Female patients with DLBCL and involvement of the reproductive organs have poor outcomes and markedly increased risk of CNS relapse with R-CHOP(-like) therapy

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Background

Diffuse large B-cell lymphomas (DLBCL) involving the reproductive organs are rare. While testicular involvement with DLBCL has been well described, less is known about the outcome of DLBCL involving the internal female reproductive organs (ovaries and uterus).

Patients

This is a retrospective study of patients with newly diagnosed DLBCL presenting to hospitals in Denmark, British Columbia Cancer Agency (Canada), Guys and St. Thomas' Hospital (UK), and Peter MacCallum Cancer Center (Australia) identified through searches of national/local registries and databases. Inclusion criteria were staging that included PET/CT and treatment with R-CHOP(-like) therapy ± CNS prophylaxis ± radiotherapy. Patients with known CNS involvement at diagnosis were excluded. Extranodal sites were retrieved from databases and written PET/CT reports. Medical records were reviewed for outcome including CNS relapse.

Results

Among 1,536 patients, 76 (5%) had reproductive organ involvement. Testicular involvement was seen in 48 (6%) of men, and female reproductive organ involvement in 28 (4%) of women (uterus n=15, ovaries n=11, both n=2). Amongst women, reproductive organ involvement was more frequently associated with stage III-IV disease and poor risk R-IPI score (Table I, Figure 4). The median follow-up was 44 months for women and 40 months for men. Involvement of female reproductive organs was associated with inferior overall survival (OS) in sex-stratified multivariate analysis (MVA) including R-IPI (HR 2.10, 95%CI 1.23-3.59). Testicular involvement was not adversely prognostic for OS (HR 1.23, 95%CI 0.70—2.16) in MVA. The OS and progression-free survival (PFS) curves for men and women with reproductive organ involvement are shown in Figure 1 and 2. The 3-yr risk for CNS events was higher for women with reproductive organ involvement (Table II). The increased risk of CNS events was confirmed for uterine involvement in MVA with adjustments for CNS prophylaxis and high-risk disease according to the recently validated DSHNHL risk model (Savage 394a, ASH 2014) for CNS relapse (5 IPI risk factors + kidney/adrenal involvement), but not for ovarian involvement (Table III). Testicular involvement was associated with a trend for increased risk of CNS relapse in MVA despite frequent use of CNS prophylaxis (Table III). The cumulative incidences of CNS relapse in men and women with reproductive organ involvement are shown in Figure 3.

Table I: Patient characteristics and treatment	Female reproductive organ DLBCL (n=28)	Testicular DLBCL (n=48)	P
Median age	64 (33-84)	73 (45-84)	0.02
R-IPI risk group, n (%)			
• Very good risk (0 risk factors)	0	7 (15)	
• Good risk (1-2 risk factors)	10 (36)	28 (58)	<0.01
• Poor risk (3-5 risk factors)	18 (64)	13 (27)	
Ann Arbor stage, n (%)			
• I-II	4 (14)	30 (63)	<0.01
• III-IV	24 (86)	18 (37)	
>1 extranodal site, n (%)	18 (64)	13 (27)	<0.01
LDH > upper normal value, n (%)	18 (64)	9 (19)	<0.01
ECOG performance ≥2	7 (25)	7 (15)	0.4
Radiotherapy in 1st line treatment, n (%)	8 (29)	29 (60)	<0.01
CNS prophylaxis in 1st line treatment, n (%)			
• Any CNS prophylaxis	8 (29)	38 (79)	
• Intratechal CNS prophylaxis	6 (21)	29 (60)	<0.01
• Systemic CNS prophylaxis	5 (18)	17 (35)	

Table II: Outcome	Female reproductive organ involvement (n=28)	Testicular involvement (n=48)	P
3-yr overall survival, %	47 (28-64)	75 (60-85)	0.01*
3-yr progression-free survival, %	43 (25-61)	73 (57-84)	0.01*
3-yr cumulative CNS relapse risk, %	30 (16-53)	8 (2-21)	0.04*

*Log-rank entire follow-up period. All analyses stratified by sex.

Conclusions

Although involvement of reproductive organs in women mainly occurred in the context of disseminated DLBCL, the number of CNS events was strikingly high among women with uterine DLBCL, and screening for occult CNS disease at diagnosis and consideration of CNS-directed prophylaxis may be appropriate in these patients. The widespread use of CNS prophylaxis for patients with testicular lymphomas likely reduced their risk for CNS events. Involvement of female reproductive organs carries a dismal prognosis.

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Figure 1: Overall survival according to reproductive DLBCL involvement in women (left) and men (right)

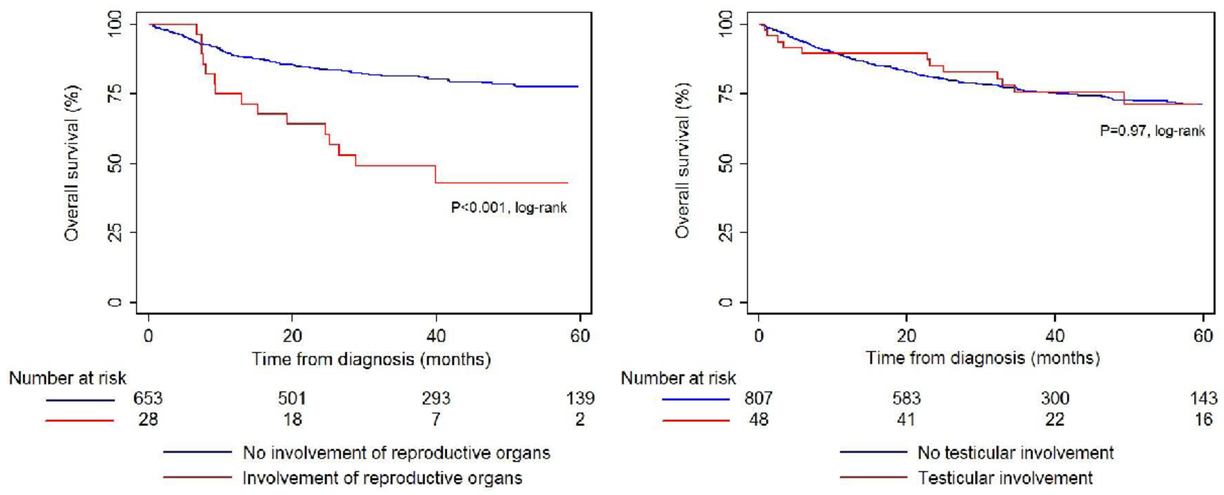


Figure 2: Progression-free survival according to reproductive DLBCL involvement in women (left) and men (right)

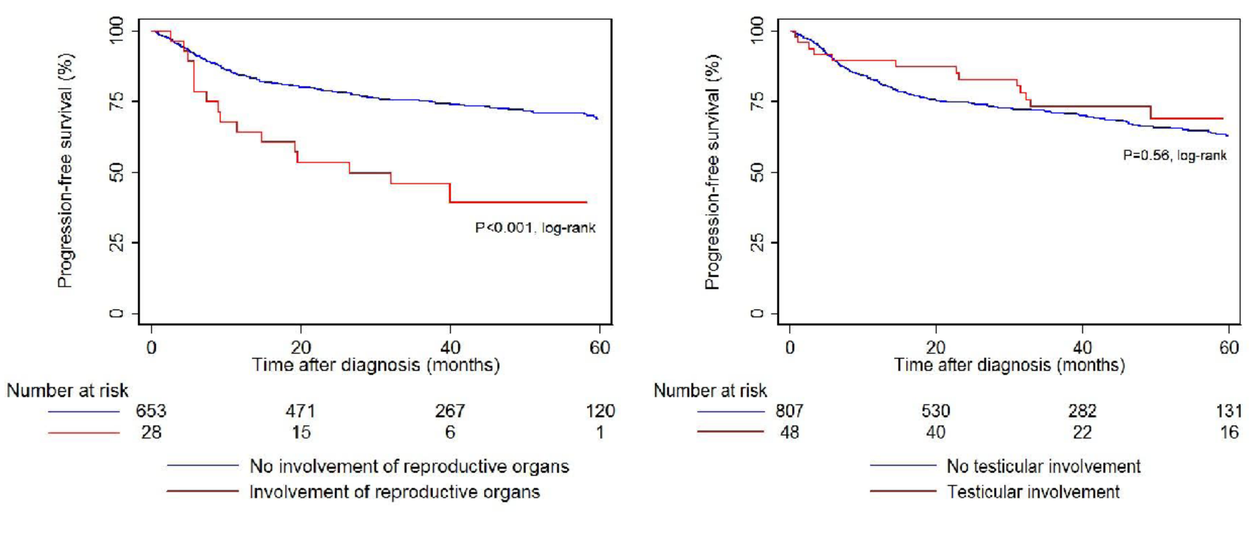


Table III: Risk factors for CNS relapse	Women (n=681)		Men (n=855)	
	Univariate HR	Multivariate HR	Univariate HR	Multivariate HR
Reproductive organ involvement*	8.94 (3.77-21.22)	6.34 (2.36-17.01)	2.53 (1.04-6.15)	2.18 (0.86-5.48)
Reproductive organ involvement, specified (women)				
• Ovary	4.26 (1.01-18.04)	1.98 (0.39-10.11)		
• Uterus	16.65 (7.01-39.54)	15.08 (6.83-33.28)		
DSHNHL high risk for CNS relapse	9.38 (4.08-21.58)	8.25 (3.44-19.78)	3.96 (2.02-7.76)	3.80 (1.93-7.48)

*Testicular involvement in men, female reproductive organ involvement in women (ovary and/or uterus). Univariate and multivariate analyses with death before CNS relapse as competing risk (stcrreg). Multivariate analyses include reproductive organ involvement, DSHNHL high-risk disease, and CNS prophylaxis. All analyses stratified by sex

Figure 3: Cumulative incidence for CNS relapse according to reproductive DLBCL Involvement in women (left) and men (right). Deaths before CNS relapse are treated as competing risks

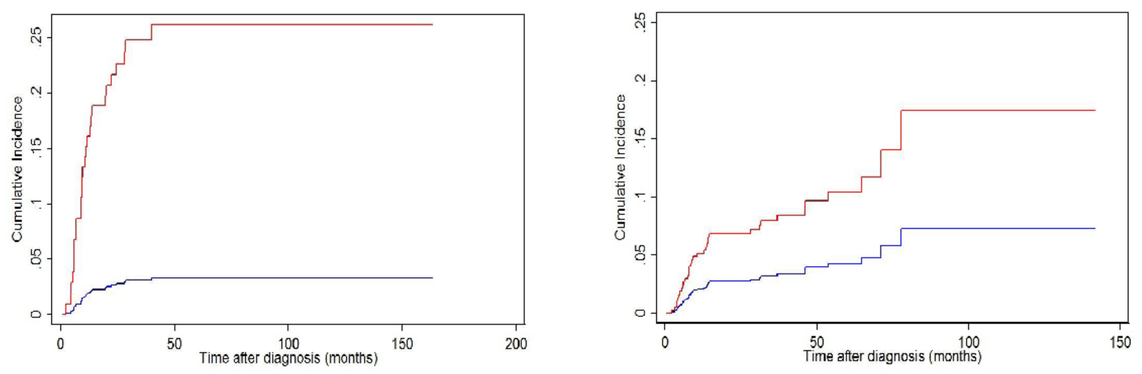
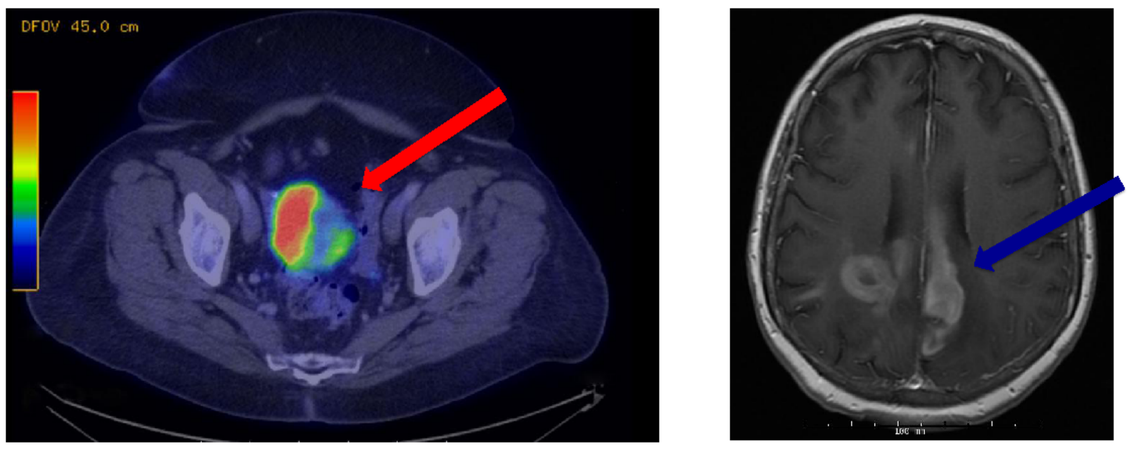


Figure 4: 62-year old woman with stage 4B DLBCL involving the uterus (PET/CT, red arrow). She was diagnosed with CNS relapse (CT, blue arrow) shortly after completing R-CHOP therapy. No CNS prophylaxis was given.



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