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**Lack of effectiveness of routine clinic and blood test-based follow-up for diffuse large B cell lymphoma**

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Key Words:	LYMPHOID MALIGNANCIES, follow up, LDH

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4 Lack of effectiveness of routine clinic and blood test-based follow-up  
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7 for diffuse large B cell lymphoma  
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5 The optimal approach to surveillance following remission with first line therapy for diffuse  
6 large B cell lymphoma (DLBCL) remains controversial with a paucity of evidence whether  
7 follow up is effective in early relapse detection, role of blood tests, optimal frequency and  
8 duration of follow up, and little data in the modern rituximab era (Cohen, *et al* 2015).  
9  
10 There is no guideline consensus. British Society of Haematology guidelines in 2016  
11 recommend clinical follow up for two years followed by discharge, based on the observation  
12 that <10% of patients relapse after more than two years (Chaganti, *et al* 2016). The  
13 National Institute of Clinical Excellence (NICE) guidelines in 2016 recommend follow up for  
14 three years (National Institute of Clinical Excellence). By contrast, the 2014 Lugano  
15 consensus recommends longer follow up, 3 monthly for 2 years, 6 monthly for 3 years and  
16 then annual follow up (Cheson, *et al* 2014). We have evaluated the approach in our centre  
17 in the rituximab era with clinical follow up for at least 5 years with routine blood tests  
18 including lactate dehydrogenase (LDH) without routine imaging.  
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30 Patients with DLBCL treated in the Leeds Cancer Centre between 2006-2014 were  
31 retrospectively identified. Criteria for inclusion were: age >18 at diagnosis, pathological  
32 diagnosis of DLBCL, curative intent treatment with rituximab and anthracycline-containing  
33 chemotherapy, response consistent with remission. Exclusion criteria were: palliative  
34 treatment including attenuated chemotherapy, transformed indolent lymphoma,  
35 concurrent low grade lymphoma, CNS disease. Standard follow up schedule was: clinic 3  
36 monthly for 1 year, 4 monthly for 1 year, 6 monthly for 3 years, option of discharge or  
37 annual follow up, with a bloods including LDH at each appointment. Imaging was not  
38 routinely performed, although occasionally at clinician discretion. Relapse was categorised  
39 as symptomatic (including patient-detected lymph nodes) or asymptomatic (including  
40 abnormal examination findings not been noticed by the patient). Methods of relapse  
41 detection were categorised: patient reported at routine clinic, clinical examination at  
42 routine clinic (abnormality not reported by patient), detection via routine clinic blood tests,  
43 early clinic visit, routine imaging, other route (e.g. Accident and Emergency (A&E)  
44 department attendance, via General Practitioner (GP)).  
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4 185 patients were identified who entered routine follow up. Patient and treatment  
5 characteristics are shown in Supplementary Table 1. Median follow-up was 57.2 months  
6 (range 5.9-109 months). Two and five year relapse-free survival and overall survival were  
7 87.4%, 84.6% and 90.2%, 79.5% respectively. 30/185 (16.2%) of patients relapsed during  
8 follow up. 7/30 (23%) of relapses were in patients with stage I/IIA disease. Median time to  
9 relapse was 16 months post diagnosis. 23/30 relapses (77%) occurred within 24 months of  
10 diagnosis.  
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18 Regarding relapse presentation, 26/30 (87%) were symptomatic at time of relapse. Of these,  
19 10 presented with pain, 7 with a new patient-detected lump, three with CNS symptoms, and  
20 one each with lethargy, dyspnoea, ascites, increased sweating, weight loss and a  
21 dermatological lesion. Table 1 summarises the method of relapse detection. 10/30 (33%)  
22 relapses were via self-reports at routine clinic appointments and 8/30 (27%) self-reports  
23 between clinics (via a telephone call from patients regarding new concerning symptoms,  
24 prompting unscheduled clinic assessment). 3/30 (10.0%) relapses were identified after a GP  
25 referral and 5/30 (16.7%) as the result of attendance at an A&E department. 4 patients who  
26 had a relapse detected were asymptomatic and did not report any concerns. This included  
27 two patients had abnormal lymph nodes detected at routine clinic examination. One  
28 patient had pancytopenia detected on a routine bloods 12 months post treatment at follow  
29 up; this patient had bone marrow disease at presentation. One patient had relapse  
30 identified on a CT scan repeated 3 months following post-treatment imaging in view of a  
31 complete response unconfirmed. Overall, 16/30 (53.3%) relapses were identified outside  
32 routine clinical follow up appointments. Figure 1 summarises methods of relapse detection.  
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46 These data show that this clinically based follow up schedule incorporating regular blood  
47 monitoring was ineffective at detection of asymptomatic disease recurrence. The pattern of  
48 the majority of relapses occurred early is consistent with other series (El-Galaly, *et al* 2015,  
49 Thompson, *et al* 2014). A large majority of relapses were detected via symptomatic  
50 presentation, consistent with reports of clinical follow up programmes pre-rituximab (Elis, *et*  
51 *al* 2002, Weeks, *et al* 1991). Despite a frequent schedule of routine clinic visits/blood  
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3 monitoring, most patients with relapse presented between regular clinic intervals, with a  
4 majority (53%) of relapses detected via either unscheduled appointments or GP/A&E visits.  
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8 Routine blood monitoring led to the detection of relapse in a single asymptomatic patient in  
9 this series. There were no cases of asymptomatic relapse detection based upon LDH  
10 elevation. A study in the pre-rituximab era (Weeks, *et al* 1991) led to the widespread  
11 implementation of LDH in routine surveillance. However, it has been shown that most  
12 patients with relapse preceded by an LDH elevation also have symptoms (El-Sharkawi, *et al*  
13 2012), and that a raised LDH has limited sensitivity (44-69%) and poor positive predictive  
14 value (9-38%) (Cheah and Seymour 2014). The lack of utility of routine blood tests,  
15 including LDH, in our series suggests that routine blood monitoring has little value.  
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24 The question of whether it is feasible to detect early asymptomatic recurrence should  
25 underpin the design of evidence-based follow up programmes. Imaging surveillance is not  
26 recommended (Cheson, *et al* 2014); in studies with CT or PET, the majority of relapses were  
27 identified symptomatically outside of the timeframe of scheduled visits with no survival  
28 benefit (El-Galaly, *et al* 2015, Thompson, *et al* 2014). DLBCL relapse is generally aggressive  
29 with rapidly developing symptoms. Rapid disease progression translates into a short lead  
30 time for preclinical diagnosis. This is reflected in our results with the observation of a very  
31 high proportion of relapses being symptomatic and often detected at unscheduled visits or  
32 via other healthcare routes, with the use of routine bloods being ineffective. These data  
33 suggest that follow up programmes should be reconfigured to improve responsiveness to  
34 patient reported symptoms. Long term routine face-to-face clinic follow up of  
35 asymptomatic patients is of little value, and early discharge with education and rapid clinic  
36 access for re-evaluation can be recommended.  
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## Figures

Figure 1: Pattern of relapse detection over time. Relapses detected via routine clinic follow up (blue) and outside of routine clinic follow up (red).

For Peer Review

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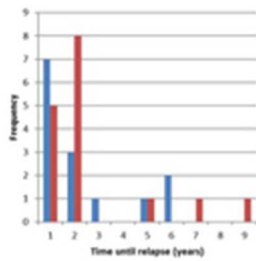
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Table 1: Method of relapse detection

Method of relapse detection	Overall	Relapse within 2 years of diagnosis	Relapse after 2 years of diagnosis
Patient self-reporting between routine clinics	8	6	2
Patient self-reporting at routine clinics	10	7	3
Clinical examination during routine clinics	2	1	1
Routine blood tests	1	1	0
Routine radiological investigations	1	1	0
GP referral	3	3	0
A&E admission	5	4	1

Supplementary Table 1: Patient, disease, treatment characteristics of patients entering routine follow up

	n (total =185)	%
<b>Age (years):</b>		
Mean	62	
Median	65	
Range	20 – 91	
<b>Sex:</b>		
Male	109	58.9
Female	76	41.1
<b>Stage:</b>		
Stage IA/IIA:	76	41.1
Stage IA	38	20.5
Stage IIA	38	20.5
Stage IB/IIB/III/IV:	109	58.9
Stage IB	2	1.1
Stage IIB	6	3.2
Stage IIIA/IIIB	26	14.1
Stage IVA/IVB	75	40.5
B symptoms	37	20.0
Extranodal	30	16.2
<b>Treatment regimen:</b>		
R-CHOP	179	96.8
R-CODOX-M/IVAC	6	3.2
<b>All patients:</b>		
3 x R-CHOP + radiotherapy	19	10.3
6-8 x R-CHOP	109	58.9
6-8 x R-CHOP + radiotherapy	27	14.6
<6 x R-CHOP*	24	13.0
R-CODOX-M/IVAC	6	3.2
<b>Response assessment:</b>		
CT	131	70.8
PET	46	24.9
Other**	8	4.3

\*Planned for 6-8 x R-CHOP but stopped early due to toxicity (8 with stage I/IIA disease).

\*\*No radiologically assessable disease (either excised at diagnosis or detectable by endoscopy only)