research article

A multi-institutional analysis of diffuse large B-cell lymphoma (DLBCL) treated with consolidative radiotherapy and the impact of cell-of-origin on outcomes

Chrishanthi Rajasooriyar[1], Jeremy Tey[2], Lea Choung Wong[2], Michelle Poon[3], Rao Nandini[4], Ivan Tham[2], Balamurugan Vellayappan[2]

[1] Department of Oncology, Teaching Hospital, Jaffna, Sri Lanka
[2] Department of Radiation Oncology, National University Cancer Institute Singapore, National University Health System, Singapore
[3] Department of Haematology-Oncology, National University Cancer Institute Singapore, National University Health System, Singapore
[4] Department of Pathology, Tan Tock Seng Hospital, Singapore

Radiol Oncol 2019; 53(4): 473-479.

Received 26 June 2019
Accepted 11 August 2019

Correspondence to: Assist. Prof. Balamurugan Vellayappan MBBS, FRANZCR, MCI, Department of Radiation Oncology, National University Cancer Institute Singapore, National University Health System, 1E Kent Ridge Road, Level 7 Tower Block, Singapore 119228.
E-mail: bala_vellayappan@nuhs.edu.sg

Disclosure: No potential conflicts of interest were disclosed.

Background. Patients with diffuse large B-cell lymphoma (DLBCL) with bulky disease and/or those who fail to achieve complete response benefit from the addition of radiotherapy (RT). We aim to review the outcome, as well as determine the impact of cell-of-origin, on patients undergoing consolidative RT.

Patients and methods. Patients with DLBCL treated with radical intent consolidative RT were included. Clinical, pathological and treatment characteristics were extracted from electronic medical records. Survival outcomes and factors that predict for disease-free survival (DFS) were analysed.

Results. Seventy-four patients were included in this analysis. The median follow up was 3 years (0.7–16 years). Fifty-eight percent of patients had stage I–II disease, and 61% received at least 6 cycles of chemotherapy. Cell-of-origin was discernible in 60% of patients, and approximately half were classified as Germinal centre origin. The 5-year overall survival (OS) of this group was excellent at 92% (median survival not reached). The 5-year DFS was 73% (95% CI 57–83%). Seven percent (n = 5) of patients experienced local recurrence at a median time of 6 months. Failure to achieve complete response post RT and/or initial bulky disease are significant predictors of inferior DFS. There was no association between cell-of-origin and DFS or OS.

Conclusions. The outcome of patients who received radiotherapy as consolidation is excellent. Patients who fail to achieve complete response after radiotherapy had poorer outcomes. Despite using radiotherapy, presence of bulky disease remains a significant predictor of disease recurrence. We did not find any association of poorer outcomes, with regards to cell-of-origin, in the use of consolidative RT.

Key words: lymphoma; cell-of-origin; radiotherapy; consolidation

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma in adults, accounting for about 30–60% of all cases.[1] It has an aggressive natural history, with a prognosis of less than a year without treatment.[2] Radiotherapy (RT), historically, has been an integral part of DLBCL

treatment.[3] However, with the implementation of new systemic therapy agents, the use of RT has declined.[4,5] The discovery of the chimeric monoclonal antibody rituximab against CD20 receptors has greatly improved the control and cure of DLBCL.[6] Data from the MINT studies suggest that rituximab reduced the risk posed by bulky disease, but did not eliminate it.[7] In line with that, many studies have shown the improved outcome with the addition of RT, especially in the context of bulky disease.[8,9]

However, clinicians have noticed that the behaviour of DLBCL can be varied, and attempts have been made to better classify DLBCL.[10] Based on gene expression profiling studies, DLBCL can be divided into 2 distinct subtypes: Germinal Centre B cell (GCB) and non-Germinal Centre B- cell subtype (non-GCB).[11] Immunohistochemistry based algorithms have been shown to have good concordance with gene expression profiling for cell-of-origin classification.[12] Studies based on Western populations have suggested that GCB-subtypes are associated with improved outcomes.[13] However, these findings could not be replicated in the Asian population.[14] It is important to note that these patients were treated primarily with chemotherapy, and the impact of cell-of-origin for patients undergoing consolidative RT is unclear.

The aim of this study is to report the outcome of patients with DLBCL treated with

rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone (R-CHOP) or R-CHOP like chemotherapy and consolidative RT. In addition, we classified patients according to cell-of-origin (where information available) and determined the impact on the outcomes.

Patients and methods

Patient selection criteria

This was a retrospective cohort study carried out at two tertiary hospitals in Singapore. (National University Hospital and Tan Tock Seng Hospital). Institutional review board approval was obtained and waiver of consent was granted. From June 2001 to August 2015, patients with histologically confirmed DLBCL, stages I–IV, who received R-CHOP, or R-CHOP like chemotherapy, and received consolidative RT were identified through the institutional RT database. Only patients treated with curative intent were included.

Staging was based on Ann Arbor Classification. Bulky disease was defined as any nodal or extra-nodal mass with a dimension of more than 7.5 cm in any direction. International prognostic index (IPI) score was based on age, Eastern Cooperative Oncology Group (ECOG) performance status, serum lactate dehydrogenase (LDH), stage of the disease and the number of extra-nodal sites.[15]

Patient records were carefully reviewed and the following parameters were extracted: Age, gender, ethnicity, stage, use of positron emission tomography / computed tomography (PET/CT) for staging, extra-nodal involvement, baseline PET standardized uptake value (SUV), Eastern Cooperative Oncology Group (ECOG) performance status, B symptoms, presence of bulky disease, elevated LDH, IPI score, number of cycles of chemotherapy, pre-RT response (complete response *vs.* not in complete response) and RT dose-fractionation. For cell-of-origin, patients were classified based on the Hans algorithm (Figure 1).

Treatment details

All patients received R-CHOP or R-CHOP like chemotherapy. Patients with IPI 0–1 and limited stage received 3–4 cycles of chemotherapy, whereas all other patients received 6 or more cycles of chemotherapy. All patients had a response assessment scan post-chemotherapy, before proceeding onto RT. The cell-of-origin did not influence the treatment decision.

The decision for RT was made based on consensus at the multidisciplinary board meeting, taking into account the bulky disease, number of chemotherapy cycles and response to chemotherapy (assessed on PET/CT or contrast-enhanced CT using established guidelines).[16] Patients with complete response were treated to a dose of 30–36 Gy, and patients with partial response or stable disease were treated to 40–50 Gy, both in 1.8–2 Gy fractions. RT was delivered using either using a 3-dimensional conformal or intensity-modulated tech-

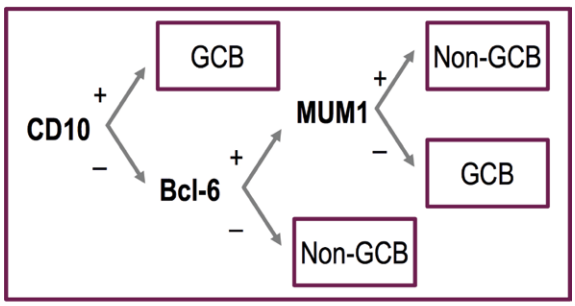


FIGURE 1. Hans classification.

nique, at the discretion of the treating physician. Involved-field radiotherapy (IFRT) was used in cases who were not staged by PET/CT.[17] Involved-site radiotherapy (ISRT), described below, was used in cases who were staged with PET/CT.[18] PET/CT staging was available from 2011 and routinely used from 2014. In both situations, the staging and post-chemotherapy scans were utilized to determine the target volume.

ISRT technique: The gross tumour volume [GTV] was the residual tumour post-chemotherapy. The clinical target volume [CTV] included the GTV, craniocaudal extent of the pre-chemotherapy tumour volume and the circumferential extent of the post-chemotherapy tumour volume with the addition of 1–1.5 cm craniocaudal margin and 0.5–1 cm of circumferential margin. When there was a complete response to chemotherapy, the CTV was based on pre-chemotherapy volumes respecting anatomical boundaries for lateral extent of tumour. The planning target volume [PTV] was created by adding 0.5–1cm to the CTV. Image guidance was performed primarily with electronic portal imaging. On-board kilovoltage cone beam CT was used for selected cases (available since 2011).

Follow up

Patients were followed up with PET/CT or contrast-enhanced CT scan 3 months after the completion of RT. The complete responders were reviewed every 3 months for the first 2 years alternating with the haematologist and for 6 months from 3rd to the 5th year. A full blood count and lactate dehydrogenase were checked at each follow-up, together with clinical history and examination for signs of recurrence. Re-imaging and further investigations were performed when there was a suspicion of recurrence.

Outcome assessment

Overall survival (OS) was defined as the time from diagnosis to death due to any cause. Disease-free survival (DFS) was defined as the time from diagnosis to recurrence, or death. Patterns of relapse: local in-field (*i.e.* within radiation field), in the nodal regions (out-of-field) and distant sites. The time to local relapse was studied time from date of completion of RT to date of relapse.

Prognostic factors examined

We analysed the influence of age, gender, ECOG performance status, stage, presence of B symptoms, LDH, IPI score, presence of bulky disease, baseline SUV on PET, number of chemotherapy cycles, radiation dose, response to radiation and cell-of-origin on OS and DFS.

Statistical analysis

Descriptive statistics were used to summarize clinical and treatment characteristics. DFS and OS were analyzed using the Kaplan-Meier methods and graphically presented. The actuarial 5-year survival rates were estimated. For DFS, patients without recurrence were censored at death or date of last follow up. For OS, patients who were still alive were censored at the date of last follow-up. Patterns of relapse were reported with descriptive statistics. Univariable analysis was carried out on factors that may influence outcomes such as DFS and OS. Univariable factors with a P-value of < 0.1 were included in the multivariable analysis. The Cox regression model was used to compare sur-

TABLE 1. Patient characteristics and treatment details

Variable	Level	Number of patients (%)
All patients		74 (100)
Age	Median (range)	61 (14–88)
Gender	Males Females	43 (58) 31 (42)
Ethnicity	Chinese Malay Indian Others	54 (73) 10 (14) 1 (1) 9 (12)
Stage	I–II III–IV	43 (58) 31 (42)
Staging PET/CT	No Yes SUV max ≤ 20 SUV max > 20	44 (59) 30 (41) 12 (40) 18 (60)
Involvement of extra-nodal sites	Nodal only Extra-nodal +/- nodal	19 (26) 55 (74)
ECOG	0 1 2 3	20 (27) 47 (64) 3 (4) 4 (5)
Bulky disease	≤ 7.5cm > 7.5 cm	37 (57) 28 (43)
IPI score	0–1 2 3 4–5	28 (38) 26 (35) 13 (18) 7 (9)
Number of chemotherapy cycles	< 6 ≥ 6	28 (39) 44 (61)
Radiotherapy dose	≤ 36 Gy > 36 Gy	45 (61) 29 (39)
Cell-of-origin	Germinal centre Non-germinal centre Unknown	20 (27) 22(30) 32 (43)

ECOG = Eastern Cooperative Oncology Group performance status; IPI = international prognostic index; SUV = standardized uptake value

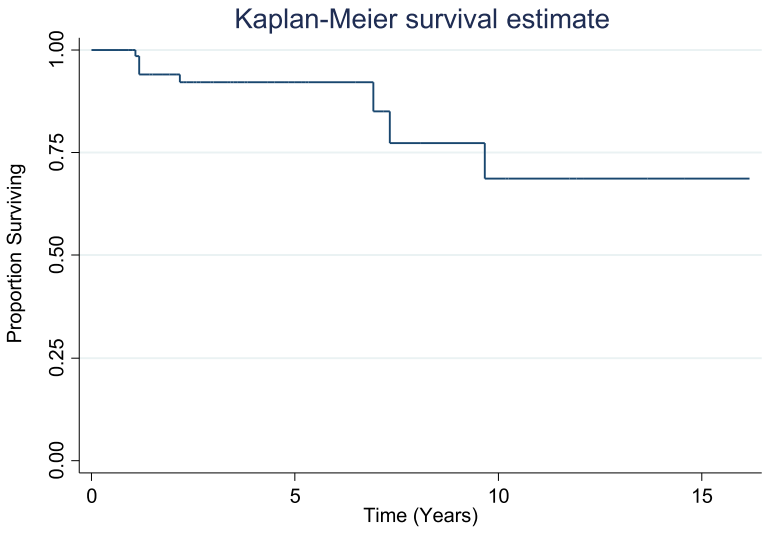


FIGURE 2. Overall survival.

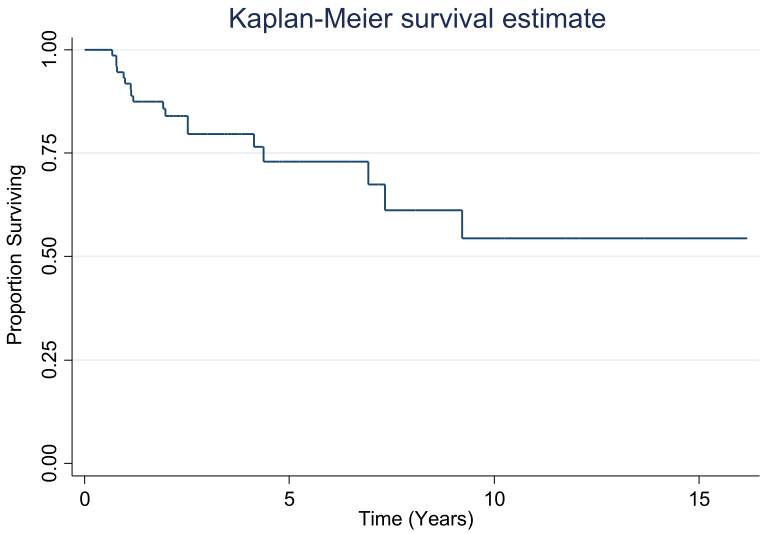


FIGURE 3. Disease-free survival.

vival estimates and calculate P values and hazard ratios. A P-value of < 0.05 was considered to be statistically significant. Statistical analysis was carried out using Stata Statistical Software (Release 14, College Station, TX: StataCorp LP)

Results

Seventy-four patients were included in the study and the demographic characteristics are shown in Table 1. The median age was 61 years ranging from 14–88 years. Fifty-eight percent were males and the same proportion had early-stage disease (Stage I–II). Bulky disease was seen in 43% of patients. About a third of the included patients had IPI scores of 0–1. Sixty-one percent had at least 6 cycles of chemotherapy. About two-thirds of the patients were treated to a dose of 36 Gy or less. Information on cell-of-origin was available in 60% of patients and was equally distributed between GCB and non-GCB origin. Median follow up of the cohort was 3 (0.7–16) years.

Survival and patterns of relapse

The 5-year OS was 92% (median survival not reached) (Figure 2) and 5-year DFS was 73% (median survival not reached) (Figure 3).

Fifty-three patients (72%) were in complete remission post-RT. Patients who achieved complete remission had a significantly better DFS (HR 11.05, 95% CI 4.11–29.69, P < 0.01). (Figure 4). The presence of initial bulky disease was associated with an inferior DFS (HR 3.16, 95% CI 1.02–9.78, P = 0.04) (Figure 5).

Uni-variable and multi-variable analysis for DFS and OS are presented in Table 2. Response to RT (P < 0.001) and tumour bulk (P < 0.02) were significant predictors of DFS. Only response to RT (P = 0.011) was a significant predictors of OS. There was no association between cell-of-origin and DFS or OS (P = 0.16, P = 0.61 respectively).

Patterns of relapse

In total 13 (18%) patients failed. Among those failed, 5 (7%) failed locally inside the treatment field, 11(15%) outside the treatment field in nodal regions and 10 (14%) at distant sites.

The median time for local recurrence was 6 [0–23] months. All five patients who recurred in-field, received doses between 36–40 Gy. These 5 patients also recurred in nodal regions outside the treatment field or at distant sites. Three of these patients were salvaged and were alive at the last follow up and two died due to progressive disease.

Discussion

DLBCL is an aggressive condition, which can behave variably.[10] The decision on whether to use consolidative RT remains controversial, especially in advanced stages where complete response has been achieved.[19] In this study, we report the outcomes of our patients treated with consolidative RT.

TABLE 2. UNI- and multivariable analysis for disease-free survival (DFS) and overall survival (OS)

Variable	DFS						OS		
	Univariable analysis			Multivariable analysis			Univariable analysis		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age (continuous)	1.03	1–1.06	0.081	1.02	0.98–1.06	0.37	1	0.96–1.05	0.86
Gender (ref: male)	1.78	0.70–4.51	0.23				1.38	0.34–5.51	0.65
ECOG (continuous)	1.64	0.92–2.95	0.096	0.42	0.18–1.00	0.05	1.05	0.35–3.15	0.93
Stage 1–2 (ref) *vs.* 3–4	1.19	0.46–3.01	0.71				1.84	0.44–.64	0.4
B symptoms (ref: yes)	0.51	0.8–1.48	0.22				0.25	0.5–1.23	0.088
Elevated LDH yes (ref) *vs.* no	1.06	0.34–3.34	0.92				2.38	0.28–20.18	0.43
IPI (ref) *vs.* 2–5	1.48	0.55–3.99	0.43				2.32	0.46–11.69	0.31
Bulk < 7.5 cm(ref) *vs.* ≥ 7.5 cm	3.16	1.02–9.78	**0.045**	6.10	1.34–27.87	**< 0.02**	3.19	0.46–22.15	0.24
Baseline PET SUV ≤ 20 (ref) *vs.* > 20	0.25	0.45–1.35	0.11				-	-	-
Chemotherapy < 6 cycles (ref) *vs.* ≥ 6 cycles	2.24	0.78–6.34	0.13				1.73	0.39–7.69	0.47
Dose < 36 Gy (ref) *vs.* ≥ 36 Gy	0.89	0.34–2.30	0.81				2.21	0.52–9.37	0.28
RT response CR(ref) *vs.* non CR	11.05	4.11–29.70	**<0.001**	5.64	2.78–11.45	**<0.001**	**6.26**	**1.53–25.7**	**0.011**
Cell of origin (ref GC) NGC unknown	 3.72 3.60	 0.74–18.54 0.79–16.50	 0.11 0.10				 2.57 3.77	 0.23–28.94 0.44–32.49	 0.44 0.23

ECOG = Eastern Cooperative Oncology Group performance status; GC = germinal centre B cell (GCB); IPI = international prognostic index; NGC = non-GC; RT = radiotherapy; SUV = standardized uptake value

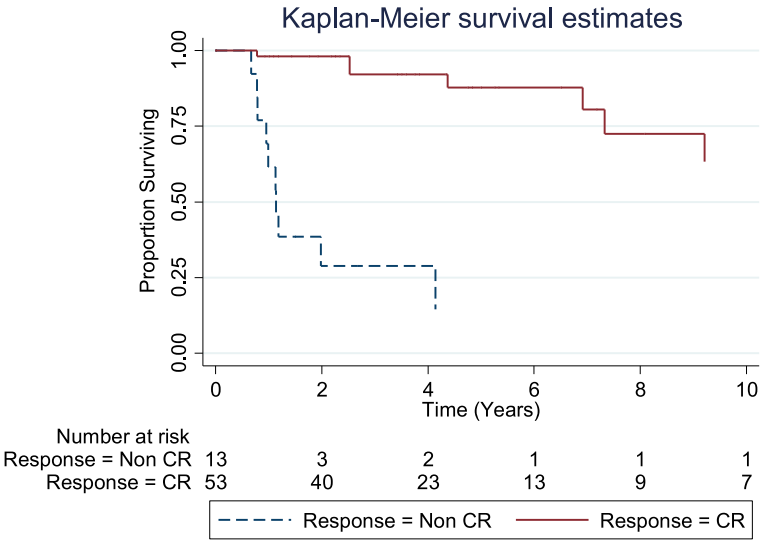
TABLE 3. Survival outcomes of aggressive lymphoma treated with consolidative RT

Author	Year of publication	Limited/advanced disease	DFS	OS
Horning *et al*.	2004	Limited	73% (6 yr)	82% (6 yr)
Reyes *et al*.	2005	Limited	74 (5 yr)	81 (5 yr)
Bonnet *et al*.	2007	Limited	63% (5 yr)	68% (5 yr)
Held *et al*.	2014	Limited & advanced	68% (3 yr)	78% (3 yr)
Aviles *et al*.	2018	Advanced	Not reported	91% (5 yr)
Lamy *et al*.	2018	Limited	92% (5 yr)	96% (5yr)
Pfreundschuh *et al*.	2018	Limited & advanced	84% (3 yr)	93% (3 yr)
Rajasooriyar et al.	2019	Limited & advanced	73% (5 yr)	92% (5 yr)

DFS = disease-free survival; OS = overall survival

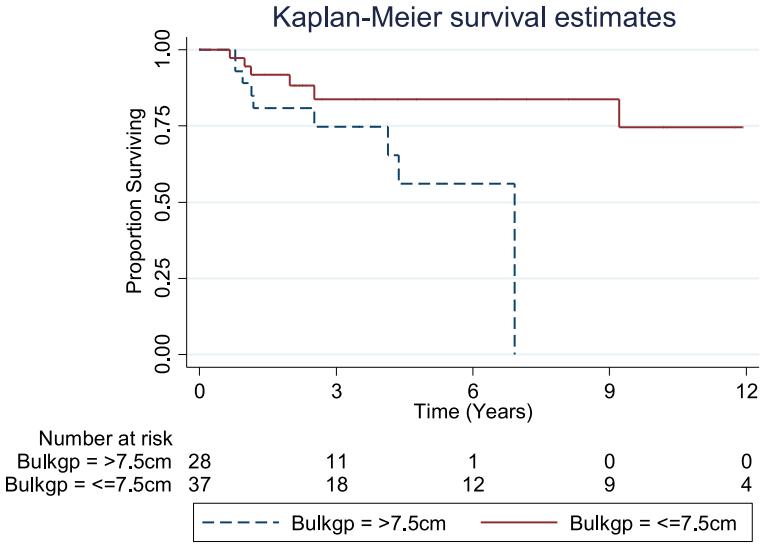
We report encouraging survival and disease control rates in this cohort–5-year OS of 92% and 5-year DFS of 73%. Our results are congruent with other contemporary series[9,20-25], which are summarised in Table 3. While assessing for predictors for improved DFS, we found that patients who were in complete response (post-RT) had improved DFS on multivariable analysis (HR 5.64, 95% CI 2.78–11.45, P < 0.001). This was not an unexpected finding as it is likely suggestive of better tumour biology. In addition, patients who had bulky disease (> 7.5cm) had an increased risk of relapse (HR 6.1 95% CI 1.34–27.87, P < 0.02). Bulky disease (at initial presentation) is considered to be an indication for consolidative RT, although the definition of bulk has varied across studies, from 5 cm(8, 26) to 10 cm.[20] In our institution, we use 7.5 cm as a definition of bulk, in line with the MINT studies.[7] As such, it is likely that consolidative RT reduces the risk of disease recurrence, but does not prevent it. As for OS, only complete response (post-RT) was predictive of improved OS.

Secondly, we were able to classify about two-thirds of our patients by cell-of-origin (into GCB



CR = complete response

FIGURE 4. Disease-free survival by response to radiotherapy.



Bulkgp = the bulky disease greatest dimension of mass in any direction (where >7.5cm is considered bulky)

FIGURE 5. Disease-free survival by presence of initial bulky disease.

vs. non-GCB). IHC markers of CD10, BCL-6 and MUM-1 were routinely performed from 2013. As such, 27% were classified to have GCB, 29% non-GCB and remainder were unclassified. Based on univariate analysis, non-GCB was not deemed to be a significant predictor of worse DFS or OS. (HR 3.72 95% CI 0.74–18.54, P = 0.11; HR 2.57 95% CI 0.23–28.94, P = 0.44), compared to GC. This should only be considered as hypothesis-generating as the number of events from our cohort is relatively small. In addition, we would like to qualify that there were no statistically significant differences between the GCB and non-GCB groups, in terms of initial bulky disease (P = 0.09) or response to RT (P = 0.27)

Thirdly, with regards to patterns of recurrence, some previous studies have analysed the patterns of failure in patients with DLBCL. Shi *et al.* analysed patients with DLBCL, who achieved complete remission after R-CHOP.[26] Almost half of the patients with advanced-stage DLBCL failed at the initial presenting sites even after achieving complete remission with R-CHOP. In addition, around half of such local failures occurred at initial bulky or bony sites. The local failure rate was 44% in the R-CHOP alone group compared to 7% with R-CHOP plus consolidative RT. Our series echoes the findings of Shi *et al.*, where only 7% of patients failed inside the treatment field with a local control rate of 93%. However, it is important to note that these were not isolated local failures. As such, RT continues to provide excellent local control for bulky and/or residual disease.

The UNFOLDER study examining the role of consolidative RT (for bulky and/or extranodal sites) in patients who had achieved complete response to chemotherapy underwent early termination of the no-RT arm, due to increased number of recurrences.[27] The full results are eagerly awaited.

Our study has several strengths. Our data is well-curated, as all the patients were treated at two institutions which rely on electronic medical records, electronic PACS (picture archiving and communication system), and where the management of majority of the cases are discussed at the weekly lymphoma tumour board meetings. Moreover, the patients were regularly followed up by haematologists and radiation oncologists. Secondly, we are the first to examine the clinical relevance of cell-of-origin on RT outcomes. However, we acknowledge the limitations of our study. Despite close follow-up, there are patients with missing data, as with any retrospective study. In addition, we captured all patients who received consolidative RT - and this included patients with both limited and advanced disease, where the outcomes can be different. Our data spans over 15 years, where staging methodology, chemotherapy choices and response assessment modalities have evolved. Moreover, there is evidence to show that the survival of DLBCL patients has improved over the years.[28] Lastly, the overall number of events (recurrence or death) in our analysis was small, so it is possible

that we had insufficient power to detect prognostic factors (type II error). It would also have been useful to have a control group of patients who were treated with chemotherapy alone.

Conclusions

Although DLBCL is considered to be an aggressive form of non-Hodgkin's Lymphoma, it has an excellent outcome with modern treatment. RT contributes significantly towards local control and survival in patients with bulky disease or residual disease following first-line chemotherapy. The cell-of-origin, by Hans algorithm, may not be a relevant prognostic factor in patients undergoing consolidative RT. A well-designed randomised controlled trial, comparing patients treated with chemotherapy alone, would be useful to determine the additional benefit of RT.

References

1. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; **26(Suppl 5):** v116-25. doi: 10.1093/annonc/mdv304
2. Fisher RI, Miller TP, O'Connor OA. Diffuse aggressive lymphoma. *Hematology Am Soc Hematol Educ Program* **2004;** 221-36. doi: 10.1182/asheducation-2004.1.221
3. Bush RS, Gospodarowicz M, Sturgeon J, Alison R. Radiation therapy of localized non-Hodgkin's lymphoma. *Cancer Treat Rep* 1977; **61:** 1129-36. PMID: 332347
4. Haque W, Dabaja B, Tann A, Khan M, Szeja S, Butler EB, et al. Changes in treatment patterns and impact of radiotherapy for early stage diffuse large B cell lymphoma after rituximab: a population-based analysis. *Radiother Oncol* 2016; **120:** 150-5. doi: 10.1016/j.radonc.2016.05.027
5. Vargo JA, Gill BS, Balasubramani GK, Beriwal S. Treatment selection and survival outcomes in early-stage diffuse large B-cell lymphoma: do we still need consolidative radiotherapy? *J Clin Oncol* 2015; **33:** 3710-7. doi: 10.1200/JCO.2015.61.7654
6. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002; **346:** 235-42. doi: 10.1056/NEJMoa011795
7. Pfreundschuh M, Kuhnt E, Trumper L, Osterborg A, Trneny M, Shepherd L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. *Lancet Oncol* 2011; **12:** 1013-22. doi: 10.1016/S1470-2045(11)70235-2
8. Phan J, Mazloom A, Medeiros LJ, Zreik TG, Wogan C, Shihadeh F, et al. Benefit of consolidative radiation therapy in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy. *J Clin Oncol* 2010; **28:** 4170-6. doi: 10.1200/JCO.2009.27.3441
9. Held G, Murawski N, Ziepert M, Fleckenstein J, Poschel V, Zwick C, et al. Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. *J Clin Oncol* 2014; **32:** 1112-8. doi: 10.1200/JCO.2013.51.4505
10. Chapuy B, Stewart C, Dunford AJ, Kim J, Kamburov A, Redd RA, et al. Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. *Nat Med* 2018; **24:** 679-90. doi: 10.1038/s41591-018-0016-8
11. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature* 2000; **403:** 503-11. doi: 10.1038/35000501
12. Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood* 2004; **103:** 275-82. doi: 10.1182/blood-2003-05-1545
13. Lenz G, Wright G, Dave SS, Xiao W, Powell J, Zhao H, et al. Stromal gene signatures in large-B-cell lymphomas. *N Engl J Med* 2008; **359:** 2313-23. doi: 10.1056/NEJMoa0802885
14. Chong VC, Yap ES, Xin L, Chin ST, Jeyasekharan A, Chee Y-L, et al. Immunophenotypic and genetic characteristics of diffuse large B-cell lymphoma (DLBCL), and prognostic significance of cell of origin (COO) in a southeast Asian cohort. *Blood* 2018; **132(Suppl 1):** 4222. doi: 10.1182/blood-2018-99-119672
15. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 1993; **329:** 987-94. doi: 10.1056/NEJM199309303291402
16. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014; **32:** 3059-68. doi: 10.1200/JCO.2013.54.8800
17. Yahalom J, Mauch P. The involved field is back: issues in delineating the radiation field in Hodgkin's disease. *Ann Oncol* 2002; **13(Suppl 1):** 79-83. doi: 10.1093/annonc/13.s1.79
18. Illidge T, Specht L, Yahalom J, Aleman B, Berthelsen AK, Constine L, et al. Modern radiation therapy for nodal non-Hodgkin lymphoma-target definition and dose guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys* 2014; **89:** 49-58. doi: 10.1016/j.ijrobp.2014.01.006
19. Specht L. Does radiation have a role in advanced stage Hodgkin's or Non-Hodgkin lymphoma? *Curr Treat Options Oncol* 2016; **17:** 4. doi: 10.1007/s11864-015-0377-x
20. Horning SJ, Weller E, Kim K, Earle JD, O'Connell MJ, Habermann TM, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. *J Clin Oncol* 2004; **22:** 3032-8. doi: 10.1200/JCO.2004.06.088
21. Reyes F, Lepage E, Ganem G, Molina TJ, Brice P, Coiffier B, et al. ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. *N Engl J Med* 2005; **352:** 1197-205. doi: 10.1056/NEJMoa042040
22. Bonnet C, Fillet G, Mounier N, Ganem G, Molina TJ, Thieblemont C, et al. CHOP alone compared with CHOP plus radiotherapy for localized aggressive lymphoma in elderly patients: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol* 2007; **25:** 787-92. doi: 10.1200/JCO.2006.07.0722
23. Aviles A, Nambo MJ, Calva A, Neri N, Cleto S, Silva L. Adjuvant radiotherapy in patients with diffuse large B-cell lymphoma in advanced stage (III/IV) improves the outcome in the rituximab era. *Hematology* 2019; **24:** 521-5. doi: 10.1080/10245332.2018.1423880
24. Lamy T, Damaj G, Soubeyran P, Gyan E, Cartron G, Bouabdallah K, et al. R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma. *Blood* 2018; **131:** 174-81. doi: 10.1182/blood-2017-07-793984
25. Pfreundschuh M, Murawski N, Ziepert M, Altmann B, Dreyling MH, Borchmann P, et al. Radiotherapy (RT) to bulky (B) and extralymphatic (E) disease in combination with 6xR-CHOP-14 or R-CHOP-21 in young good-prognosis DLBCL patients: results of the 2x2 randomized UNFOLDER trial of the DSHNHL/GLA. *J Clin Oncol* 2018; **36(15 Suppl):** 7574. doi: 10.1200/JCO.2018.36.15_suppl.7574.
26. Shi Z, Das S, Okwan-Duodu D, Esiashvili N, Flowers C, Chen Z, et al. Patterns of failure in advanced stage diffuse large B-cell lymphoma patients after complete response to R-CHOP immunochemotherapy and the emerging role of consolidative radiation therapy. *Int J Radiat Oncol Biol Phys* 2013; **86:** 569-77. doi: 10.1016/j.ijrobp.2013.02.007
27. Fridrik MA. ASCO update on lymphoma. *Memo* 2017; **10:** 218-9. doi: 10.1007/s12254-017-0372-y
28. Issa DE, van de Schans SA, Chamuleau ME, Karim-Kos HE, Wondergem M, Huijgens PC, et al. Trends in incidence, treatment and survival of aggressive B-cell lymphoma in the Netherlands 1989-2010. *Haematologica* 2015; **100:** 525-33. doi: 10.3324/haematol.2014.107300