

R-CHOP and Consolidation Radiotherapy for Limited-stage and Low-IPI High-Grade B-Cell Lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements: a Single-center Case Series and Review of Literature

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ABSTRACT

High-Grade B-Cell Lymphoma (HGBCL) with gene rearrangements in *MYC* and *BCL2* and/or *BCL6* is an aggressive malignancy usually presenting in advanced stages. Current recommendations suggest the use of regimens more intensive than R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, prednisone), which are based on retrospective studies and single-arm prospective trials that included patients who are mostly in the advanced stage, and did not receive consolidation radiotherapy.

The optimal approach and treatment of HGBCL, whether limited-stage (LS) or advanced-stage, remains to be determined. Here we describe the promising outcomes of three patients with LS and low IPI HGBCL with the use of R-CHOP as induction chemotherapy regimen, which was followed by consolidation radiotherapy.

Three women, 54-, 60-, and 64-years of age diagnosed to have HGBCL with *MYC*, and *BCL2* and/or *BCL6* rearrangements, with Ann Arbor stages I-IIe were included in this case series. All three patients had complete metabolic response to 6 cycles of R-CHOP and was subsequently treated with consolidation involved site radiotherapy (ISRT; total dose 30-36 Gy). Chemotherapy and radiotherapy were tolerated very well. All patients remain to be in remission, with the longest being at 23 months.

Outcomes of patients with HGBCL generally remain to be poor, but this may not be the case for patients with limited-stage disease and favorable clinicopathologic risk profile. Nevertheless, the treatment of HGBCL is currently evolving and more studies are needed to determine the ideal approach and preferred chemotherapy regimen. Also, more studies are needed to elucidate the potential role of consolidation radiotherapy in patients with limited-stage HGBCL to improve survival outcomes. Findings of this case series suggest that patients with LS HGBCL may still derive benefit from R-CHOP followed by consolidation ISRT, but prospective trials are needed to confirm this.

Keywords: R-CHOP, High-Grade B-Cell Lymphoma, HGBCL, low-IPI, *MYC* and *BCL2* translocation, consolidation radiotherapy



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INTRODUCTION

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common form of lymphoma and accounts to about 30% of all non-Hodgkin lymphomas.¹ The approach to definitive treatment is guided by the Ann Arbor staging with the IPI as the prediction tool for overall and progression free survival.^{2,3} Limited stage (LS)-disease, usually defined as Ann Arbor Stage I-II, has excellent 10-year survival of at least 70-80%.⁴

Combined modality treatment with chemotherapy and radiotherapy has been the standard of care for LS-disease and has been shown to have better outcomes compared to chemotherapy alone.^{5,6} The inclusion of Rituximab, an anti-CD20 monoclonal antibody, to standard chemotherapy regimens has greatly improved outcomes of patients with DLBCL through increased rates of complete remissions and prolonged overall survival (OS) of patients.^{7,8}

Advancement of molecular techniques have led to the classification of DLBCL into two major subtypes: germinal center B-cell like (GCB) and activated B-cell like (ABC).⁹ These subtypes have been shown to impact the prognosis of patients with the ABC subtype (or non-GCB) having poorer prognosis and inferior response rates to the standard R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, prednisone).¹⁰⁻¹² Further studies have shown that DLBCL harboring gene rearrangements in *MYC* and *BCL2* and/or *BCL6* have an even more aggressive behavior, presenting at more advanced stages, and with tendency toward CNS involvement and poor responses to the standard R-CHOP.¹³⁻¹⁵

Currently, there is no preferred induction chemotherapy regimen for HGBCL and benefits of upfront stem cell transplantation after first remission remains questionable. Nevertheless, more intensive chemotherapy regimens are currently recommended especially in advanced disease.¹⁶⁻¹⁹ A more recent retrospective study however suggests that R-CHOP and ISRT may have favorable outcomes when used in LS disease.²⁰ Here, we present the promising outcomes of three cases of limited-stage HGBCL with low IPI, who received 6 cycles of R-CHOP and consolidation radiotherapy.

Significance of the Study

The ideal treatment of HGBCL continues to be an area of debate, in which the standard regimen R-CHOP is being challenged and more intensive regimens are being investigated, especially in the setting of limited-stage disease as most patients present in advanced stages. Here we describe the remission of three patients with limited-stage and low IPI HGBCL with translocations in *MYC*, *BCL2* and/or *BCL6*, through the use of R-CHOP as induction chemotherapy regimen, which was followed by consolidation radiotherapy.

CASE SERIES

Case 1

A 54-year-old female presenting with a 4-month history of a gradually enlarging and painful left breast mass. Core-needle biopsy and subsequent Immunohistochemistry (IHC) studies were done revealing B-cell Lymphoma. Baseline PET-CT scan with contrast revealed an intensely FDG-avid left breast mass and enlarged left axillary lymph nodes (both Deauville score [DS] 5; Figure 1). She then received 6 cycles of R-CHOP which she tolerated well. Cytogenetic studies with FISH for Non-Hodgkin lymphoma (NHL) Panel testing for *BCL6*, *IGH/CCND1*, *BCL2*, *MYC*, *CEP12*, *IGH/14q32* was carried out after the fourth cycle of chemotherapy revealing gene rearrangements for *BCL2*, *BCL6*, and *MYC*. Post-treatment surveillance showed complete metabolic response, but with a residual 4.2 x 3.6 x 2.7cm (DS 1) lesion in the left breast. Consolidation ISRT of 30 Gy in 15 fractions was delivered to the breast, with boost of residual masses to 36 Gy using intensity modulated techniques (IMRT). Treatment was delivered with 6-MV photons using a Clinac® CX linear accelerator (Varian Medical Systems, CA, USA). She remains to be in remission for 23 months.

Case 2

A 64-year-old female presenting with a 1-year history of a gradually enlarging left lateral neck mass eventually associated with worsening pain. She was referred for nasopharyngoscopy with punch biopsy of a nasopharyngeal mass and incision biopsy of the lateral neck mass. Results were consistent with a round cell neoplasm, subsequent IHCs confirmed B-Cell Lymphoma expressing *BCL2*, *BCL6*, and C-MYC and a Ki67 of 50-60%. Baseline PET-CT showed intensely FDG-avid (DS 5) confluent lymph nodes in the left lateral neck, mediastinum (para-aortic, pre-vascular, sub-aortic, paratracheal, pre-carinal), and left axillary areas (Figure 2). She subsequently received 6 cycles of R-CHOP with no untoward events. Cytogenetic studies with FISH came out after the 4th cycle of chemotherapy and showed gene rearrangements for *BCL2*, *BCL6*, and *MYC*. Post-treatment PET-CT showed complete metabolic response (DS 2), with a residual 3.5 x 3.1 x 3.3cm mass in the left lateral neck on CT. She subsequently received consolidation radiotherapy with 30 Gy in 15 fractions to the left lateral neck and left axilla, with boost of grossly enlarged nodes to 36 Gy in 18 fractions, delivered via IMRT with 6-MV photons using a Clinac® CX linear accelerator (Varian Medical Systems, CA, USA). She is in remission for 23 months.

Case 3

A 60-year-old female presenting with a 3-month history of throat discomfort eventually associated with hemoptysis and odynophagia. A nasopharyngoscopy was done revealing a nasopharyngeal mass with biopsy findings showing a round

cell neoplasm. Subsequent Immunohistochemistry studies revealed B-Cell lymphoma, positive for BCL2 and MYC expression. Baseline contrast-enhanced CT scan of the neck, chest, and abdomen revealed an enhancing nasopharyngeal mass measuring 2.8 x 3.4 x 3.5cm with enlarged level II lymph nodes of the neck bilaterally (largest measuring 1.5cm). She then received 6 cycles of R-CHOP with interval resolution of throat discomfort and hemoptysis. Cytogenetic studies were available after the 5th cycle of chemotherapy revealing gene re-arrangements for *MYC* and *BCL2*. Post-treatment PET-CT scan with contrast showed complete metabolic response (Figure 3). There were however findings of an FDG-avid (DS 4) anorectal focus which was not seen on subsequent colonoscopy. She then received consolidative involved-site radiotherapy (ISRT) to localized disease in the nasopharynx, and was treated to 30 Gy in 15 fractions, delivered using highly conformal volumetric arc techniques (VMAT) with 6-MV photons using an Elekta Harmony linear accelerator (Elekta AB, Stockholm, Sweden). She is now in remission for 20 months.

DISCUSSION

All three patients had complete metabolic response to 6 cycles of R-CHOP and were subsequently followed by consolidation radiotherapy (R-CHOP dose in Appendix A; Summary table shown in Table 1). Grade 1 neutropenia was the most documented hematologic toxicity and grade 1 fatigue as the most patient-reported non-hematologic toxicity. Consolidative involved site radiotherapy (ISRT) covered disease sites with consideration of anatomic changes and following recent published guidelines by the International Lymphoma Radiation Oncology Group (ILROG).^{21,22} Delivery techniques through intensity modulation (IMRT) remain standard, although advanced, highly conformal techniques such as volumetric arc therapy (VMAT) have been employed with improved therapeutic ratios.²³⁻²⁵ All three patients developed radiation induced dermatitis (grade 2 at most) while grade 2 dysphagia and grade 1 stomatitis were reported by two of the patients.²⁶ For all the three cases, systemic chemotherapy and consolidation radiotherapy were well-tolerated with no interruptions noted during treatment.

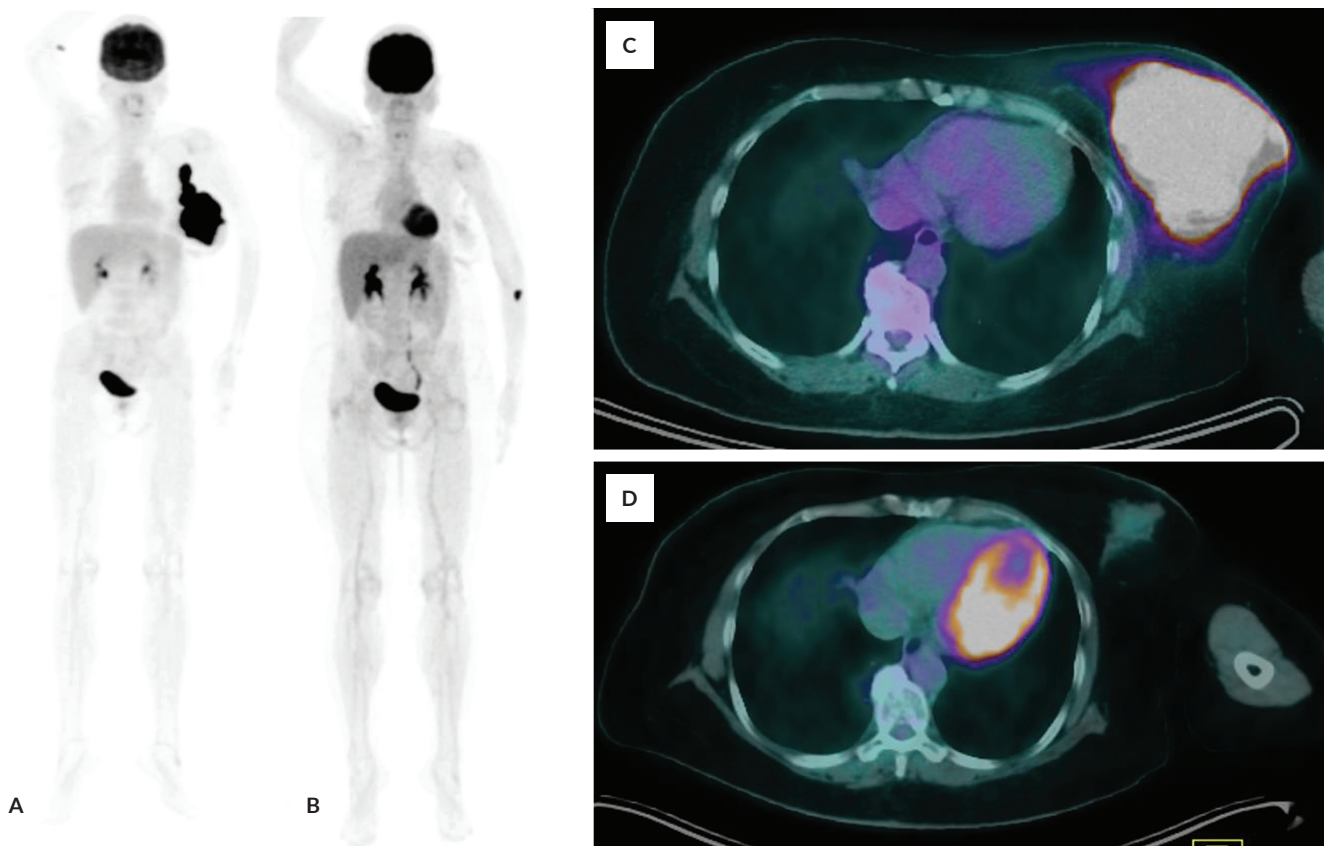


Figure 1. Pre- and post-treatment PET-CT scan with contrast images of Case 1. (A) and (C) are pre-treatment PET-CT scans showing an intensely FDG-avid left breast mass measuring 11.3 x 8.5 x 8.3 cm and left axillary lymph nodes (both Deauville score 5). (B) and (D) are post-treatment PET-CT images showing complete metabolic response and a 4.2 x 3.6 x 2.7 cm residual lesion in the left breast.

All patients remain to be in remission as of the writing of the case series, with the longest remission at 23 months. They are currently on surveillance follow-ups with neck, chest, and abdominopelvic CT scan with contrast every six months.

The optimal management of HGBCL with translocations of *MYC* and *BCL2* and/or *BCL6* remains to be determined with current evidence suggesting benefit of the use of intensive chemotherapy regimens. Dose-adjusted EPOCH-R (etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone, rituximab) was shown to have favorable survival outcomes in a single-arm prospective study of 53 patients and a retrospective study involving 311 patients.^{18,27} However, patients included in both studies (81%) had Stage III-IV disease, which could have overestimated the benefits of this intensive chemotherapy regimen. In

patients who achieve complete response after induction chemotherapy (CR1), a study has shown that there is a statistically significant improvement in 3-year recurrence free survival (RFS) when more intensive regimens were used compared to R-CHOP, but with similar median OS. Upfront stem cell transplantation after CR1 also did not show statistically significant improvement in survival.

The reported complete response rate to R-CHOP only ranges from 40-48%, and the use of R-CHOP provided a median progression free survival (PFS) of 7.8 months¹⁸, but it must be noted that most of these patients were in advanced stages, had higher IPIs, and did not receive consolidation radiotherapy. Although patients with limited-stage disease were under-represented in these studies, these patients had similar complete response rates across all treatment regimens

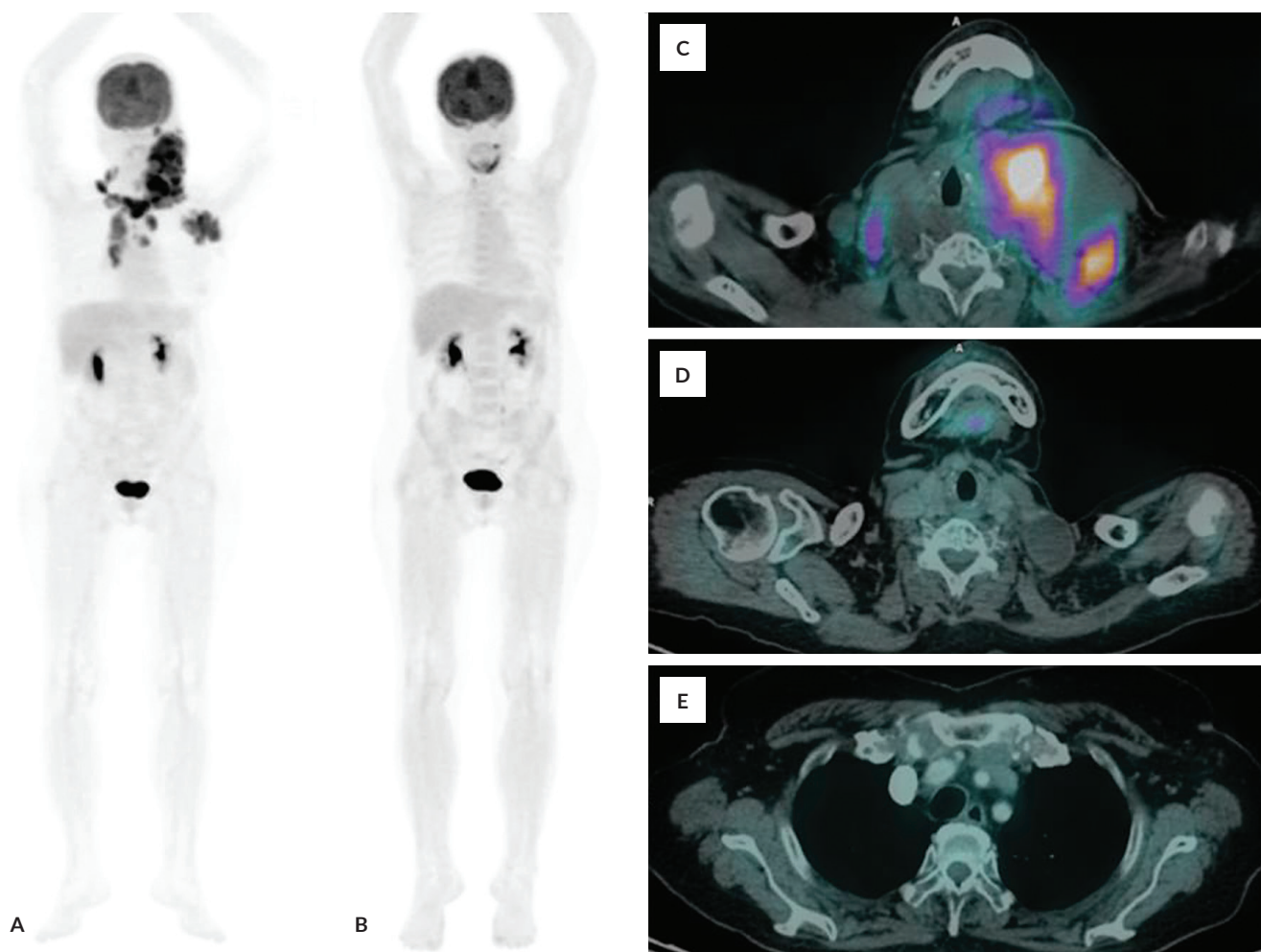


Figure 2. Pre- and post-treatment PET-CT scan with contrast images of Case 2. (A) and (C) showing intensely FDG-avid (DS 5) confluent lymph nodes in the left lateral neck, insinuating medially into the left carotid and parapharyngeal space and extending inferiorly into the thoracic inlet with an aggregate measure of 8.7 x 8.5 x 15.5 cm. There were also FDG-avid lymph nodes (DS 5) in the mediastinum (para-aortic, pre-vascular, sub-aortic, paratracheal, pre-carinal, and left axillary areas). (B), (D), and (E) are post-treatment images revealing complete metabolic response and a residual 3.5 x 3.1 x 3.3 cm mass in the left lateral neck, level IV.

(R-CHOP, R-EPOCH, and R-HyperCVAD/MA), which was not significantly different from advanced disease (60% vs. 54%, $p = 0.628$), and that EFS and OS were poor across all stages except for the five patients with Stage I disease who remained in remission for almost three years (2 treated with R-CHOP, 3 with R-EPOCH). EFS and OS were also better with lower IPI scores.¹⁷ This questions the use of intensive regimens for those with limited-stage disease, who may still benefit from the standard R-CHOP.

The National Comprehensive Cancer Network (NCCN) Guidelines for B-cell Lymphomas recommends inclusion of high-grade B-cell lymphoma cases in clinical trials, with preference for consolidative ISRT among those with localized disease (Category 2A). Although such treatment

recommendation is clearly defined for early stage and/or bulky DLBCL^{28,29}, evidence remains scarce for its role in HGBCL³⁰.

Notably, a small retrospective cohort found that among patients with HGBCL attaining complete response from chemotherapy, 55% relapsed at the initial site of involvement suggesting the potential role of consolidation radiotherapy in initial disease sites.³¹ A multivariate analysis done on the same cohort showed the consolidation RT was associated with statistically significant improvement in PFS. This is supported by a study on a larger cohort wherein a subset of low-IPI, double and triple-expressors treated with rituximab-based therapy had improved freedom from relapse with consolidation RT (71% vs 11%, $p=0.04$).³² Adequate initial

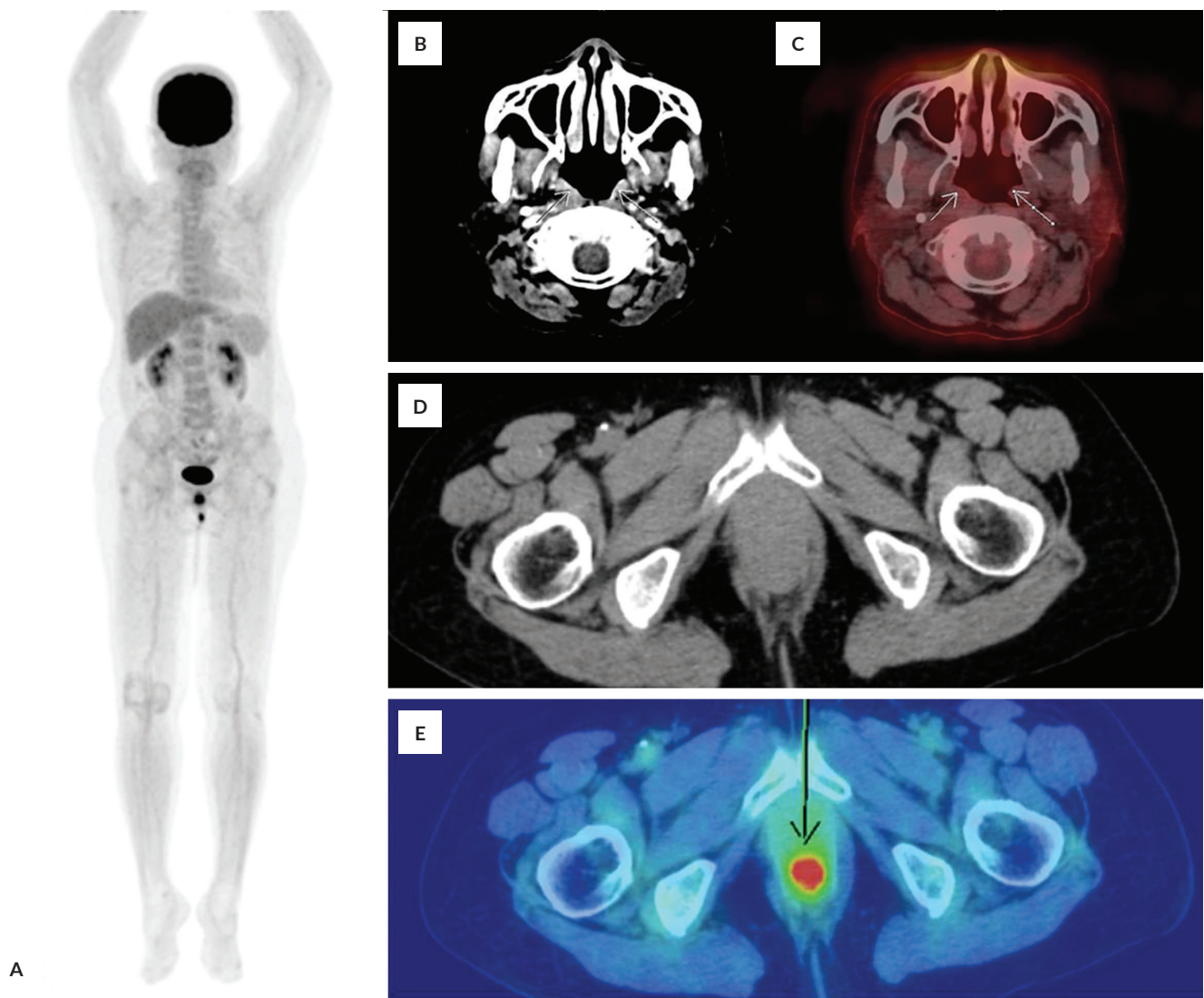


Figure 3. Post-treatment PET-CT scan with contrast of Case 3. (A) Whole body image. (B) and (C) representative neck cuts showing complete metabolic response and residual mucosal thickening. (D) and (E) shows an FDG-avid anorectal focus which did not have CT correlation findings. Only a baseline contrast-enhanced CT scan was done for the patient (the images of which could not be retrieved).

treatment for these high-grade histologies is essential, given poorer oncologic outcomes after relapse.³³

In a retrospective multi-center study, which looked at outcomes of limited-stage B-Cell lymphoma that harbor *MYC* with or without *BCL2* and *BCL6* translocations (not all HGBCL by WHO definition), PFS and OS were similar in patients receiving involved field radiotherapy (IFRT) vs. no IFRT, and R-CHOP vs. intensive immunochemotherapy.²¹ Complete response rates, however were higher in patients receiving IFRT (98% vs 72%; $p < 0.001$). This retrospective study provided a historical benchmark that limited-stage double-hit lymphomas may have better outcomes than previously recognized and questioned the role of intensive immunochemotherapy in LS disease failing to show survival benefits to standard R-CHOP. The current case series is consistent with the findings of this retrospective trial, supporting the hypothesis that limited-stage HGBCL may

still benefit from standard R-CHOP and consolidation radiotherapy and may have similar outcomes compared to the use of intensive chemotherapy regimens.

As for the limitations of this study, only fixed dose of rituximab at 500mg were given to the patients per cycle, instead of the recommended 375 mg/m² which was largely due to financial constraints. Another limitation of this study was that the patients did not undergo bone marrow aspiration and biopsy due to delays and restrictions brought about by the COVID-19 pandemic and treatment was decided to start immediately to address the symptoms of the patients. The follow-up periods for these patients are still relatively short, hence the durability of remission with the employed approach cannot be reported, nevertheless, complete metabolic response was achieved which is predictive of better survival outcomes.

Table 1. Summary of Clinicopathologic Profiles of Patients, Treatment, and Outcomes

	Case 1	Case 2	Case 3
Age	54	64	60
Sex	Female	Female	Female
Eastern Cooperative Oncology Group Performance Score	0	0	0
Diagnosis	High-grade B-cell lymphoma		
Translocations	<i>MYC</i> , <i>BCL2</i> , and <i>BCL6</i>		<i>MYC</i> and <i>BCL2</i>
Involved sites	Left breast, left axillary nodes	Left lateral neck, mediastinum, left axilla	Nasopharynx, bilateral cervical lymph nodes level II
GCB or ABC subtype (Appendix B)	Non-GCB	GCB	Non-GCB
Immunohistochemistry (Appendix C)			
BCL2	Moderate to strong, <5% of tumor cells	Moderate to strong, 20-25% of tumor cells	Strong, >90% of tumor cells
BCL6	Moderate to strong, 40% of tumor cells	Moderate to strong, 80-90% of tumor cells	Weak to moderate, <5% of tumor cells
C-MYC	Strong, >90% of tumor cells	Strong, 90-95% of neoplastic cells	Moderate to strong, >90% of tumor cells
Ki67	80-90% proliferative index	50-60% proliferative index	60-70% Proliferative index
Cytogenetic profile (FISH) (Appendix D)			
BCL2	Positive	Positive	Positive
BCL6	Positive	Positive	Negative
MYC	Positive	Positive	Positive
Ann Arbor Stage	IIE	II	I
International Prognostic Index	1, low risk (elevated LDH)	2, low-intermediate (Age >60, elevated LDH)	1, low risk (Age >60)
Chemotherapy regimen	R-CHOP x 6 cycles		
Treatment Response	Complete metabolic response, residual left breast mass measuring 4.2 x 3.6 x 2.7 cm	Complete metabolic response, with a residual 3.5 x 3.1 x 3.3 cm mass in the left lateral neck, level IV.	Complete metabolic response, no residual disease
Radiotherapy	Consolidation ISRT, 30 Gy in 15 fractions to the left breast with boost of residual mass to 36 Gy in 18 fractions, via IMRT	Consolidation ISRT, 30 Gy in 15 fractions to the left lateral neck and left axilla, with boost of enlarged nodes to 36 Gy in 18 fractions, via IMRT	Consolidation ISRT, 30 Gy in 15 fractions to the nasopharynx via Volumetric Modulated Arc Therapy/VMAT
Outcome and duration of remission	Remission, 23 months	Remission, 23 months	Remission, 20 months

CONCLUSION

Outcomes of patients with HGBCL remain to be poor, especially in cases of relapsed or refractory disease, but this may not be the case for patients with limited-stage disease and favorable clinicopathologic risk profile. Currently, there is an unmet need in determining the optimal approach and chemotherapy regimen for limited-stage and advanced-stage HGBCL. Also, more studies are needed to elucidate the potential role of consolidation radiotherapy in patients with limited-stage HGBCL to improve survival outcomes. This multimodality approach may also spare patients from toxicities of intensive chemotherapy regimens. Findings of this case series suggest that R-CHOP and consolidation ISRT may benefit patients with LS HGBCL, but prospective trials are needed to confirm this.

Ethical Approval

This study has been approved by the Department of Medicine and Division of Medical Oncology of the University of the Philippines – Philippine General Hospital. This was also submitted to the Research Grants Administration Office of the Philippine General Hospital for research registration and archiving. Accordingly, consent of the patients to participate and publication of research were obtained prior to drafting of the manuscript.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors of this study have no competing interests to declare.

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REFERENCES

1. Cancer Stat Facts: NHL — Diffuse Large B-Cell Lymphoma (DLBCL). National Institutes of Health, National Cancer Institute [Internet]. 2019 [cited 2022 Sep]. Available from: <https://seer.cancer.gov/statfacts/html/dlbcl.html>
2. Rosenberg SA. Validity of the Ann Arbor staging classification for the non-Hodgkin's lymphomas. *Cancer Treat Rep*. 1977 Sep;61(6):1023-7. PMID: 902260.
3. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 1993 Sep 30;329(14):987-94. doi: 10.1056/NEJM199309303291402. PMID: 8141877.
4. Hawkes EA, Barraclough A, Sehn LH. Limited-stage diffuse large B-cell lymphoma. *Blood*. 2022 Feb 10;139(6):822-34. doi: 10.1182/blood.2021013998. PMID: 34932795.
5. Miller TP, Dahlberg S, Cassady JR, Adelstein DJ, Spier CM, Grogan TM, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *N Engl J Med*. 1998 Jul 2;339(1):21-6. doi: 10.1056/NEJM199807023390104. PMID: 9647875.
6. 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 Nov 10;33(32):3710-7. doi: 10.1200/JCO.2015.61.7654. PMID: 26261253.
7. Coiffier B, Thieblemont C, Van Den Neste E, Lepeu G, Plantier I, Castaigne S, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood*. 2010 Sep 23;116(12):2040-5. doi: 10.1182/blood-2010-03-276246. PMID: 20548096; PMCID: PMC2951853.
8. Pfreundschuh M, Kuhnt E, Trümper L, Osterborg A, Trneny M, Shepherd L, et al; MabThera International Trial (MInT) Group. 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 Oct;12(11):1013-22. doi: 10.1016/S1470-2045(11)70235-2. PMID: 21940214.
9. 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 Feb 3;403(6769):503-11. doi: 10.1038/35000501. PMID: 10676951.
10. Scott DW, Mottok A, Ennishi D, Wright GW, Farinha P, Ben-Neriah S, et al. Prognostic significance of diffuse large B-cell lymphoma cell of origin determined by digital gene expression in formalin-fixed paraffin-embedded tissue biopsies. *J Clin Oncol*. 2015 Sep 10;33(26):2848-56. doi: 10.1200/JCO.2014.60.2383. PMID: 26240231; PMCID: PMC4554747.
11. Staiger AM, Ziepert M, Horn H, Scott DW, Barth TFE, Bernd HW, et al; German High-Grade Lymphoma Study Group. 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 Aug 1;35(22):2515-26. doi: 10.1200/JCO.2016.70.3660. PMID: 28525305.
12. Gutiérrez-García G, Cardesa-Salzmann T, Climent F, González-Barca E, Mercadal S, Mate JL, et al; Grup per l'Estudi dels Limfomes de Catalunya I Balears (GELCAB). Gene-expression profiling and not immunophenotypic algorithms predicts prognosis in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *Blood*. 2011 May 5;117(18):4836-43. doi: 10.1182/blood-2010-12-322362. PMID: 21441466.
13. Johnson NA, Savage KJ, Ludkovski O, Ben-Neriah S, Woods R, Steidl C, et al. Lymphomas with concurrent BCL2 and MYC translocations: the critical factors associated with survival. *Blood*. 2009 Sep 10;114(11):2273-9. doi: 10.1182/blood-2009-03-212191. PMID: 19597184; PMCID: PMC2745846.
14. Barrans S, Crouch S, Smith A, Turner K, Owen R, Patmore R, 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 Jul 10;28(20):3360-5. doi: 10.1200/JCO.2009.26.3947. PMID: 20498406.
15. Green TM, Young KH, Visco C, Xu-Monette ZY, Orazi A, Go RS, 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. *J Clin Oncol*. 2012 Oct 1;30(28):3460-7. doi: 10.1200/JCO.2011.41.4342. PMID: 22665537.
16. Landsburg DJ, Falkiewicz MK, Maly J, Blum KA, Howlett C, Feldman T, et al. Outcomes of patients with double-hit lymphoma who achieve first complete remission. *J Clin Oncol*. 2017 Jul 10;35(20):2260-7. doi: 10.1200/JCO.2017.72.2157. PMID: 28475457; PMCID: PMC6366297.
17. Oki Y, Noorani M, Lin P, Davis RE, Neelapu SS, Ma L, et al. Double hit lymphoma: the MD Anderson Cancer Center clinical experience. *Br J Haematol*. 2014 Sep;166(6):891-901. doi: 10.1111/bjh.12982. PMID: 24943107.

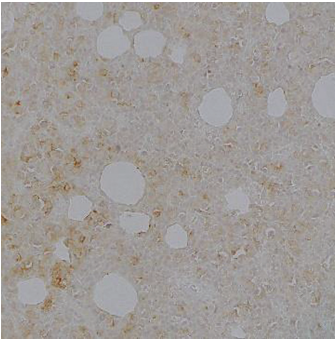
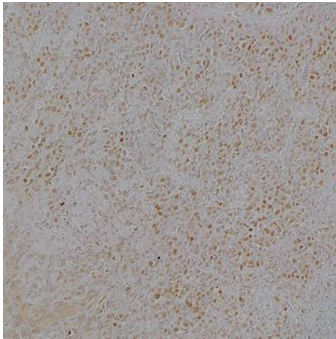
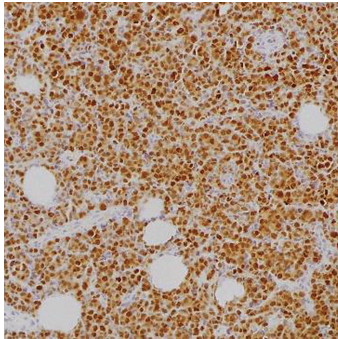
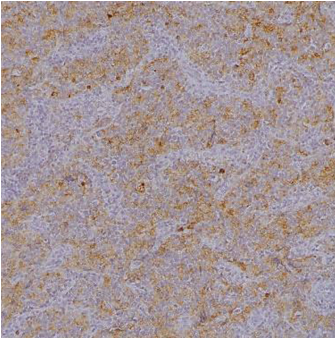
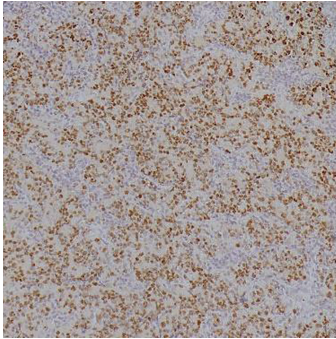
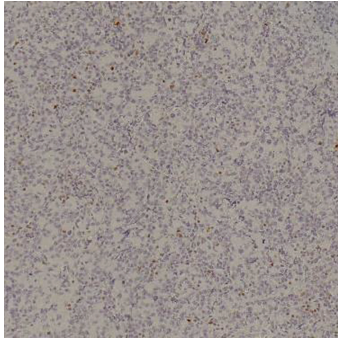
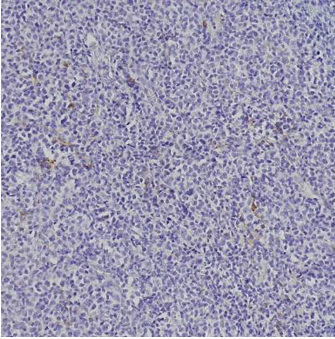
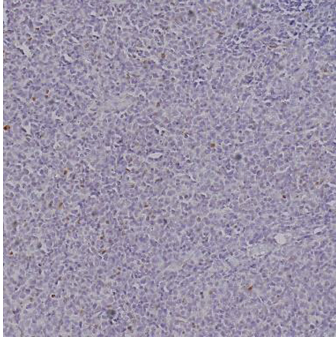
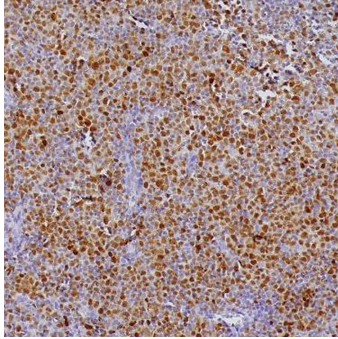
18. Petrich AM, Gandhi M, Jovanovic B, Castillo JJ, Rajguru S, Yang DT, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. *Blood*. 2014 Oct 9;124(15):2354-61. doi: 10.1182/blood-2014-05-578963. PMID: 25161267.
19. National Comprehensive Cancer Network (2019). NCCN Clinical Practice Guidelines in Oncology B-cell Lymphomas Version 5.2022 [Internet]. 2022 [cited 2022 Sep]. Available from: https://www.nccn.org/guidelines/category_1
20. Torka P, Kothari SK, Sundaram S, Li S, Medeiros LJ, Ayers EC, et al. Outcomes of patients with limited-stage aggressive large B-cell lymphoma with high-risk cytogenetics. *Blood Adv*. 2020 Jan 28;4(2):253-62. doi: 10.1182/bloodadvances.2019000875. PMID: 31945157; PMCID: PMC6988401.
21. Illidge T, Specht L, Yahalom J, Aleman B, Berthelsen AK, Constine L, et al; International Lymphoma Radiation Oncology Group. 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 May 1;89(1):49-58. doi: 10.1016/j.ijrobp.2014.01.006. PMID: 24725689.
22. Wirth A, Mikhael NG, Aleman BMP, Pinnix CC, Constine LS, Ricardi U, et al. Involved site radiation therapy in adult lymphomas: an overview of International Lymphoma Radiation Oncology Group Guidelines. *Int J Radiat Oncol Biol Phys*. 2020 Aug 1;107(5):909-33. doi: 10.1016/j.ijrobp.2020.03.019. PMID: 32272184.
23. Liu X, Yang Y, Jin F, He Y, Zhong M, Luo H, et al. A comparison of volumetric modulated arc therapy and sliding-window intensity-modulated radiotherapy in the treatment of Stage I-II nasal natural killer/T-cell lymphoma. *Med Dosim*. 2016 Spring;41(1):42-6. doi: 10.1016/j.meddos.2015.07.003. PMID: 26428072.
24. Petersen PM, Mikhael NG, Ricardi U, Brady JL. Harnessing benefit of highly conformal RT techniques for lymphoma patients. *Br J Radiol*. 2021 Nov 1;94(1127):20210469. doi: 10.1259/bjr.20210469. PMID: 34379521; PMCID: PMC8553193.
25. Higby C, Khafaga Y, Al-Shabanah M, Mousa A, Ilyas M, Nazer G, et al. Volumetric-modulated arc therapy (VMAT) versus 3D-conformal radiation therapy in supra-diaphragmatic Hodgkin's Lymphoma with mediastinal involvement: A dosimetric comparison. *J Egypt Natl Canc Inst*. 2016 Sep;28(3):163-8. doi: 10.1016/j.jnci.2016.04.007. PMID: 27245145.
26. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [Internet]. [cited 2021 Apr]. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm
27. Dunleavy K, Fanale MA, Abramson JS, Noy A, Caimi PF, Pittaluga S, et al. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: a prospective, multicentre, single-arm phase 2 study. *Lancet Haematol*. 2018 Dec;5(12):e609-e617. doi: 10.1016/S2352-3026(18)30177-7. PMID: 30501868; PMCID: PMC6342507.
28. Held G, Murawski N, Ziepert M, Fleckenstein J, Pöschel V, Zwick C, et al. Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. *J Clin Oncol*. 2014 Apr 10;32(11):1112-8. doi: 10.1200/JCO.2013.51.4505. PMID: 24493716.
29. Berger MD, Trelle S, Büchi AE, Jegerlehner S, Ionescu C, Lamy de la Chapelle TL, et al. Impact on survival through consolidation radiotherapy for diffuse large B-cell lymphoma: a comprehensive meta-analysis. *Haematologica*. 2021 Jul 1;106(7):1923-31. doi: 10.3324/haematol.2020.249680. PMID: 32554560; PMCID: PMC8252950.
30. Avilés A, Neri N, Delgado S, Pérez F, Nambo MJ, Cleto S, et al. Residual disease after chemotherapy in aggressive malignant lymphoma: the role of radiotherapy. *Med Oncol*. 2005;22(4):383-7. doi: 10.1385/MO:22:4:383. PMID: 16260856.
31. Tumati V, Trivedi L, Li HC, Patel P, Scaglioni PP, Vusirikala M, 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 Apr 1;100(5):1126-32. doi: 10.1016/j.ijrobp.2018.01.041. PMID: 29722657.
32. Grass GD, Mills MN, Ahmed KA, Liveringhouse CL, Montejo ME, Robinson TJ, et al. Radiotherapy for early stage diffuse large B-cell lymphoma with or without double or triple hit genetic alterations. *Leuk Lymphoma*. 2019 Apr;60(4):886-93. doi: 10.1080/10428194.2018.1506586. PMID: 30457458; PMCID: PMC6596288.
33. Kim A, Stevenson P, Cassaday RD, Soma L, Fromm JR, Gopal AK, et al. Impact of double- or triple-hit pathology on rates and durability of radiation therapy response among patients with relapsed or refractory large B-cell lymphoma. *Pract Radiat Oncol*. 2020 Jan-Feb;10(1):44-52. doi: 10.1016/j.prro.2019.09.013. PMID: 31585205.

APPENDICES

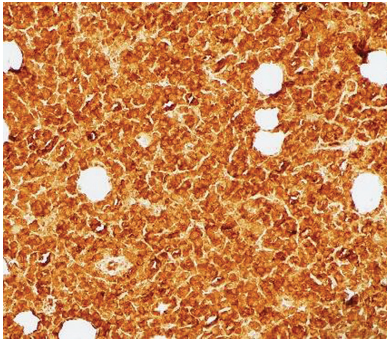
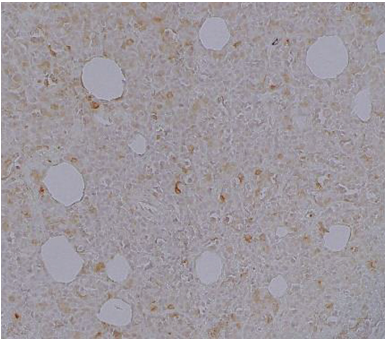
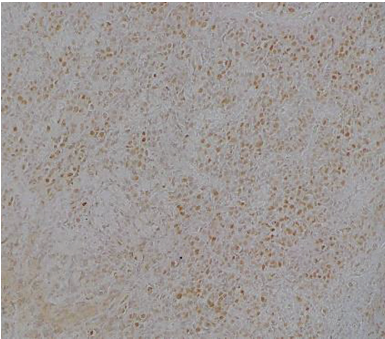
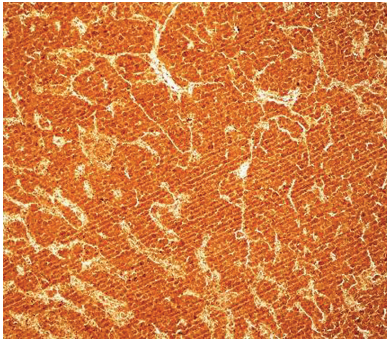
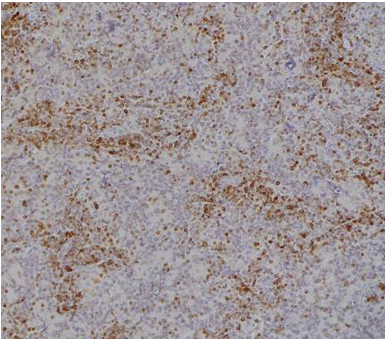
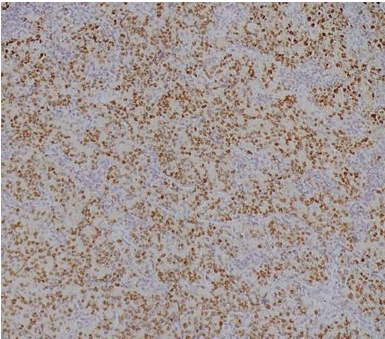
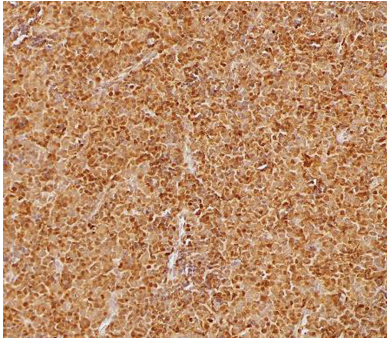
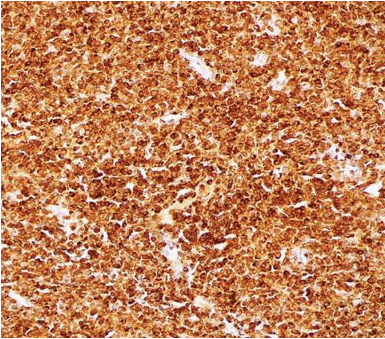
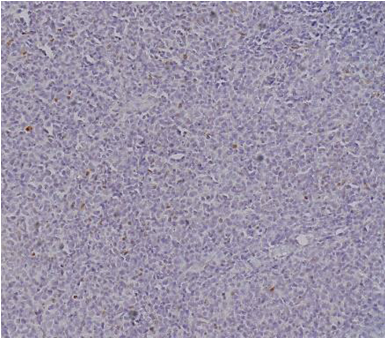
Appendix A. R-CHOP regimen used in this study (given every three weeks)

Drug	Dose	Route	Treatment Days
<i>Rituximab</i>	500 mg (fixed)	Intravenous	Day 1
<i>Cyclophosphamide</i>	750 mg/m ²	Intravenous	Day 1
<i>Doxorubicin</i>	50 mg/m ²	Intravenous	Day 1
<i>Vincristine</i>	1.4 mg/m ² (max dose 2 mg)	Intravenous	Day 1
<i>Prednisone</i>	100 mg in 2 divided doses	Oral	Days 1 -5

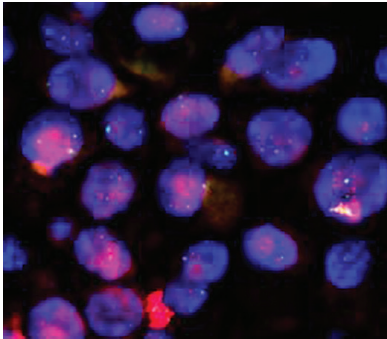
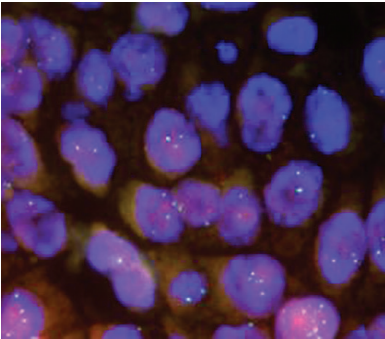
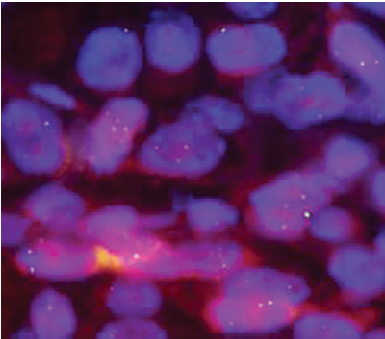
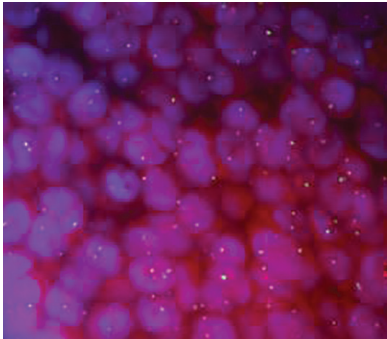
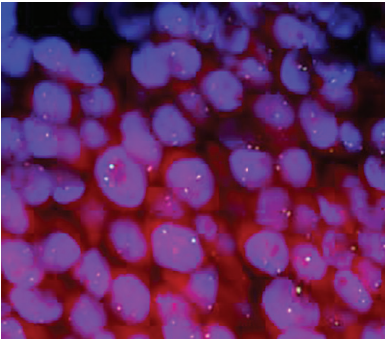
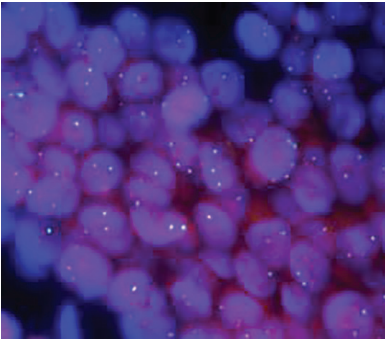
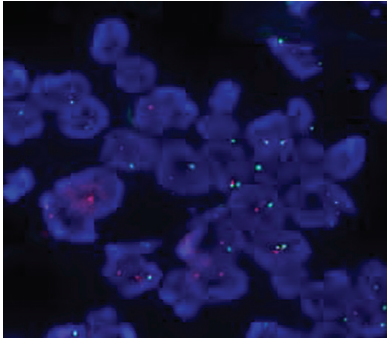
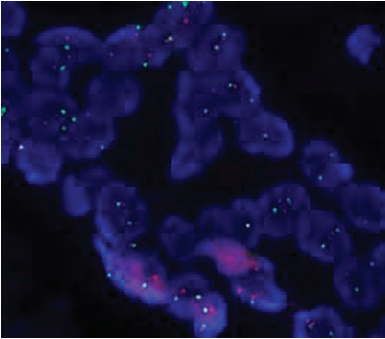
Appendix B. Cells of origin (Hans Algorithm)

	CD10	BCL6	MUM1	Interpretation
Case 1				Non-Germinal Center B-Cell-Like Subtype
	Weak to moderate staining in <20% of tumor cells	Moderate to strong staining in >40% of tumor cells	Strong staining in >90% of tumor cells	
Case 2				Germinal Center B-Cell-Like Subtype
	Weak to moderate staining in 60-70% of tumor cells	Moderate to strong staining in 80-90% of tumor cells	Weak staining in <5% of tumor cells	
Case 3				Non-Germinal Center B-Cell-Like Subtype
	Weak staining in 5% of tumor cells	No staining seen in tumor cells	Strong staining in >90% of tumor cells	

Appendix C. MYC, BCL2, and BCL6 protein expression

	MYC	BCL2	BCL6
Case 1	 Strong staining in >90% of tumor cells	 Moderate to strong staining in <5% of tumor cells	 Moderate to strong staining in >40% of tumor cells
Case 2	 Strong staining in 90-95% of tumor cells	 Moderate to strong staining in 20-25% of tumor cells	 Moderate to strong staining in 80-90% of tumor cells
Case 3	 Moderate to strong staining in >90% of tumor cells	 Strong staining in >90% of tumor cells	 No staining seen in tumor cells

Appendix D. MYC, BCL2, and BCL6 gene rearrangements (fluorescence in situ hybridization)

	MYC	BCL2	BCL6
Case 1	 MYC gene rearrangements seen in 4.76% of tumor cells	 BCL2 gene rearrangements seen in 10.20% of tumor cells	 BCL6 gene rearrangements seen in 9.09% of tumor cells
Case 2	 MYC gene rearrangements seen in 9.09% of tumor cells	 BCL2 gene rearrangements seen in 12.28% of tumor cells	 BCL6 gene rearrangements seen in 10.71% of tumor cells
Case 3	 MYC gene rearrangements seen in 9.90% of tumor cells	 BCL2 gene rearrangements seen in 9.09% of tumor cells	