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Primary diffuse large B-cell lymphoma of the uterus

A SEER database analysis

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Abstract

Uterine diffuse large B-cell lymphoma (DLBCL) is a rare clinical condition. Most studies for uterine DLBCL are derived from case reports and series. Our main objective was to present a new case while also investigating the demographic, clinical characteristics, and survival of women with primary uterine DLBCL as compared to non-uterine DLBCL using the Surveillance, Epidemiology, and End Results incidence database. We queried the Surveillance, Epidemiology, and End Results database for women aged 18 years or older with a diagnosis of primary DLBCL from 1975 to 2017. The most common site of primary uterine DLBCL is the cervix uteri not otherwise specified, followed by endometrium, uterus not otherwise specified, corpus uteri, myometrium and isthmus uteri. Non-uterine DLBCL cases tend to be older than uterine DLBCL cases. Uterine DLBCL is most common among women aged 40 to 64 years. Patients with uterine DLBCL showed greater survival than non-uterine DLBCL patients, and patients treated in the rituximab era also exhibited a survival benefit. Both the elderly and African American cohorts experienced worse overall survival.

Abbreviations: CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, DLBCL = diffuse large B-cell lymphoma, HR = Hazard Ratio, NHL = non-Hodgkin lymphoma, NOS = not otherwise specified, OS = overall survival, SEER = Surveillance, Epidemiology, and End Results.

Keywords: diffuse large B-cell lymphoma, non-Hodgkin lymphoma, survival, uterus

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive form of non-Hodgkin lymphoma (NHL). According to 2018 World Health Organization data, NHL ranks among the most common malignancies with an estimated incidence percentage of 2.8%.[1] DLBCL is the most common subtype of NHL worldwide, representing approximately 30% to 40% of all cases.[2,3] The American Cancer Society estimates about 77,240 people (42,380 males and 34,860 females) will be diagnosed with NHL in 2020 with an estimated 19,940 deaths from NHL during the year.[4] One-third of NHL cases affects extranodal regions including the female genital tract with an incidence rate of 0.5% to 1.5%.[5–7]

Although DLBCL is the most common subtype of NHL, uterine and reproductive organ involvement is rare and not well documented. Primary lymphomas of the female genital tract represent 0.2% to 1.1% of all extranodal lymphomas.[8] Most cases of lymphoma of the uterus are due to secondary involvement of disease,[9] while the female genital tract, in particular the ovaries, is commonly involved in 7% to 30% of secondary disseminated lymphomas.[10] Because of the rarity of uterine DLBCL and presentation of non-specific clinical symptoms, diagnosis is difficult. Few studies presently exist, and therefore, there is no current standard of treatment for uterine DLBCL. However, multiple studies on DLBCL, not specific to the female genital tract, have investigated the efficacy of various treatment regimens, and currently, the standard therapy for patients with DLBCL is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with a cure rate of approximately 60% to 70% and a relapse/refractory rate of 30% to 40%.[2,11] Based on a review of the literature and recent case studies, R-CHOP seems to be the current preferred treatment regimen for uterine DLBCL.[5,12–14] Long term survival for uterine DLBCL is not known. Herein, we review the population-based cancer registry Surveillance, Epidemiology, and End Results (SEER) for primary uterine DLBCL survival.

2. Methods

2.1. Data source

This retrospective cohort study is based on the SEER population-based cancer registries incidence data which covers approxi-

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The datasets generated during and/or analyzed during the current study are publicly available.

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mately 34.6% of the U.S. population and includes cases through the November 2019 submission which was released April 2020. SEER*Stat was used to create case listings from SEER Research Data 9, 13, and 18 incidence files. Age, race, ethnicity, date of diagnosis, primary site of disease, disease morphology, and overall survival (OS) information were collected. Only primary uterine DLBCL cases were considered as uterine DLBCL. All DLBCL cases with primary site codes (i.e., ICD-0-3 Site CODES) C538 (Overlapping sites of cervix uteri), C539 (Cervix Uteri, not otherwise specified [NOS]), C540 (Isthmus uteri), C541 (Endometrium), C542 (Myometrium), C549 (Corpus uteri), and C559 (Uterus, NOS) were included.

2.2. Statistical methods

Differences in patient-level characteristics between female cohorts (uterine vs non-uterine) such as age group, race, and ethnicity were compared using a chi-square test. Survival follow-up was estimated using the Kaplan-Meier method of potential follow-up. Survival time was calculated from date of diagnosis to the date of death due to any cause or the last date of follow-up for patients still alive at last contact. Survival was estimated using the method of Kaplan-Meier and the method of Brookmeyer and Crowley was used to construct 95% confidence intervals for the quantiles of the survival distribution. Univariate differences in survival were assessed by the log-rank test and multivariate Cox proportional hazards models were used to assess covariate adjusted survival differences. Confidence intervals for the survivor function (e.g., 10-year OS) are based on the log-log transformation. Significance tests and confidence limits for the hazard ratios are based on Wald tests. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC). Statistical significance was defined as $P < .05$.

3. Results

A total of 397,712 unique NHL patients were identified with year of diagnosis distributed from 1975 to 2017. Of the 397,712 unique NHL patients, 137,909 (34.67%) were diagnosed with DLBCL (62,443 [45.27%] females and 75,466 [54.73%] males). Among the female cohort identified, 62,297 subjects included survival information. Of these 62,297 subjects, 223 (0.35%) were identified as primary DLBCL of the uterus. The morphology of most cases is malignant lymphoma, large B-cell, diffuse, unspecified (non-uterine = 98% & uterine = 99%) (Table 1). Median follow-up among the 223 uterine cases was 119 months (range: 0–388) and 118 months (0–515) among non-uterine cases.

Among the 223 cases identified as primary DLBCL of the uterus, the most common site was cervix uteri NOS (56.1%), followed by endometrium (17.9%), uterus NOS (17.0%), corpus uteri (6.3%), myometrium (1.8%), and isthmus uteri (1.9%). Among the uterine cases, most women were between 40 and 64 years (45.7%) and 35.4% were ≥65 years; whereas, the non-uterine cases tended to be older with 62.4% aged 65 years or older ($P < .0001$) (Table 2). Most cases in both cohorts were Caucasian (non-uterine: 84.8% and uterine: 73.1%); however, there is a significant difference ($P < .0001$) in race distribution between the uterine and non-uterine cases with nearly twice as many African American uterine cases (12.6%) as non-uterine African American cases (6.5%) as well as nearly twice as many Asian uterine cases (12.1%) as non-uterine Asian cases (7.1%)

Table 1

Morphology distribution.

Morphology	Primary site		
	Other	Uterus	Total
Malignant lymphoma, large B-cell, diffuse, NOS	60,638 97.69	221 99.10	60,859
Malignant lymphoma, large B-cell diffuse, immunoblastic, NOS	1240 2.00	2 0.90	1242
T-cell/histiocyte-rich large B-cell lymphoma	128 0.21	0 0.00	128
Plasmablastic lymphoma	49 0.08	0 0.00	49
ALK-positive large B-cell lymphoma	8 0.01	0 0.00	8
Large B-cell lymphoma arising in HHV8 associated multicentric Castleman disease	11 0.02	0 0.00	11
Total	62,074	223	62,297

NOS = not otherwise specified.

(Table 2). Ethnicity was not significantly different between these 2 topology cohorts ($P = .1149$) with both cohorts including roughly 90% non-Hispanics (Table 2). Although summary stage is only known for 76% of the cases, there is a statistically significant difference between the 2 topology cohorts with respect to stage ($P < .0001$). Non-uterine cases tend to be more advanced; that is, 50.2% of the non-uterine cases are distant compared to 31% of the uterine cases (Table 3).

Impact on survival was investigated by primary site (uterine vs non-uterine), introduction of rituximab (<1997 vs ≥1997), age (0–64 vs 65+), race (Caucasian vs Black vs Other, with Caucasian as the reference group), and ethnicity (Hispanic vs non-Hispanic). A univariate model revealed that primary site was a significant predictor of survival ($P < .0001$) with the uterine cases possessing the survival benefit (Hazard Ratio (HR): 0.48, 95% Confidence Interval: [0.39,0.60]) (Table 4 and Fig. 1). Univariate models also indicated survival benefit for the rituximab era ($P < .0001$, HR: 0.75), African Americans ($P = .0007$, HR: 0.93), "Other" race ($P < .0001$, HR: 0.90), and Hispanics ($P < .0001$, HR: 0.86). Older subjects experienced a worse survival ($P < .0001$, HR: 3.02). Although the survival benefit due to primary site ($P = .0002$, HR: 0.66) and rituximab ($P < .0001$, HR: 0.74)

Table 2

Patient-level characteristics.

Factor	Study cohort		*P* value
	Non-uterine	Uterine	
Age (years)			<.0001
0–19	634 (1.0%)	1 (0.5%)	
20–39	3979 (6.4%)	41 (18.4%)	
40–64	18,758 (30.2%)	102 (45.7%)	
65+	38,703 (62.4%)	79 (35.4%)	
Race			<.0001
American Indian/Alaska Native	325 (0.5%)	2 (0.9%)	
Asian or Pacific Islander	4768 (7.7%)	27 (12.1%)	
Black	4061 (6.5%)	28 (12.6%)	
Unknown	287 (0.5%)	3 (1.4%)	
White	52,633 (84.8%)	163 (73.1%)	
Ethnicity			0.1149
Non-Spanish-Hispanic-Latino	54,911 (88.5%)	205 (91.9%)	
Spanish-Hispanic-Latino	7163 (11.5%)	18 (8.1%)	

Table 3

SEER summary stage by primary site.

	Primary site		
Summary stage	Other	Uterus	Total
Localized	13,688	81	13,769
	29.03	43.32	
Regional	9814	48	9862
	20.81	25.67	
Distant	23,649	58	23,707
	50.16	31.02	
Total	47,151	187	47,338

Summary stage is missing for 14,923 non-uterine cases and 36 uterine cases.
SEER = Surveillance, Epidemiology, and End Results.

was maintained in the multivariate model, African Americans ($P < .0001$, HR: 1.21) joined the elderly ($P < .0001$, HR: 3.06) as experiencing worse survival. The significant survival benefit was also lost among the "Other" race ($P = .73$, HR: 1.01) and Hispanics ($P = .23$, HR: 1.02). Figure 2 presents Kaplan-Meier survival function estimates by time period and primary site. Figure 2A indicates that OS has improved among uterine DLBCL cases post the introduction of rituximab, but the small sample size prior to 1997 renders the finding insignificant ($P = .16$). Figure 2B demonstrates OS has significantly improved for non-uterine DLBCL since the introduction of rituximab ($P < .0001$). Prior to rituximab, DLBCL of the uterus was less aggressive than non-uterine DLBCL ($P = .0038$) (Fig. 2C). In the rituximab era, DLBCL of the uterus remains less deadly than the non-uterine counterpart ($P < .0001$) (Fig. 2D). We also compared OS between 2 cohorts (uterine vs non-uterine) for those subjects with localized disease, the OS was significantly different ($P < .0001$). For subjects with localized disease, the 2-year survival for uterine subjects was 92.3%, but only 69.2% for the non-uterine cases.

4. Discussion

Uterine DLBCL is a rare disease with a non-specific clinical presentation. The current incidence rates for NHL and DLBCL in females are 16.40 and 5.8 per 100,000 persons respectively.[15] Internal reproductive organ involvement is estimated to occur in 2% to 4% of DLBCL cases.[16,17] B symptoms typically associated with lymphoma are not frequently seen in patients with primary lymphoma of the female genital tract; instead, patients typically present with non-descript gynecologic symptoms such as abnormal vaginal or uterine bleeding, abdominal pain, perineal discomfort, persistent vaginal discharge, and urinary obstruction.[8,13,18–21] These symptoms are common among many gynecological diseases complicating the ability to make a definitive differential diagnosis.

Given the paucity of information available on uterine DLBCL, definitive diagnostic testing is crucial for accurate diagnosis, staging, and treatment. Papanicolaou smears are not good diagnostic tools because uterine DLBCL is a stromal and not epithelial disease. They may only be used for diagnosis once ulceration of the epithelial cells has occurred.[5] There is no consensus or standard diagnostic protocol for uterine DLBCL. Majority of cases used biopsies and histological examination[5]; however, Nasioudis et al[8] suggest biopsies are possible but not routinely recommended. Instead, primary lymphoma of the female genital tract is commonly discovered on final pathology of surgical staging procedures, especially for lymphoma of the uterus and cervix as these are difficult locations to biopsy.

Data support the ovary to be the most frequent site of extranodal NHL of the female genital tract.[5,8,21–23] It has been suggested the rarity of ovarian DLBCL may be attributed to absence of lymphoid tissue in this organ. However, this may not be true for uterine DLBCL as lymphoid follicles are frequently present in the endometrium. The small number of uterine DLBCL cases may be attributed to the difficulty of histological diagnosis.[18]

According to a previous study by El-Galaly et al,[17] patients with uterine involvement had worse progression-free and OS rates as compared to patients without reproductive organ or ovarian only involvement. Our analysis discovered contradictory findings to this study as patients with uterine DLBCL had better OS as compared to non-uterine DLBCL patients in both the univariate and multivariate models. Mandato et al[5] completed an extensive review of 144 cases/case studies of uterine DLBCL and found patients with uterine DLBCL had more favorable

Table 4

Overall survival.

			Univariate		Multivariate	
Factor	Sample size	Median OS (95% CI)	HR	*P*	HR	*P*
Primary site						
Non-uterine	62,074	54 (52,55)				
Uterine	223	302 (137,-)	0.48 (0.39,0.60)	<.0001	0.66 (0.53,0.82)	.0002
Time period						
<1997	11,157	22 (21,24)				
≥1997	51,140	64 (63,67)	0.75 (0.74,0.77)	<.0001	0.74 (0.72,0.75)	<.0001
Age						
0–64	23,515	208 (203,214)				
65+	38,782	22 (21,23)	3.02 (2.95,3.10)	<.0001	3.06 (2.99,3.14)	<.0001
Race						
White	52,796	53 (51,54)				
Black	4089	54 (44,63)	0.93 (0.89,0.97)	.0007	1.21 (1.16,1.26)	<.0001
Other	5122	64 (56,71)	0.90 (0.87,0.94)	<.0001	1.01 (0.97,1.05)	.7300
Ethnicity						
Non-Hispanic	55,116	52 (50,54)				
Hispanic	7181	74 (68,79)	0.86 (0.83,0.89)	<.0001	1.02 (0.99,1.06)	.2267

CI = Confidence Interval, HR = Hazard Ratio.

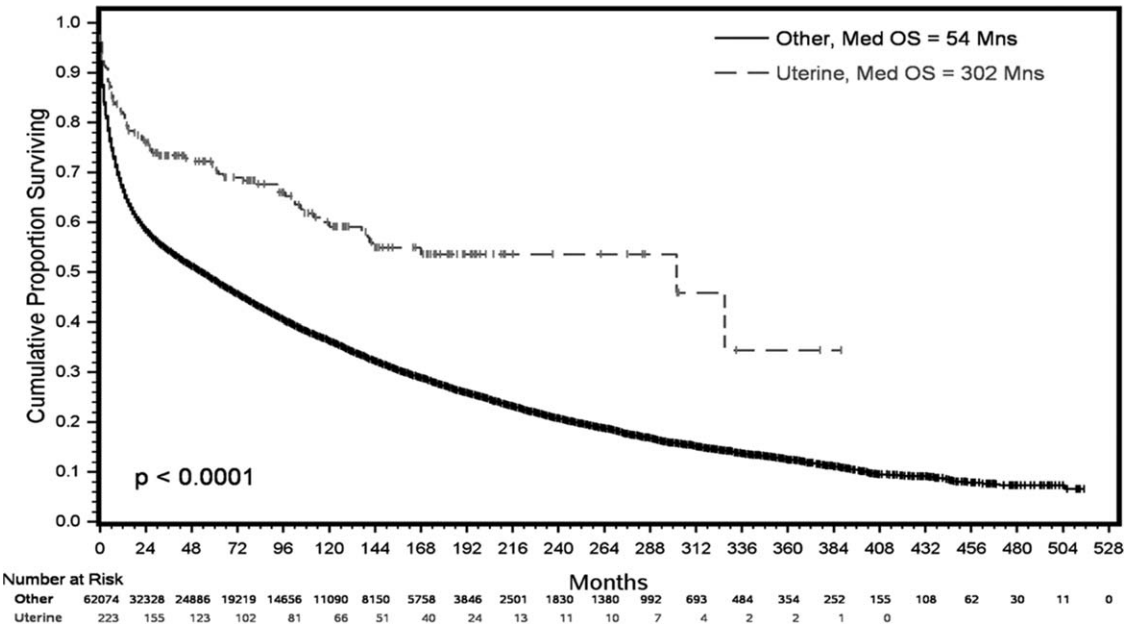

Figure 1. Overall survival comparing female non-uterine DLBCL cases to uterine DLBCL cases. DLBCL = diffuse large B-cell lymphoma.

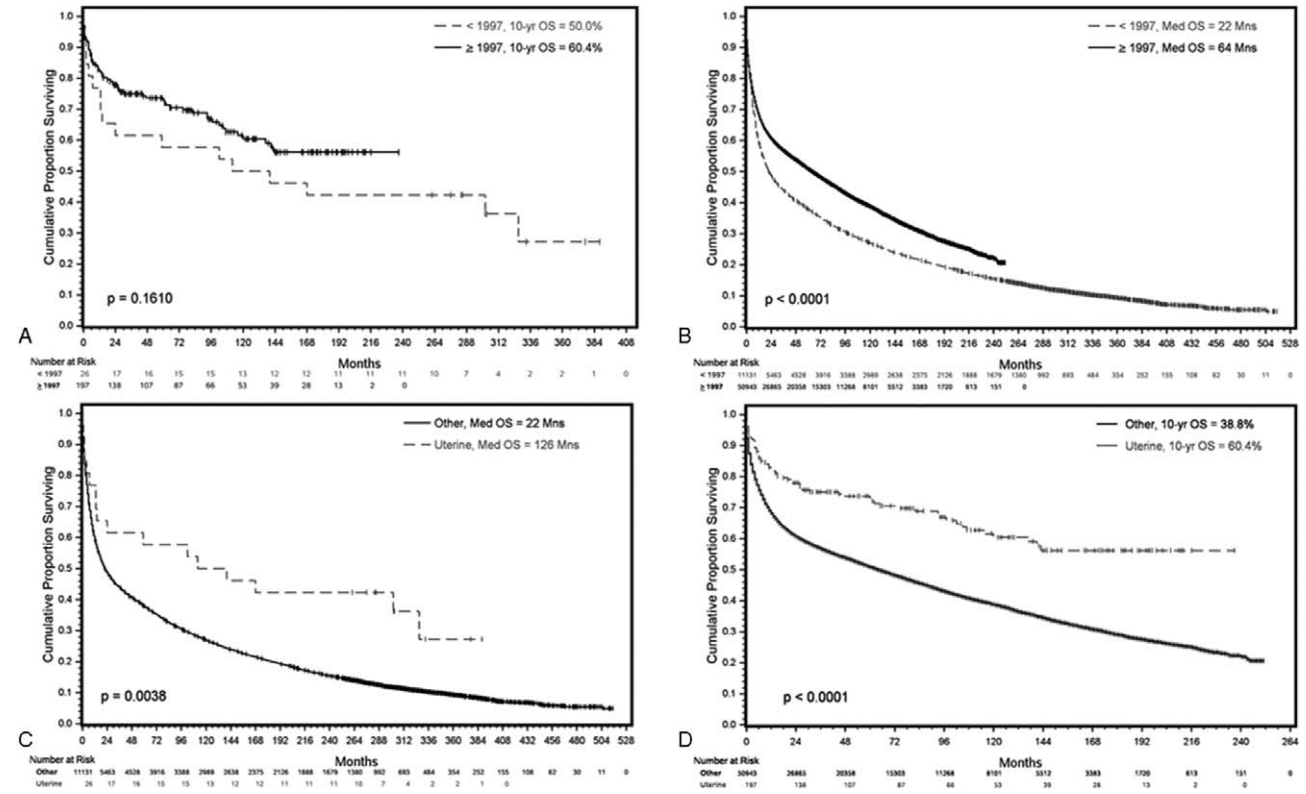

Figure 2. (A) Compares uterine DLBCL cases diagnosed prior to 1997 to uterine DLBCL cases diagnosed on or after 1997. (B) Compares female non-uterine DLBCL cases diagnosed prior to 1997 to female non-uterine DLBCL cases diagnosed on or after 1997. (C) Compares cases diagnosed prior to 1997 between uterine DLBCL and female non-uterine DLBCL. (D) Compares cases diagnosed on or after 1997 between uterine DLBCL and female non-uterine DLBCL. DLBCL = diffuse large B-cell lymphoma.

outcomes. El-Galaly et al[17] cited the contradictory results between their study and Mandato et al[5] may be due to the fact that in Mandato et al >80% of the cases had limited stage disease whereas in their study, 89% of patients with reproductive organ involvement DLBCL had advanced stage disease. Mandato et al[5] found distribution of Ann-Arbor Stage in the 144 cases to be as follows: stage I 64.58%, stage II 17.36%, stage III 2.08%, and stage IV 13.19%. Stage was not reported in 2.78% of the cases. Nasioudis et al[8] also found majority of primary lymphoma of the female genital tract to be of early stage (stage 1=42.6%, stage 2=17.9%). Although El-Galaly et al[17] is an international retrospective study of patients collected from lymphoma registries and study databases in 4 countries from 2001 to 2013, the study was only able to collect 678 female patients diagnosed with DLBCL and 17 with uterine DLBCL as compared to the 62,297 female DLBCL and 223 uterine DLBCL patients we were able to pull from SEER. Distribution of disease stage was not observed to be as strongly skewed towards advanced disease among the uterine DLBCL cohort as was noted by El-Galaly et al,[17] but rather more closely parallels the uterine DLBCL population presented in Mandato et al[5] (Table 3). Our results indicate more favorable OS results with uterine DLBCL as compared to non-uterine DLBCL.

El-Galaly et al[17] also found that patients with reproductive involvement are more likely to have secondary Central Nervous System (SCNS) involvement. However, they found that patients with only ovarian involvement did not have SCNS, but 41% of patients with uterine DLBCL had SCNS. There is an increased risk of SCNS associated with uterine DLBCL ± ovarian involvement.

CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy is currently the standard of treatment for patients diagnosed with DLBCL not necessarily of the uterus. In 1997, the FDA approved rituximab, an anti-CD20 monoclonal antibody with anti-tumor activity. Rituximab is currently approved to use as a monotherapy or in combination with CHOP, commonly referred to as R-CHOP.[24] The GELA trial[25] showed the addition of rituximab to CHOP therapy increases benefits in complete response rate and prolongs event-free survival and OS in DLBCL patients when compared to standard CHOP regimens. This was also confirmed in a study by Feugier et al[26] whose investigation also presents significant improvements in 5-year survival rates of DLBCL patients who received R-CHOP chemotherapy. Hamlin et al[11] completed a SEER analysis of efficacy of treatment options in the elderly. They found survival benefits for this group utilizing R-CHOP over CHOP therapy and rituximab monotherapy over no therapy.

From our investigation of the SEER data, we found that patients diagnosed after 1997 had greater OS benefits. Although we were not able to pull specific treatment regimen profiles in SEER, our literature review suggests the survival benefit found after 1997 may be explained by the choice to use rituximab or R-CHOP as a common treatment regimen in uterine DLBCL cases. Prior to the rituximab era, CHOP chemotherapy with radiation therapy was the common treatment modality.[5,21] The use of surgery as a treatment modality is also debated. A rationale against surgery stems from attempts to preserve patients' reproduction abilities.[5,27] Data suggest the age of presentation is younger for uterine DLBCL than non-uterine DLBCL ($P < .0001$). Efforts to protect the reproductive abilities in premenopausal uterine DLBCL patients should be taken. However, diagnosis for uterine DLBCL may occur after surgery for suspected gynecologic malignancy.[8]

In a model adjusted for age and primary site, the survival benefit experienced by African Americans, Hispanics, and "Other" race categories disappears. Based on our extensive literature review, this is the first study to evaluate the OS benefits of uterine DLBCL by race and ethnicity.

5. Conclusion

Although there is currently no standard treatment for patients with uterine DLBCL possibly due to the rarity of the disease; our review of the literature to include recent case studies suggests that R-CHOP is preferred in this setting. DLBCL of the uterus continues to be less deadly and tends to be diagnosed at an earlier stage. The uterine DLBCL cohort tends to be younger than their non-uterine counterparts.

Author contributions

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