

Table I: Baseline characteristics of all patients

	All patients N=690	Under 80 N=452	80 and over N=238
Age, median (years; range)	77.2 (69.5- 96.4)	74.8 (69.5- 79.99)	83.3 (80.0- 94.3)
Sex			
Male	350 (50.7)	234 (51.8)	116 (48.7)
Female	340 (49.3)	218 (48.2)	122 (51.3)
Bulky disease (>10cm) at baseline			
No	551 (80.2)	360 (80.0)	191 (80.6)
Yes	136 (19.8)	90 (20.0)	46 (19.4)
Number of extra nodal sites, median (range)	1 (0-5)	1 (0-5)	1 (0-5)
0	248 (35.9)	157 (34.7)	91 (38.2)
1	229 (33.2)	138 (30.5)	91 (38.2)
2	122 (17.7)	90 (19.9)	32 (13.4)
3	53 (7.7)	40 (8.8)	13 (5.5)
4	27 (3.9)	20 (4.4)	7 (2.9)
5	11 (1.6)	7 (1.5)	4 (1.7)
IPI Factors			
Stage			
I-II	218 (31.6)	136 (30.1)	82 (34.5)
III/IV	472 (68.4)	316 (69.9)	156 (65.5)
ECOG Performance status			
0-1	408 (59.4)	281 (62.3)	127 (53.8)
>1	279 (40.6)	170 (37.7)	109 (46.2)
Missing	3	1	2
LDH			
Normal	235 (35.0)	149 (33.9)	86 (37.2)
Raised	436 (65.0)	291 (66.1)	145 (62.8)
Missing	19	12	7
Extra nodal sites			
<2	477 (69.1)	295 (65.3)	182 (76.5)
2+	213 (30.9)	157 (34.7)	56 (23.5)
Any extranodal site	443 (64.2)	295 (65.3)	147 (61.8)
High IPI*			
IPI 1-2	231 (33.9)	147 (32.7)	84 (36.2)
IPI 3-5	451 (66.1)	303 (67.3)	148 (63.8)
Missing	8	2	6
CNS IPI score			
Renal and/or Adrenal involvement at baseline			
No	629 (91.2)	405 (89.6)	224 (94.1)
Yes	61 (8.8)	47 (10.4)	14 (5.9)
Renal involvement at baseline			
No	231 (33.9)	416 (92.0)	227 (95.4)
Yes	451 (66.1)	36 (8.0)	11 (4.6)
Adrenal involvement at baseline			
No	671 (97.2)	437 (96.7)	234 (98.3)
Yes	19 (2.8)	15 (3.3)	4 (1.7)
CNS IPI score			
1	82 (12.3)	53 (12.1)	29 (12.7)
2	145 (21.7)	90 (20.5)	55 (24.0)
3	173 (25.9)	113 (25.7)	60 (26.2)
4	159 (23.8)	104 (23.7)	55 (24.0)
5	87 (13.0)	61 (13.9)	26 (11.4)
6	22 (3.3)	18 (4.1)	4 (1.7)
Missing	22	13	9
CNS IPI grouped*			
Low risk CNS IPI (0-1)	82 (12.0)	53 (11.8)	29 (12.5)
Intermediate risk CNS IPI (2-3)	327 (47.9)	205 (45.6)	122 (52.6)
High risk CNS IPI (4-6)	271 (39.7)	185 (41.1)	86 (37.1)
Missing	10	9	1

*Includes patients who were missing baseline LDH but could be grouped regardless of its value. Abbreviations: CNS: central nervous system; IPI: international prognostic index; ECOG PS: Eastern co-operative oncology group performance status; LDH: lactate dehydrogenase.

Table II: Prophylaxis received by CNS-IPI risk category

	None N (%)	IT only N (%)	IV only N (%)	Both N (%)	Any Prophylaxis N (%)
Low risk (0-1)	70 (85.4)	7 (8.5)	3 (3.7)	2 (2.4)	12 (14.6)
Intermediate risk (2-3)	292 (89.3)	26 (8.0)	2 (0.6)	7 (2.1)	35 (10.7)
High risk (4-6)	190 (70.1)	64 (23.6)	9 (3.3)	8 (3.0)	81 (29.9)

Fisher's exact test risk group/CNS prophylaxis (in categories) $p < 0.001$, Chi squared any prophylaxis $p < 0.001$. Abbreviations: CNS: central nervous system; IPI: international prognostic index; IT: intrathecal; IV: intravenous

Table III: Multivariable analysis of the risk of an infective admission during R-CHOP immunochemotherapy

Baseline factor	All Patients			Patients alive and progression free at 6 months		
	Events/N	Odds ratio (95% CI)	p value	Events/N	Odds ratio (95% CI)	p value
CNS prophylaxis						
None	134/534	1.00		107/432	1.00	
IT prophylaxis	41/93	2.20 (1.31-3.67)	0.010	33/77	2.24 (1.26 – 4.00)	0.021
IV high dose prophylaxis	2/14	0.43 (0.09-2.03)		2/13	0.49 (0.10 – 2.43)	
IT and IV high dose prophylaxis	6/16	1.56 (0.53-4.63)		6/15	1.83 (0.58 – 5.72)	
Number of complete cycles*	183/657	0.90 (0.79 – 1.03)	0.11	148/537	0.85 (0.71 – 1.03)	0.099
Age*	183/657	0.96 (0.92 – 0.99)	0.016	148/537	0.95 (0.91 – 0.99)	0.017
Stage						
I-II	42/206	1.00	0.15	36/182	1.00	0.14
III-IV	141/451	1.41 (0.89 – 2.25)		112/355	1.49 (0.87 – 2.54)	
ECOG						
0-1	95/399	1.00	0.13	82/348	1.00	0.079
2+	88/258	1.36 (0.91 – 2.03)		66/189	1.50 (0.95 – 2.36)	
LDH						
Normal	52/232	1.00	0.19	42/200	1.00	0.049
Raised	131/425	1.31 (0.88 – 1.96)		106/337	1.58 (1.00 – 2.50)	
Extra nodal sites						
0-1	114/455	1.00	0.55	96/383	1.00	0.47
2+	69/102	1.15 (0.73 – 1.81)		52/154	1.21 (0.72 – 2.03)	
Renal or adrenal involvement						
No	167/602	1.00	0.074	139/487	1.00	0.035
Yes	16/55	0.52 (0.26 – 1.06)		9/40	0.39 (0.16 – 0.94)	
CIRS-G score*	183/657	1.01 (0.96-1.06)	0.79	148/537	1.00 (0.95 – 1.07)	0.89
Haemoglobin (g/dL)*	183/657	0.98 (0.97-0.995)	0.006	148/537	0.97 (0.95 – 0.996)	0.019
Albumin (g/L)*	183/657	0.99 (0.96-1.01)	0.35	148/537	0.99 (0.96 – 1.02)	0.66

657 patients with data on all variables (537 at 6 months). *continuous variable. Abbreviations: CIRS-G: Cumulative Illness Rating Scale-Geriatric; CNS: central nervous system; IPI: international prognostic index; IT: intrathecal; IV: intravenous. N.B. Echo was available n= 385 and results were consistent when added into the multivariable model. **OR for IT prophylaxis (all patients) when adjusted for CNS IPI (instead of component parts) 2.22 (1.36 – 3.61), just those alive and progression free at 6 months: 2.14 (1.25 – 3.67).**

Table IV: Univariable analysis of the risk of CNS relapse

Factor	events/N	SHR (95% CI)	p-value	3 year Cumulative incidence
Age (for an increase of 10 years)	19/689	1.07 (0.45 - 2.54)	0.88	-
Age (grouped)				
Under 80	11/451	1.00	0.43	2.6% (0.1 – 4.7)
80 and over	8/238	1.45 (0.58 – 3.60)		4.3% (2.1 – 8.6)
Sex				
Male	11/350	1.00	0.53	3.9% (0.2 – 7.0)
Female	8/339	0.75 (0.30 – 1.86)		2.3% (1.1 – 4.8)
Bulky disease				
Absent	16/550	1.00	0.74	3.3% (2.0 – 5.4)
Present	3/136	0.81 (0.24 – 2.80)		2.5% (0.8 – 7.5)
Stage				
I/II	5/218	1.00	0.54	2.3% (0.9 – 6.1)
III/IV	14/471	1.37 (0.49 – 3.82)		3.5% (2.1 – 5.9)
ECOG*				
0-1	6/410	1.00	0.020	1.8% (0.7 – 4.3)
2-4	12/276	3.03 (1.14 – 8.06)		4.8% (2.7 – 8.3)
LDH*				
Normal	3/235	1.00	0.058	1.0% (0.2 – 3.8)
Raised	16/435	3.10 (0.90 – 10.65)		4.5% (2.7 – 7.3)
Extra nodal sites				
0-1	11/476	1.00	0.23	2.6% (1.4 – 4.9)
>1	8/213	1.74 (0.70 – 4.33)		4.2% (2.1 – 8.3)
IPI score*				
1-2	4/231	1.00	0.20	1.7% (0.5 – 5.4)
3-5	15/450	2.03 (0.67– 6.11)		3.9% (2.3 – 6.4)
Renal/adrenal sites				
Not involved	14/628	1.00	0.004	2.5% (1.4 – 4.3)
Involved	5/61	4.08 (1.47 – 11.34)		10.0% (4.2 – 22.7)
CNS IPI (grouped)				
Low risk (0-1)	3/82	1.00	0.076	2.9% (0.7 – 10.9)
Intermediate risk (2-3)	3/326	0.26 (0.05 – 1.28)		1.4% (0.5 – 4.5)
High risk (4-6)	13/271	1.44 (0.41 – 5.04)		5.5% (3.2 – 9.3)
CNS IPI**				
0-3	6/413	1.00	<0.001	1.7% (0.7 – 4.1)
4	5/157	2.26 (0.69 – 7.41)		3.6% (1.5 – 8.4)
5	3/87	2.69 (0.67 – 10.77)		3.8% (1.2 – 11.3)
6	4/22	15.45 (4.35 – 54.85)		21.8% (8.6 – 49.3)
CNS Prophylaxis				
No	13/559	1.00	0.12	2.7% (1.5 – 4.7)
Yes	6/130	2.11 (0.80 – 5.56)		5.1% (2.3 – 11.1)
CNS Prophylaxis				
None	13/559	1.00	0.25	2.7% (1.5 – 4.7)
IT only	5/99	2.32 (0.83 – 6.52)		5.5% (2.3 – 12.7)
Includes HDMTX	1/31	1.45 (0.19 – 11.12)		3.9% (0.6 – 24.5)
Ratio of intention to given (for an increase of 0.1)	19/689	1.03 (0.81 – 1.30)	0.84	-

*Fails the assumption of proportional hazards so HR can only be considered an average. Log-rank p-value and rates remain appropriate. **1 CNS relapse unable to categorise. Abbreviations: CNS: central nervous system; IPI: international prognostic index; ECOG PS: Eastern co-operative oncology group performance status, LDH: lactate dehydrogenase.

Table V: Univariable and adjusted risk of CNS relapse – according to CNS prophylaxis and CNS-IPI

Factor	Events/N	Univariable (complete cases)* HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
CNS prophylaxis					
No	12/550	1.00	0.09	1.00	0.59
Yes	6/129	2.27 (0.85 – 6.04)		1.34 (0.46 – 3.86)	
CNS IPI					
0-3	6/413	1.00	<0.001	1.00	0.012
4	5/157	2.26 (0.69 – 7.41)		2.20 (0.67 – 7.25)	
5	3/87	2.69 (0.67 – 10.77)		2.47 (0.60 – 10.28)	
6	4/22	15.45 (4.35 – 54.85)		13.60 (3.51 – 52.77)	
Patients alive and PFS free at 6 months					
CNS prophylaxis					
No	9/439	1.00	0.61	1.00	0.85
Yes	3/109	1.41 (0.38 – 5.20)		0.87 (0.21 – 3.65)	
CNS IPI					
0-3	5/351	1.00	0.016	1.00	0.08
4	4/126	2.34 (0.63 – 8.72)		2.37 (0.63 – 8.90)	
5	1/59	1.34 (0.16 – 11.50)		1.41 (0.16 – 12.66)	
6	2/12	13.71 (2.65 – 70.96)		14.74 (2.46 – 88.36)	

*i.e. excludes patients with missing CNS scores, this includes 1 patient with a CNS event.