier is a valid method for evaluating the prognosis of DLBCL; in the GCB subtypes, MUM1-positivity is associated with a more favorable outcomes [36]. Reportedly, primary central nervous system lymphoma and primary testicular lymphoma are characterized by high frequency of oncogenic mutations in MYD88, an adapter protein that mediates toll-like receptor and interleukin-1 receptor signaling, and CD79B, involved in active B-cell receptor signaling [37]. The MYD88 and CD79B mutations activate the nuclear factor-kappa B (NF-κB) pathway [38]. Iyengar et al. [39] used the definition proposed by Fox [40] for uterine and ovarian lymphoma. We distinguished primary lymphoma as follows: at the initial diagnosis, the disease process was confined to the FGT; full investigation

revealed no evidence of the disease in other organs of the body; peripheral blood and bone marrow did not contain cells indicating leukemia; and no remote organs were involved within 6 months [41]. Even though, lymphoma and what is secondary involvement of an extra-nodal site by a lymphoma originating in a lymphoid organ is not always easy, there are still many disputes on this. Monterroso V [42] thought IE classified by Ann Arbor staging was classified to primary lymphoma of female genital tract (PLFGT), on this point Niitsu N [43] thought both IE and IIE are meet the criterion.

Teenage patients for whom radiotherapy treatment is indicated may benefit from ovarian transposition. In this procedure, the ovaries are sutured into the paracolic gutter to postoperatively maintain them external to the radiation field [44]. Temporary ovarian suppression with the use of gonadotropin-releasing hormone agonists may reduce the risk of premature ovarian failure, and after a 5-year follow-up of 129 patients, a prospective randomized trial confirmed that there is no evidence on the benefit of preserving ovarian function and fertility in lymphoma survivors treated with chemotherapy [45, 46].

During post-treatment follow-up, tumor remission is usually evaluated by PET-CT. Follow-up PET-CT 16 months postoperatively revealed increased possibility of recurrence in the body, and extension of rituximab therapy by 2 years was recommended. Recurrence sites include the bones, lung, brain, cervical lymph nodes, skin, and manubrium [21]. FGT DLBCL has a relatively poor prognosis with preferential dissemination in the CNS [18, 19, 47]. In our cohort, there were two cases wherein the patients died 3 and 11 months, respectively, following the confirmed diagnosis of brain metastasis. For disease of the FGT, we recommend the administration of intermediate-dose methotrexate (1 g/m^2 d1 daily for 21 days; four cycles) or intrathecal chemotherapy with cytarabine for CNS prophylaxis.

Occurrence of lymphoma of FGT is rare. As with other rare diseases, a prospective review chart is difficult to perform. Our retrospective review chart is, therefore, valuable, but it has limitations of data accessibility. Lymphoma of FGT patients exhibits a high frequency of MYD88 and CD79B mutations [22], and although the presence of these mutations does not affect survival, it may offer additional therapeutic options worth studying further [18]. The small cohort in this study better clarifies the standard stages in the FIGO and Ann Arbor staging systems, although improved treatment of lymphoma of FGT is required through larger multi-institutional studies.

In conclusions, the FIGO and Ann Arbor staging systems were found to be significantly correlated with OS. Surgical treatment had no significant value in this cohort. The possibility of lymphoma of FGT metastasizing to the central nervous system should be considered and the use of drugs should be considered to prevent this. Perhaps a diagnosis by puncture and no reduction in tumor surgery can bring minimal harm to the patient. In the face of each patient, a personalized chemotherapy or radiotherapy treatment plan should be developed in conjunction with the latest literature.

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Disclosure of conflict of interest

None.

Address correspondence to: Damin Chai and Yisheng Tao, Department of Pathology, The First Affiliated Hospital of Bengbu Medical University, Bengbu Medical University, Bengbu, Anhui, China. E-mail: msautumn@163.com (DMC); taoyishengbbyxy@163.com (YST); Z Peter Wang, Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA. E-mail: zwang6@bidmc.harvard.edu

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Supplementary Table 1. Immunohistochemistry at the Time of Initial Diagnosis of These 25 cases

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
CD20	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	/	+
CD79α	-	+	/	+	+	+	/	+	/	/	/	+	+	/	+	/	/	+	/	+	-	/	/	/	/
Bcl-2	-	+	/	-	/	/	/	/	/	/	/	/	/	/	/	+	/	/	+	/	/	/	/	+	/
Bcl-6	-	/	+	+	/	+	/	/	/	/	-	/	/	/	/	+	/	/	/	+	/	/	/	/	/
Vim	/	/	+	/	-	/	+	+	+	-	/	+	-	/	/	/	/	+	/	/	-	-	+	/	/
PAX-5	-	+	+	+	/	+	+	/	+	/	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUM1	-	/	+	-	+	-	/	/	/	+	+	/	/	/	/	/	/	/	+	+	/	/	/	/	+
CD3	-	-	-	-	-	-	-	-	-	/	/	-	-	/	-	-	-	+	-	-	-	-	-	/	-
CD45RO	/	/	+	/	/	/	-	/	/	/	/	+	/	+	/	+	/	+	/	/	/	+	/	/	/
CD10	-	-	-	+	-	-	/	/	/	/	-	/	/	/	/	+	/	-	-	-	-	-	/	/	-
CD30	-	/	/	/	/	/	/	/	/	/	+	/	/	/	/	-	/	/	/	/	/	/	-	-	/
CD21	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	+	/	/	/	/	/	/	/	/	/
CK (Pan)	-	-	-	/	-	/	-	+	-	-	/	-	-	-	/	/	-	-	/	-	-	-	-	/	-
Ki-67 (%)	80	80	90	90	70	80	20	85	90	80	90	90	90	90	95	35	90	60	50	60	20	80	90	/	70
CD23	/	/	/	/	-	/	/	/	-	/	/	/	/	/	-	+	/	/	/	/	/	/	/	/	/
CD99	+	/	/	/	/	/	/	/	/	/	/	-	/	/	-	/	/	/	/	/	/	/	/	/	-
P63	+	/	/	/	/	/	/	/	/	/	/	/	/	+	/	/	/	/	/	/	/	/	/	/	/
MPO	-	/	/	/	/	/	/	-	/	/	/	/	/	/	/	/	/	/	-	-	-	/	/	/	/
CD43	-	+	-	-	/	-	/	-	-	/	/	/	-	/	-	-	/	/	+	+	+	/	+	/	+
CyclinD1	-	-	/	/	-	/	/	/	/	/	/	/	/	/	-	/	/	/	-	/	-	/	/	/	-
CD5	/	-	/	/	-	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	-	/
HMB45	/	/	-	/	/	/	/	/	/	/	/	/	/	/	/	/	-	/	/	/	/	/	/	/	/
Inhibin-α	/	/	-	/	/	/	-	-	-	-	/	-	-	/	-	/	/	/	/	/	/	/	-	/	/	/
Calretinin	/	/	-	/	/	/	/	/	-	/	/	-	/	/	/	/	/	/	/	/	/	/	-	/	/	-

Supplementary Table 2. Primary Antibodies Used In This Study

Antigen	Source	Item Number	Clone
CD20	MaiXin	Kit-0001	L26
CD79a	MaiXin	MAB-0258	HM47/A9
Bcl-2	MaiXin	MAB-0014	8C8
Bcl-6	MaiXin	MAB-0598	LN22
Vimentin	MaiXin	Kit-0019	V9
PAX-5	MaiXin	RMA-0611	SP34
MUM1	MaiXin	MAB-0573	MUMp
CD3	MaiXin	Kit-0003	SP7
CD45R0	MaiXin	MAB-0039	UCHL-1
CD10	MaiXin	MAB-0668	MX002
CD30	MaiXin	MAB-0023	Ber-H2
CD21	MaiXin	MAB-0339	2G9
CK (Pan)	MaiXin	MAB-0671	MX005
Ki-67	MaiXin	MAB-0672	MX006
CD23	MaiXin	RMA-0504	SP23
CD43	MaiXin	MAB-0032	DF-T1
MPO	MaiXin	RAB-0032	polyclone
CD99	MaiXin	MAB-0059	O13
P63	MaiXin	MAB-0694	MX013
CyclinD1	MaiXin	RMA-0541	SP4
CD5	MaiXin	Kit-0033	SP19
Melanoma	MaiXin	MAB-0098	HMB45
Inhibin-α	MaiXin	MAB-0268	R1
Calretinin	MaiXin	RMA-0542	SP13

Supplementary Table 3. Clinical Characteristics and Pathological Subtypes in the 25 Patients Included In This Study

Case number	Age (years)	Presenting complaint	Primary Sites	Pathologic Subtype	FIGO Staging	Ann Arbor Staging	IPI	Treatment	Status	Survival Time
1	52	Vaginal bleeding	Cervix	DLBCL	II	IIE	1	Surgery + R-CHOP*6 + RT	M	53
2	60	Vaginal bleeding	Cervix	DLBCL	IV	IVE + S	3	R-CHOP*5 + ESAHP*2	M	36
3	73	Vaginal bleeding	Uterine corpus	DLBCL	II	IIE	1	R-COP*1	NR	71
4	68	Abdominal pressure	Uterine corpus	DLBCL	II	IVE	3	Surgery + TP*2	NR	62
5	60	Abdominal pressure	Ovary	DLBCL	IVA	IIIE	3	Surgery + CHOP*5 + R-CHOP*4	M	46
6	35	Abdominal pressure	Ovary	DLBCL	II	IVE	2	Surgery + R-CHOP*6	NR	84
7	41	Abdominal pressure	Ovary	DLBCL	III	IVE	2	Surgery + R-CHOP*6	NR	67
8	51	Abdominal pressure	Ovary	SLL	II	IIE	1	Surgery + E-CHOP*6 + R-ICE*7	M	91
9	69	Abdominal pressure	Ovary	DLBCL	III	IIIE	3	Surgery + R-CHOP*6	NR	64
10	63	A pelvic mass	Ovary	DLBCL	II	IIE	1	Surgery + E-CHOP*17	NR	94
11	20	Abdominal pressure	Ovary	DLBCL	III	IIIE	1	CHOP*1 + R-GDP*3	NR	71
12	47	Abdominal pressure	Ovary	DLBCL	II	IIE	0	R-CHOP*7	NR	86
13	70	Abdominal pressure	Ovary	DLBCL	III	IIIE	4	TP*2	D	61
14	66	Vaginal discharge	Cervix	DLBCL	IVB	IVE	3	CHOP*2 + E-CHOP*6	NR	71
15	77	Abdominal pressure	Ovary	DLBCL	IVA	IIE	3	Surgery + R-CHOP*6	NR	85
16	66	A pelvic mass	Ovary	FL	III	IVE	3	Surgery + R-CHOP*6	NR	67
17	68	Vaginal discharge	Cervix	DLBCL	III	IIIE	3	Surgery + R-CHOP*6	D	74
18	45	Vaginal discharge	Cervix	DLBCL	IVB	IIIE	2	Surgery + R-CHOP*6	NR	63
19	61	Abdominal pressure	Cervix	DLBCL	IVA	IIIE	4	Surgery + CHOP*6	D	35
20	72	Vaginal discharge	Cervix	DLBCL	IV	IVE	3	Surgery + CHOP*6	D	72
21	76	Vaginal bleeding	Uterine corpus	DLBCL	II	IVE	2	R-CHOP*6	NR	90
22	53	Abdominal pressure	Ovary	DLBCL	II	IIE	2	Surgery + R-CHOP*6	NR	83
23	42	Abdominal pressure	Ovary	DLBCL	II	IIE	1	Surgery + R-CHOP*6	NR	96
24	51	Abdominal pressure	Ovary	DLBCL	III	IVE	2	Surgery + CHOP*6	D	40
25	49	A pelvic mass	Ovary	DLBCL	III	IIIE	1	Surgery + R-CHOP*6	NR	75