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Radiotherapy for early stage diffuse large B-cell lymphoma with or without double or triple hit genetic alterations

George Daniel Grass^{a,*}, Matthew N. Mills^{b,*}, Kamran A. Ahmed^a, Casey L. Liveringhouse^b, Michael J. Montejo^a, Timothy J. Robinson^a, Julio C. Chavez^c, Louis B. Harrison^a, and Sungjune Kim^a

^aDepartment of Radiation Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

^bUniversity of South Florida College of Medicine, Tampa, FL, USA

^cDepartment of Malignant Hematology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

Abstract

We investigated whether adding radiation (RT) to systemic therapy improved outcomes in early stage diffuse large B-cell lymphoma (DLBCL) patients with or without double- or triple-hit lymphoma (DHL/THL) biology. This analysis included 183 patients profiled with fluorescent in situ hybridization (FISH) for alterations in *MYC*, *BLC2*, and/or *BCL6*. A total of 146 (80%) were non-DHL/THL, 27 (15%) were DHL, and 10 (6%) were THL. Systemic therapy without RT resulted in inferior freedom from relapse (FFR) (HR: 2.28; 95% CI, 1.10–4.77; $p = .02$). The median FFR for non-DHL/THL was not reached and was 33 and 22.3 months for DHL and THL, respectively; $p < .001$. Low-risk (R-IPI < 2) DHL/THL patients treated with rituximab-based therapy had 3-year FFR rates of 11% and 71% for systemic therapy without and with RT, respectively; $p = .04$. No differences in overall survival were observed between the treatment groups. Treatment intensification with RT may improve early stage DHL/THL outcomes.

Keywords

Radiation; double hit or triple hit lymphoma; molecular genetics

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of aggressive non-Hodgkin lymphoma (NHL). Although most present with advanced disease, approximately a one-third of patients presented with early stage disease (stages I-II) [1]. Management of early stage disease has evolved over the last several decades from wide-field radiotherapy

CONTACT Sungjune Kim sungjune.kim@moffitt.org Department of Radiation Oncology, H. Lee Moffitt Cancer Center and Research Institute, 12902 USF Magnolia Dr., Tampa, FL 33612, USA.

*These authors contributed equally to this work.

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(RT) alone to multiagent immunochemotherapy consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (R-CHOP), with or without conformal consolidative RT [2,3]. Some controversy is present regarding the addition of consolidative RT to the management of early stage DLBCL in the rituximab era due to the improved outcomes achieved with systemic therapies and the potential of RT-induced late toxicities [4-7].

Stratification of DLBCL patients into those at low-risk versus high-risk for relapse is an area of intense investigation. The most common prognostic indices are the International Prognostic Index (IPI) and the revised-IPI (R-IPI) [8]. Furthermore, advances in gene expression profiling have demonstrated that DLBCL is a heterogeneous disease consisting of various molecular subtypes, including germinal center B-cell (GCB), activated B-cell (ABC) and type 3 DLBCL [9,10]. These cell-of-origin (COO) molecular subtypes have been found to be prognostic, though this is debated [11,12]. One of the main drivers of lymphoma biology is the *MYC* oncogene, which is found to be aberrantly expressed in about 10–15% of DLBCL patients either by rearrangements, copy number alterations, or dysregulated transcriptional/translational regulation [13]. Increased expression of *MYC* facilitates uncontrolled cell proliferation and therapy resistance, which portends a worse prognosis following R-CHOP [14,15].

Molecular characterization has demarcated *MYC* translocations coupled with either B-cell lymphoma 2 (*BCL2*), B-cell lymphoma 6 (*BCL6*) or, in rare instances, other oncogene translocations, as ‘double-hit lymphoma’ (DHL) [16]. These genetic alterations tend to have worse clinical outcomes [17]. ‘Triple-hit lymphoma’ (THL) is designated when *MYC* and any of the other two aforementioned genes are concurrently altered. Currently, DHL and THL are classified by the presence of specific ‘typical’ translocation events, yet recent evidence has identified other ‘atypical’ DHL/THL subgroups. Atypical DHL/THL, which include *MYC*, *BCL2*, or *BCL6* gene expression aberrations in the absence of the full spectrum of ‘typical’ translocations, appear to have worse outcomes relative to non-DHL/THL patients, but are similar to ‘typical’ DHL/THL patients [12,18,19].

Despite these categorizations, DLBCL patients are still treated in a uniform manner, especially regarding the receipt of RT. In this study, we provide evidence to suggest upfront identification of DHL/THL status in early stage DLBCL can identify patients that may benefit from treatment intensification with RT.

Methods

Patient population

The institutional review board approved this retrospective analysis and patient record handling complied with the Health Insurance Portability and Accountability Act. Patients with biopsy-proven early stage (I–II) DLBCL ($n = 640$) seen at our institution for treatment between February 1998 and December 2014 were reviewed. We limited our analysis to patients who were molecularly profiled by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH). Patients were excluded if they presented with central nervous system (CNS) involvement, advanced stage disease, received prior RT for DLBCL treatment

or were refractory to initial systemic therapy. Following exclusion, 183 patients were identified for analysis. Additional work-up included history and physical exam, serum lactate dehydrogenase (LDH), bone marrow biopsy and imaging with computed tomography (CT), or 18-fluorodeoxyglucose positron-emission tomography/CT (PET/CT).

Patients were separated into two cohorts based on the initial designated treatment approach: (1) those treated with multiagent systemic therapy alone and (2) those treated with multiagent systemic therapy with RT. For each patient, the recommended course of treatment was decided by input of a multidisciplinary team including a radiation oncologist, medical oncologist, pathologist, and radiologist. Consolidative radiation was delivered with a variety of techniques during the time period of this analysis, though due to the early stage disease presentation, most were similar to involved-field techniques. Clinical, treatment and tumor characteristics were abstracted from the medical chart and available radiologic images. In particular, we assessed patient demographics, Ann Arbor stage, tumor location, presence of bulky disease (≥ 7.5 cm), variables needed to calculate R-IPI, type of systemic treatment and number of cycles, dose of RT, and individual tumor response to treatment.

Classification of molecular phenotype

The diagnosis of DLBCL was based on the revised 2016 World Health Organization (WHO) criteria [20]. Categorization of DLBCL into GCB or non-GCB COO was determined by IHC evaluation using the Hans algorithm by analyzing CD10, MUM1, and BCL6 expression [21]. FISH was employed to categorize patients into DHL or THL. ‘Typical’ DHL was defined as B-cell lymphoma tumors with translocations involving *MYC* in addition to *BCL2* or *BCL6*; THL was classified as having evidence of rearrangements in *MYC*, *BCL2*, and *BCL6*. ‘Atypical’ DHL/THL were classified as tumors with concurrent *MYC*, *BCL2*, and *BCL6* abnormalities, but lacked the typical translocation profile [19]. Atypical DHL tumors were further defined as: (1) *MYC* translocation with extra copies of *BCL2* without the $t(14;18)(q32;q21)/igH-BCL2$; (2) $t(14;18)(q32;q21)/igH-BCL2$ with extra copies of *MYC*, but without evidence of *MYC* translocation; (3) extra copies of *MYC*, *BCL2*, and/or *BCL6* without translocations involving either gene. Typical and atypical cases for each DHL or THL grouping were combined for analysis.

Assessment of treatment response

Patient medical records and radiologic images were assessed for treatment response by the Lugano criteria and the five-point Deauville scale to classify tumor response into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) [22,23]. CR, PR, and SD were all considered satisfactory disease control. Method of salvage therapy, including stem cell transplant (SCT), was assessed in those patients with disease relapse. Over the span of this analysis, the follow-up method was not standardized, but was at the discretion of the treating physician. Therefore, any designation of PD required a change in oncologic management in addition to imaging findings.

Statistical analysis

The primary study endpoints of freedom from relapse (FFR) and overall survival (OS) were estimated with Kaplan-Meier rates from the time of treatment completion to PD or the date

of death, respectively, and were compared with log-rank testing. To test for differences between cohorts, the Wilcoxon, Pearson's χ^2 , and Fisher's exact tests were used as appropriate. The Cox proportional-hazards model was employed for univariable and multivariable analyses to assess the effect of patient, tumor and other predictive factors of significance on determined end points. All analyses were two-sided and used a significance level of $p < .05$. Only statistically significant variables on univariable analysis ($p < .05$) were included in the multivariable model. All statistical analyses were performed using JMP 13 (SAS Institute Inc.).

Results

Patient and treatment characteristics

Baseline demographic and tumor characteristics between patients who were treated with or without RT are summarized in Table 1. A total of 183 patients were identified for analysis and 120 (65.6%) were treated with RT. Eight patients were initially treated with RT alone. The median age was 60 years (range: 20–90 years) and the majority were male ($n = 101$; 55.2%) and Caucasian ($n = 162$; 88.5%). The disease stage of patients was: IA ($n = 83$; 45%), IB ($n = 5$; 3%), IIA ($n = 72$; 39%), and IIB ($n = 23$; 13%). The majority (85%) of patients were initially staged with PET/CT. Most tumors were extranodal ($n = 122$; 66.6%) and non-bulky ($n = 129$; 70.5%). Most patients ($n = 127$; 69.3%) had an R-IPI score of 0–1.

In those patients treated with systemic therapy alone, the median number of cycles was 6 (range: 1–10 cycles) and in patients treated with RT it was 4 cycles (range: 0–8 cycles). Rituximab was part of the multiagent chemotherapy regimen in 142 (77.6%) patients; 57 (90.5%), and 85 (70.8%) patients were treated with rituximab-based regimens in the systemic therapy alone and RT groups, respectively. The median RT dose was 36 Gy (range: 20–54 Gy). Patients treated with RT were more likely to be younger ($p = .03$), staged with PET ($p = .006$), receive less systemic therapy ($p = .001$), and have stage I disease ($p = .001$), lower R-IPI ($p = .009$), non-bulky ($p = .01$), or extranodal tumors ($p = .008$).

Molecular profiling

Using the Hans algorithm, 73 (39.8%) patients had tumors classified as the GCB subtype and of the 110 non-GCB tumors, 79 (65.8%) were treated with RT, and 31 (49.2%) received systemic therapy alone ($p = .03$). FISH analysis identified that 27 (15%) tumors were classified as DHL (6 typical and 21 atypical). Ten (5%) tumors were classified as THL (3 typical and 7 atypical).

Clinical outcomes

Freedom from relapse—The median follow-up time from treatment completion was 33.5 months (range: 0.5–204 months). A total of 41 (22.4%) patients were known to be dead at last analysis. Overall, 39 (21.3%) patients had disease relapse; 26 (14.2%) and 13 (7.1%) patients had loco-regional or distant relapses, respectively. The median FFR for all patients was 140.2 months with a 3-year FFR rate of 72%. When separating groups by treatment type, the median FFR was not reached for the RT group, whereas systemic therapy alone had a median FFR of 30.4 months ($p < .001$) (Figure 1). The 3-year FFR rates between RT and

systemic therapy alone were 84 and 46%, respectively. On univariable analysis, factors associated with FFR included omission of RT (HR: 4.28; 95% CI 2.36–7.97; $p < .001$), PET staging (HR: 0.36; 95% CI 0.19–0.71; $p = .004$), indolent to aggressive tumor transformation (HR: 3.88; 95% CI 1.81–7.61; $p = .001$), and extranodal location (HR: 0.57; 95% CI 0.32–1.00; $p = .05$) (Table 2).

Stratification of patients into non-DHL/THL versus DHL versus THL revealed differences in FFR (Figure 2(A)). The median FFR for non-DHL/THL, DHL, and THL was not reached, 33.0 and 22.3 months, respectively ($p < .001$). The 3-year FFR rates for non-DHL/THL, DHL, and THL were 80, 48, and 17%, respectively ($p < .001$). Additionally, univariable analysis demonstrated that DHL versus non-DHL/THL and THL versus non-DHL/THL were associated with inferior FFR (HR: 2.87; 95% CI 1.40–5.55; $p = .005$) and (HR: 4.47; 95% CI 1.65–10.26; $p = .005$), respectively. A multivariable model including DHL/THL status, PET staging, extranodal location, transformed disease, and receipt of RT demonstrated that THL (HR: 3.49; 95% CI 1.21–8.79; $p = .02$) and omission of RT (HR: 2.28; 95% CI 1.10–4.77; $p = .02$) were predictive of FFR (Table 2). No differences were noted in median FFR between GCB and non-GCB subtypes (HR: 0.84; 95% CI 0.45–1.51; $p = .57$). In a multivariable model limited to patients only treated with rituximab-based regimens, the omission of RT predicted for worse FFR (HR: 2.90; 95% CI 1.36–6.5; $p = .006$) compared with those treated with RT.

Within the 37 DHL/THL patients, there was no difference in FFR when comparing those that received radiation or no radiation ($p = .16$). Though, in low-risk (R-IPI < 2) DHL/THL patients treated with rituximab-based therapy ($n = 17$), the addition of RT improved tumor control (Figure 2(B)). Characteristics of this subgroup are provided in a supplementary table. In this subset of patients, the median FFR for RT was not reached, whereas systemic therapy alone had a median FFR of 15.4 months ($p = .04$). The 3-year FFR for systemic therapy alone versus RT was 11 and 71%, respectively.

Overall survival—The median OS for the cohort was not reached. The 2- and 3-year OS rates were 90 and 85%, respectively. Gender, age, R-IPI, disease stage and transformed disease were associated with OS (Table 3). Omission of RT was also associated with increased overall mortality on univariable analysis (HR: 2.72; 95% CI 1.35–5.50; $p = .008$), but lost predictive ability on multivariable analysis.

Similarly, genetic aberration status influenced OS. The median OS was not reached for non-DHL/THL or DHL, whereas THL had a median OS of 70.9 months ($p < .001$). The 2- and 3-year OS rates for non-DHL/THL, DHL, and THL were 92/87/56% and 87/83/56%, respectively (Figure 3). On univariable analysis, THL versus non-DHL/THL demonstrated reduced OS (HR: 5.37; 95% CI 1.79–13.2; $p = .005$). A multivariable model including R-IPI, age, gender, disease stage, transformed disease and receipt of RT demonstrated that THL status (HR: 5.39; 95% CI 1.64–15.3; $p = .008$) and R-IPI were predictive of OS. We found no difference in OS (HR: 1.17; 95% CI 0.58–2.31; $p = .65$) when comparing GCB versus non-GCB subtypes. Additionally, a multivariable model with the subset of patients that received rituximab-based treatment demonstrated no difference in OS between patients that were treated with or without RT ($p = .75$).

Salvage therapy—A total of 39 patients had disease relapse and were salvaged with chemotherapy alone (23%), RT alone (2.5%) or multimodality approaches of chemotherapy and RT (23%), chemotherapy and SCT (24%) and chemotherapy, RT and SCT (15.3%). Only two patients did not receive salvage therapy. Salvage with a SCT had improved median OS compared with those who did not receive SCT (69.7 vs. 15.6 months; $p = .07$).

Discussion

Consistent with previous studies, we provide further evidence that the addition of RT to rituximab-based therapy improves tumor control in early stage DLBCL compared with systemic therapy alone [7,24-27]. Furthermore, similar to Tumati et al. [28], this study provides hypothesis-generating evidence that upfront treatment intensification with RT in patients with de novo DLBCL or transformed disease with concurrent genetic alterations in *MYC*, *BCL2*, or *BCL6* may improve tumor control when added to systemic therapy and prolong the time to more aggressive salvage regimens.

The optimal management of early stage DLBCL is debated. For the most part, these patients are treated uniformly with rituximab-based regimens with RT being optional [1]. In the pre-rituximab era, consolidative RT failed to demonstrate improved outcomes in four randomized trials, yet many retrospective studies and subgroup analyses of prospective trials in the modern era have demonstrated improved tumor control with consolidative RT following rituximab-based regimens [27]. This is underscored by evidence of improved disease control in subgroup analyses of patients enrolled in the RICOVER-60 trial with disease ≥ 7.5 cm or in intent-to-treat analyses [25]. Additionally, treatment arms that omitted consolidative RT in the Unfavorable Low-Risk Patients Treated with Densification of R-Chemo Regimens (UNFOLDER) trial closed prematurely secondary to increased relapses [24]. Of note, both of these trials included patients of all disease stages and did not specifically assess the role of RT in early stage tumors. Though unfavorable risk patients may gain benefit from consolidative radiation following R-CHOP, recent results from the LYSA/GOELAMS trial 02-03 demonstrated no difference in outcomes when comparing R-CHOP followed with or without consolidative radiation in patients with non-bulky disease [29]. Though consolidative RT clearly provides disease-control benefit in the rituximab era in select groups, utilization rates of RT in early stage DLBCL have continued to decline [30], which may be secondary to the implementation of rituximab [26].

Molecular profiling has demonstrated that DLBCL is a heterogeneous disease and that certain COO groups may be prognostic [9-11,13]. Similar to Staiger et al. [12], we were unable to identify a difference in FFR or OS when comparing COO groupings, which may be due to incomplete representation of the biology driving DLBCL using this classification [31,32]. In addition to COO classification, DLBCLs can be classified with FISH as DHL or THL [16]. DHL/THL patients frequently present with advanced stage disease in extranodal locations and have a greater likelihood of treatment failure and reduced OS compared with non-DHL/THL patients [17]. For this reason, these patients are primarily treated with aggressive induction systemic regimens with refractory or relapsed disease salvaged by systemic therapy or autologous SCT [33]. Less than 20% of DHL/THL patients present with

early stage disease [17], thus data guiding appropriate treatment in this setting is very limited, especially in regard to RT.

We stratified patients into DHL/THL defined by ‘typical’ translocations or ‘atypical’ expression alterations in *MYC*, *BCL2*, or *BCL6* based on FISH. The ‘atypical’ DHL/THL designation is defined by a combination of translocations and/or copy number alterations in the aforementioned genes, which has been shown to result in similar outcomes as the classical DHL/THL categorization [19,34]. Importantly, this ‘atypical’ classification is distinct from the IHC-based double-expressor designation [31,35]. With FISH-based categorization, we found inferior tumor control in DHL and THL compared with non-DHL/THL. Furthermore, when evaluating a favorable subset of DHL/THL patients treated with rituximab-based therapy, RT improved tumor control compared with systemic therapy alone (Figure 2(B)). The 3-year FFR for systemic therapy versus RT in this DHL/THL subgroup was 11 and 71%, respectively. Notably, the relapse curve separates out between systemic therapy versus RT after 10 months, which suggests the benefit of RT in this patient cohort may be in preventing late relapse. In comparison, a large retrospective study from MD Anderson Cancer Center found that 15 stage II DHL/THL patients had a 3-year event-free survival rate just above 20%, whereas all stage I patients remained in remission; of note, only 9% of patients, which included all stages, received RT as an initial treatment and the response to RT was not formally assessed [34]. Tumati et al. recently published a series of 53 patients with double- or triple-hit biology, which included all disease stages. In this study they identified that 55% of relapses were at initially involved sites and 36% were isolated relapses [28]. These results in conjunction with our findings, support the idea that intensification of treatment with consolidative RT may prove beneficial in managing these aggressive lymphoma variants.

Our study was confined by a limited sample size, particularly the proportion of DHL/THL patients in our treatment comparison groups. Since only 5–10% of DLBCL patients are categorized as DHL/THL overall, a low yield of DHL/THL patients was expected in an analysis limited to early stage disease. Furthermore, we expanded our DHL/THL classification to include tumors with ‘typical’ *MYC*-based chromosomal rearrangements as well as ‘atypical’ alterations based on FISH, as prior studies have demonstrated atypical FISH-based DHL/THL biology also portends poor prognosis. A more in-depth analysis stratifying different oncogene rearrangement patterns or the overexpression of *MYC*, *BCL2*, and *BCL6* protein by IHC was limited by our sample size [31,33,36]. Regardless, though our grouping of ‘typical’ and ‘atypical’ cases may mask intrinsic biology to specific translocation events, it is important to recognize that rearranged or altered copy numbers of target genes in both disease entities represent a more global state of genomic instability [17].

In this study, all patients did not receive uniform treatment and 85% were initially staged with PET/CT. Only 78% of patients received standard of care rituximab-based therapy in this analysis, yet the addition of RT still provided superior tumor control despite only 71% of patients being treated with rituximab in this group versus 90% in the systemic therapy alone group. We found no difference in FFR or OS when stratifying groups by systemic therapy approaches. In fact, in the subset of patients treated with rituximab-containing

regimens, omission of RT remained an independent predictor of inferior FFR on multivariable analysis.

Intensification of systemic therapy for DHL/THL is under active investigation in prospective trials ([ClinicalTrials.gov](https://clinicaltrials.gov): NCT02272686 and NCT02815397). Unfortunately, prospectively defining the role of RT in early stage DHL/THL will be challenging given the rarity of this patient cohort. Likewise, this study suggests the potential role of RT in DHL/THL patients with an aggressive disease course, which should be reflected in multidisciplinary discussions between the treating medical and radiation oncologists.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

- [1]. Dabaja BS, Advani R, Hodgson DC, et al. ACR appropriateness criteria[®] diffuse large b-cell lymphoma. *Am J Clin Oncol*. 2015;38:610–620. [PubMed: 26583344]
- [2]. Illidge T, Specht L, Yahalom J, 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. [PubMed: 24725689]
- [3]. Campbell BA, Connors JM, Gascoyne RD, et al. Limited-stage diffuse large B-cell lymphoma treated with abbreviated systemic therapy and consolidation radiotherapy:involved-field versus involved-node radiotherapy. *Cancer*. 2012;118:4156–4165. [PubMed: 22252721]
- [4]. Persky DO, Miller TP. Localized large cell lymphoma: is there any need for radiation therapy? *Curr Opin Oncol*. 2009;21:401–406. [PubMed: 19593138]
- [5]. Wirth A The rationale and role of radiation therapy in the treatment of patients with diffuse large B-cell lymphoma in the Rituximab era. *Leuk Lymph*. 2007;48:2121–2136.
- [6]. Yahalom J Radiation therapy after R-CHOP for diffuse large B-cell lymphoma: the gain remains. *J Clin Oncol*. 2010;28:4105–4107. [PubMed: 20713874]
- [7]. Persky DO, Unger JM, Spier CM, et al. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: southwest Oncology Group study 0014. *JCO*. 2008;26:2258–2263.
- [8]. Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood*. 2007;109:1857–1861. [PubMed: 17105812]
- [9]. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature*. 2000;403:503–511. [PubMed: 10676951]
- [10]. Wright G, Tan B, Rosenwald A, et al. A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. *Proc Natl Acad Sci USA*. 2003;100:9991–9996. [PubMed: 12900505]
- [11]. Lenz G, Wright G, Dave SS, et al. Stromal gene signatures in large-B-cell lymphomas. *N Engl J Med*. 2008;359:2313–2323. [PubMed: 19038878]
- [12]. Staiger AM, Ziepert M, Horn H, et al. Clinical impact of the cell-of-origin classification and the MYC/BCL2 dual expresser status in diffuse large B-cell lymphoma treated within prospective clinical trials of the german high-grade non-Hodgkin's lymphoma study group. *J Clin Oncol*. 2017;35:2515–2526. [PubMed: 28525305]
- [13]. Sehn LH, Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. *Blood*. 2015;125:22–32. [PubMed: 25499448]
- [14]. Barrans S, Crouch S, Smith A, et al. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. *J Clin Oncol*. 2010;28:3360–3365. [PubMed: 20498406]

- [15]. Savage KJ, Johnson NA, Ben-Neriah S, et al. MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. *Blood*. 2009;114:3533–3537. [PubMed: 19704118]
- [16]. Aukema SM, Siebert R, Schuurin E, et al. Double-hit B-cell lymphomas. *Blood*. 2011;117:2319–2331. [PubMed: 21119107]
- [17]. Abramson JS. The spectrum of double hit lymphomas. *Hematol Oncol Clin North Am*. 2016;30:1239–1249. [PubMed: 27888878]
- [18]. Copie-Bergman C, Cuilliere-Dartigues P, Baia M, et al. MYC-IG rearrangements are negative predictors of survival in DLBCL patients treated with immunochemotherapy: a GELA/LYSA study. *Blood*. 2015;126:2466–2474. [PubMed: 26373676]
- [19]. Li S, Seegmiller AC, Lin P, et al. B-cell lymphomas with concurrent MYC and BCL2 abnormalities other than translocations behave similarly to MYC/BCL2 double-hit lymphomas. *Mod Pathol*. 2015;28:208–217. [PubMed: 25103070]
- [20]. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375–2390. [PubMed: 26980727]
- [21]. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004;103:275–282. [PubMed: 14504078]
- [22]. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group JCO. 2014;32:3048–3058.
- [23]. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *JCO*. 2014;32: 3059–3068.
- [24]. German High-Grade Non-Hodgkin's Lymphoma Study Group: rituximab and combination chemotherapy with or without radiation therapy in treating patients with B-cell non-Hodgkin's lymphoma. <<https://clinicaltrials.gov/show/NCT00278408>>.
- [25]. Held G, Murawski N, Ziepert M, et al. Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. *J Clin Oncol*. 2014;32:1112–1118. [PubMed: 24493716]
- [26]. Haque W, Dabaja B, Tann A, 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;120:150–155. [PubMed: 27373911]
- [27]. Ng AK, Dabaja BS, Hoppe RT, et al. Re-examining the role of radiation therapy for diffuse large b-cell lymphoma in the modern era. *J Clin Oncol*. 2016;34:1443–1447. [PubMed: 26903576]
- [28]. Tumati V, Trivedi L, Li H-C, et al. Patterns of failure in patients with double hit or double expressor lymphomas: implications for radiation therapy. *Int J Radiat Oncol Biol Phys*. 2018;100:1126–1132. [PubMed: 29722657]
- [29]. Lamy T, Damaj G, Soubeyran P, et al. R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma. *Blood*. 2018;131:174–181. [PubMed: 29061568]
- [30]. Vargo JA, Gill BS, Balasubramani GK, et al. Treatment selection and survival outcomes in early-stage diffuse large b-cell lymphoma: do we still need consolidative radiotherapy?. *JCO*. 2015;33:3710–3717.
- [31]. Green TM, Young KH, Visco C, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *JCO*. 2012;30:3460–3467.
- [32]. Wang XJ, Medeiros LJ, Bueso-Ramos CE, et al. P53 expression correlates with poorer survival and augments the negative prognostic effect of MYC rearrangement, expression or concurrent MYC/BCL2 expression in diffuse large B-cell lymphoma. *Mod Pathol*. 2017;30:194–203. [PubMed: 27739436]
- [33]. Staton AD, Cohen JB. A Clinician's approach to double-hit lymphoma: identification, evaluation, and management. *J Oncol Pract*. 2016;12:232–238. [PubMed: 26962166]
- [34]. Oki Y, Noorani M, Lin P, et al. Double hit lymphoma: the MD Anderson Cancer Center clinical experience. *Br J Haematol*. 2014;166:891–901. [PubMed: 24943107]

- [35]. Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program. *Blood*. 2013;121:4021–4031. quiz 4250. [PubMed: 23449635]
- [36]. Landsburg DJ, Petrich AM, Abramson JS, et al. Impact of oncogene rearrangement patterns on outcomes in patients with double-hit non-Hodgkin lymphoma. *Cancer*. 2016;122:559–564. [PubMed: 26565895]

Figure 1. Kaplan-Meier plots for FFR in patients treated with multiagent systemic therapy with or without radiotherapy.

Figure 2.

Kaplan–Meier plots of (A) FFR between non-DHL/THL, DHL, and THL patients, (B) FFR in low-risk (R-IPI <2) DHL/THL patients treated with rituximab-based therapies.

Figure 3.
Kaplan-Meier plots for OS between non-DHL/THL, DHL, and THL patients.

Table 1.

Patient, tumor, and treatment characteristics.

Variable	Total no. (%)	RT, no. (%)	No RT, no. (%)	p-value
No. of patients	183	120 (65.6)	63 (34.4)	
Age (year)				
Median	60	59	64	.03
Range	20–90	20–90	20–84	
Gender				
Male	101 (55)	65 (54.1)	36 (57.1)	.7
Female	82 (45)	55 (45.8)	27 (42.8)	
TNM stage				
IA	83 (45)	67 (55.8)	16 (25.4)	.001
IB	5 (3)	3 (2.5)	2 (3.2)	
IIA	72 (39)	38 (31.6)	34 (53.9)	
IIB	23 (13)	12 (10)	11 (17.4)	
R-IPI				
0	55 (30)	44 (36.6)	11 (17.4)	.009
1	72 (39)	46 (38.3)	26 (41.2)	
2	41 (22)	20 (16.6)	21 (33.3)	
3	7 (4)	3 (2.5)	4 (6.3)	
Unknown	8 (4)	7 (5.8)	1 (1.6)	
B symptoms				
Yes	28 (15)	15 (12.5)	13 (20.6)	.15
No	155 (85)	105 (87.5)	50 (79.4)	
PET staging				
Yes	155 (85)	108 (90)	47 (75)	.006
No	28 (15)	12 (10)	16 (25)	
Bulky disease				
Yes	54 (30)	28 (23.3)	26 (41.3)	.01
No	129 (70)	92 (76.7)	37 (58.7)	
Extranodal				
Yes	122 (67)	88 (73.3)	34 (54)	.008
No	61 (33)	32 (26.7)	29 (46)	
Hans cell of origin				
GCB	73 (40)	41 (34.2)	32 (50.8)	.03
Non-GCB	110 (60)	79 (65.8)	31 (49.2)	
Transformation				
Yes	17 (9)	3 (2.5)	14 (22)	.001
No	166 (91)	117 (97.5)	49 (78)	
Genetic alteration				
non-DHL/THL	146 (80)	107 (89.2)	39 (62)	.001
Typical DHL	6 (3)	2 (1.7)	4 (6.3)	

Variable	Total no. (%)	RT, no. (%)	No RT, no. (%)	<i>p</i> -value
Atypical DHL	21 (11)	8 (6.7)	13 (20.6)	
Typical THL	3 (2)	1 (0.8)	2 (3.2)	
Atypical THL	7 (4)	2 (1.7)	5 (7.9)	
No. of systemic therapy cycles				
Median	5	4	6	.001
Range	0–10	0–8	1–10	
Rituximab				
Yes	142 (78)	85 (71)	57 (90)	.002
No	41 (22)	35 (29)	6 (10)	
Site of relapse				
Loco-regional	26	13	13	.82
Distant	13	7	6	

DHL: double-hit lymphoma; GCB: germinal center B-cell; R-IPI: revised International Prognostic Index; RT: radiotherapy; THL:triple-hit lymphoma.

Table 2.

Univariable and multivariable analyses of parameters influencing freedom from relapse.

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Gender (male vs. female)	1.30 (0.72–2.26)	.41	NA	NA
Age 60 years vs. <60 years	1.00 (0.59–1.82)	.91	NA	NA
Stage				
IB vs. IA	1.62 (0.09–7.9)	.66	NA	NA
IIA vs. IA	1.62 (0.85–3.08)	.14	NA	NA
IIB vs. IA	2.18 (0.94–4.69)	.07	NA	NA
B symptoms (yes vs. no)	1.69 (0.80–3.26)	.16	NA	NA
Extranodal disease (yes vs. no)	0.57 (0.32–1.00)	.05	0.74 (0.39–1.42)	.36
Bulky disease (yes vs. no)	1.48 (0.79–2.69)	.21	NA	NA
PET staging (yes vs. no)	0.36 (0.19–0.71)	.004	0.5 (0.25–1.06)	.07
Hans cell of origin				
GCB vs. non-GCB	0.84 (0.45–1.51)	.57	NA	NA
Genetic alteration				
DHL vs. non-DHL/THL	2.87 (1.40–5.55)	.005	1.50 (0.72–3.36)	.24
THL vs. non-DHL/THL	4.47 (1.65–10.26)	.005	3.49 (1.21–8.79)	.02
THL vs. DHL	1.56 (0.54–4.03)	.39	NA	NA
Transformation (yes vs. no)	3.88 (1.81–7.61)	.001	1.96 (0.85–4.19)	.1
No RT vs. RT	4.28 (2.36–7.97)	<.001	2.28 (1.10–4.77)	.02
Systemic therapy cycles (<5 vs. 5)	0.64 (0.35–1.0)	.13	NA	NA
Rituximab (yes vs. no)	1.03 (0.53–2.17)	.92	NA	NA

GCB: germinal center B-cell; DHL: double-hit lymphoma; THL: triple-hit lymphoma; RT: radiotherapy.

Table 3.

Univariable and multivariable analyses of parameters influencing overall survival.

Variable	Univariable analysis			Multivariable analysis		
	HR (95% CI)	p-value		HR (95% CI)	p-value	
Gender (male vs. female)	2.10 (1.10–4.50)	.03		1.98 (0.93–4.40)		.08
Age 60 years vs. <60 years	2.52 (1.30–5.35)	.008		1.60 (0.65–4.10)		.32
Extranodal disease (yes vs. no)	0.77 (0.40–1.53)	.56		NA		NA
Stage						
IB vs. IA	6.30 (0.96–23.7)	.05		4.90 (0.65–24.0)		.11
IIA vs. IA	2.17 (1.03–4.71)	.04		1.50 (0.65–3.53)		.35
IIB vs. IA	2.10 (0.66–5.71)	.19		NA		NA
B symptoms (yes vs. no)	1.75 (0.70–3.80)	.12		NA		NA
Extranodal disease (yes vs. no)	0.77 (0.40–1.53)	.45		NA		NA
Bulky disease (yes vs. no)	1.09 (0.50–2.20)	.82		NA		NA
R-IPi						
1 vs. 0	2.70 (0.99–7.37)	.04		2.01 (0.65–6.29)		.21
2 vs. 0	6.21 (2.15–17.9)	<.001		5.75 (1.54–21.5)		.006
3 vs. 0	14.6 (2.70–78.9)	.01		10.8 (1.6–72.8)		.03
Hans cell of origin						
GCB vs. non-GCB	1.17 (0.58–2.31)	.65		NA		NA
Genetic alteration						
DHL vs. non-DHL/THL	1.75 (0.64–4.08)	.25		NA		NA
THL vs. DHL	3.07 (0.88–10.2)	.07		NA		NA
THL vs. non-DHL/THL	5.37 (1.79–13.2)	.005		5.39 (1.64–15.3)		.008
Transformation (yes vs. no)	3.21 (1.28–7.05)	.02		2.17 (0.74–5.63)		.15
No RT vs. RT	2.72 (1.35–5.50)	.005		1.00 (0.43–2.47)		.96

GCB: germinal center B-cell; DHL: double-hit lymphoma; R-IPi: revised International Prognostic Index; THL: triple-hit lymphoma; RT: radiotherapy.