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. 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

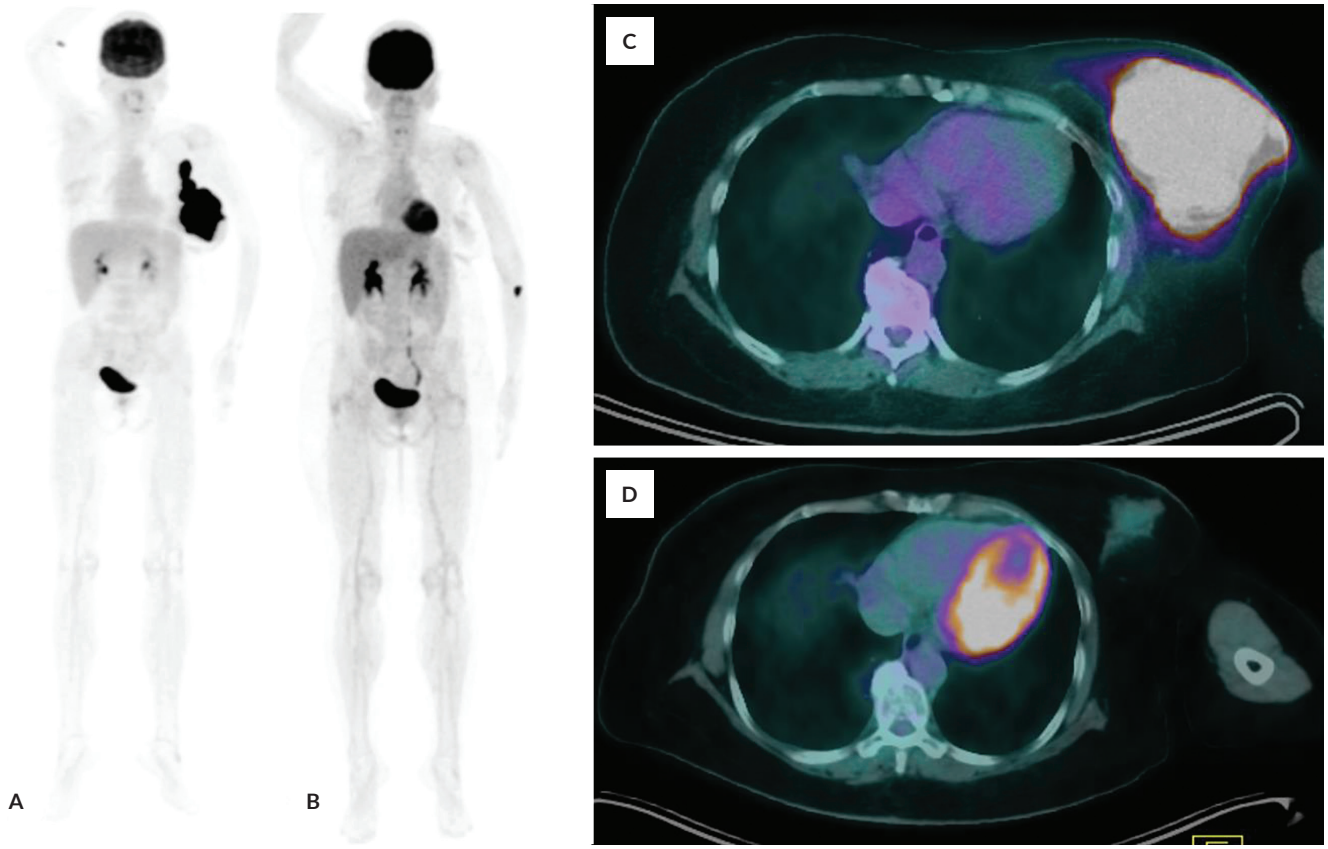

Figure 1. ***Pre- and post-treatment PET-CT scan with contrast images of Case 1.*** **(A)** and **(C)** are pre-treatment PET-CT scans showing an intensely FDG-avid left breast mass measuring 11.3 x 8.5 x 8.3 cm and left axillary lymph nodes (both Deauville score 5). **(B)** and **(D)** are post-treatment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

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 months[18], 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 (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

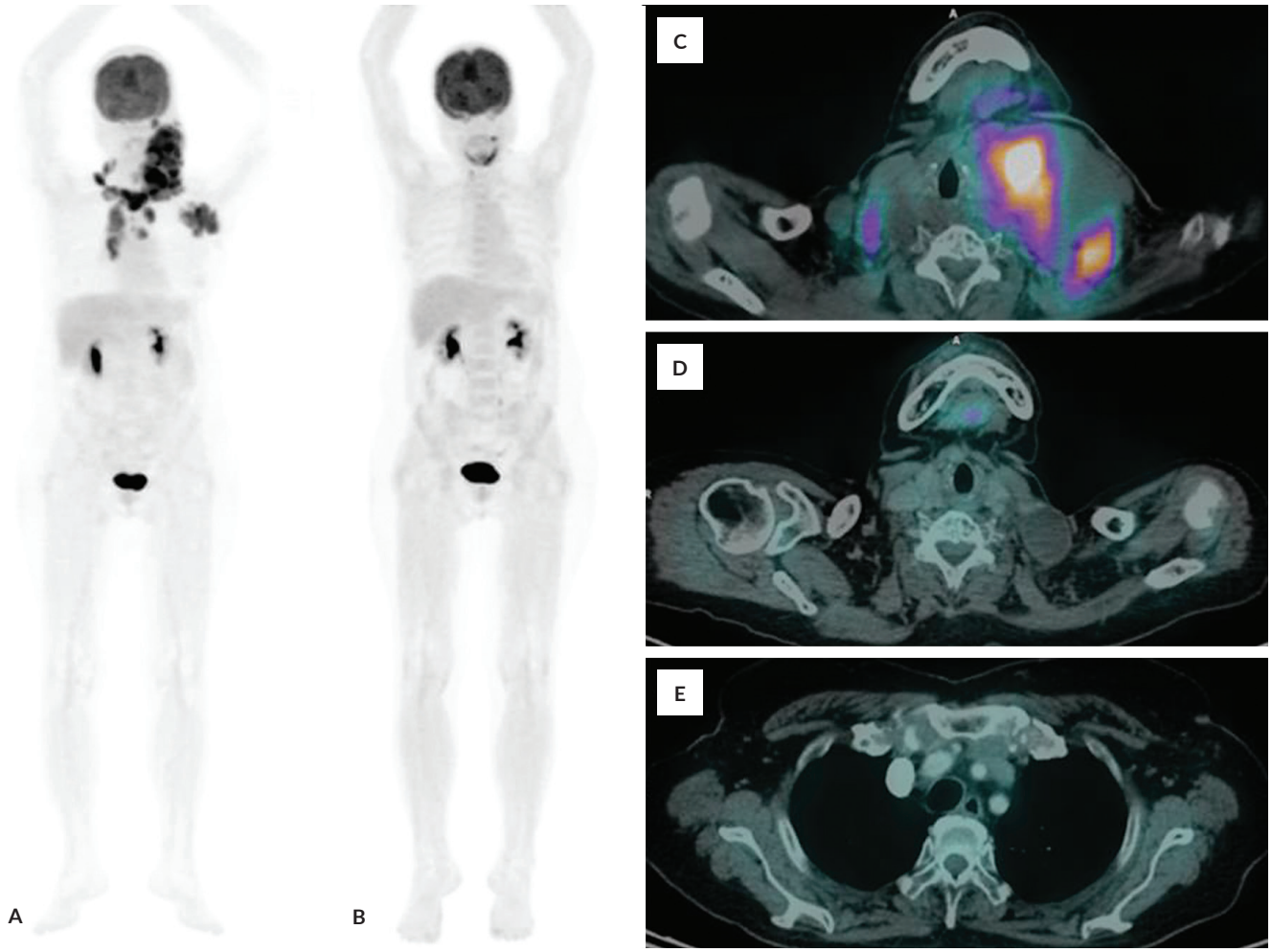

Figure 2. ***Pre- and post-treatment PET-CT scan with contrast images of Case 2.*** **(A)** and **(C)** showing intensely FDG-avid (DS 5) confluent lymph nodes in the left lateral neck, insinuating medially into the left carotid and parapharyngeal space and extending inferiorly into the thoracic inlet with an aggregate measure of 8.7 x 8.5 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.

recommendation is clearly defined for early stage and/or bulky DLBCL[28,29], evidence remains scarce for its role in HGBCL[30].

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 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 < .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

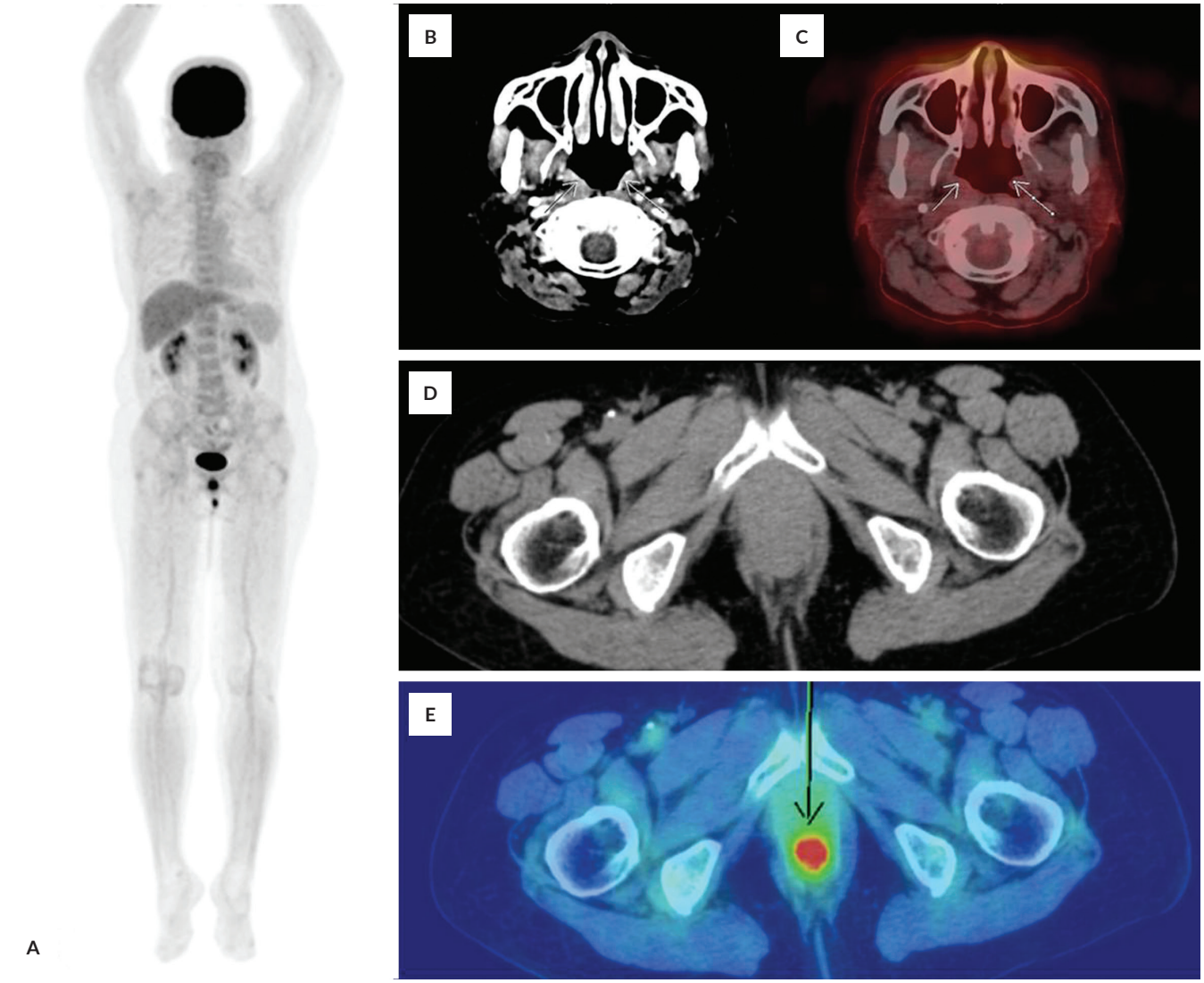

Figure 3. ***Post-treatment PET-CT scan with contrast of Case 3.*** **(A)** Whole body image. **(B)** and **(C)** representative neck cuts showing complete metabolic response and residual mucosal thickening. **(D)** and **(E)** shows an FDG-avid anorectal focus which did not have CT correlation findings.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

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/m^2 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.

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

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	*MYC*, *BCL2*, and *BCL6*		*MYC* and *BCL2*
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

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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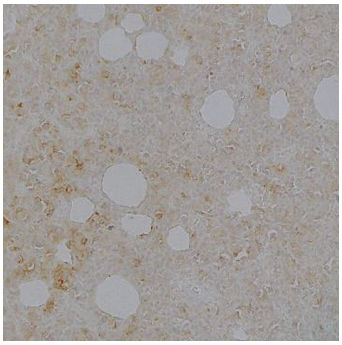
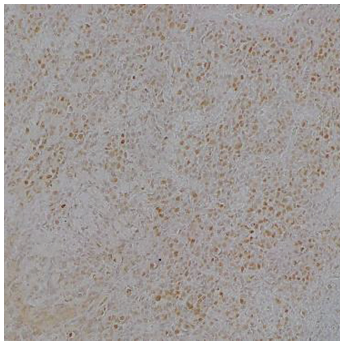
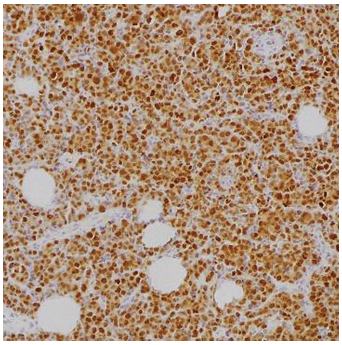
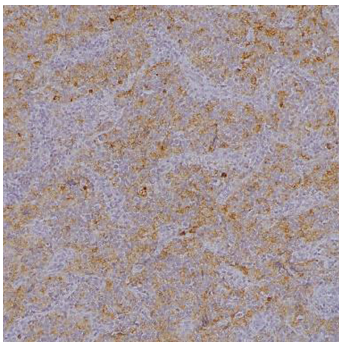
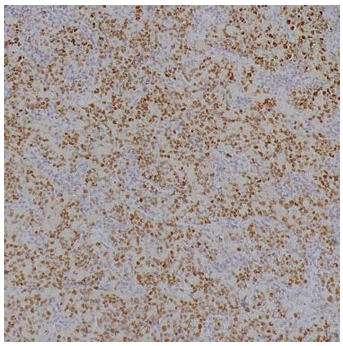
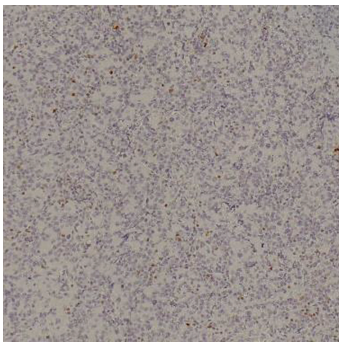
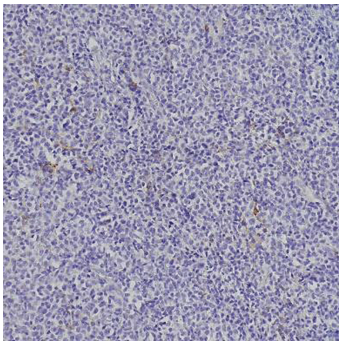
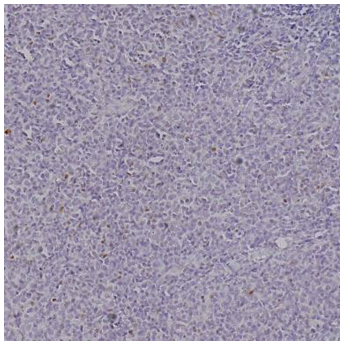
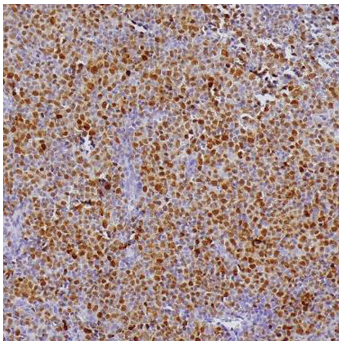
APPENDICES

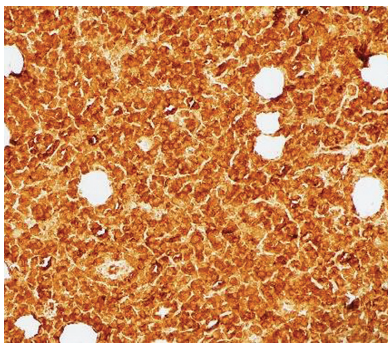
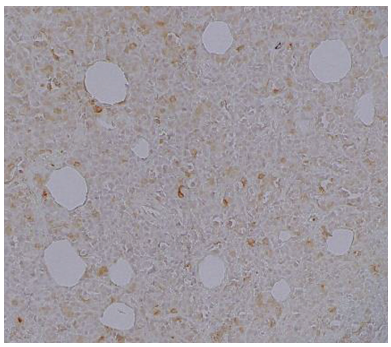
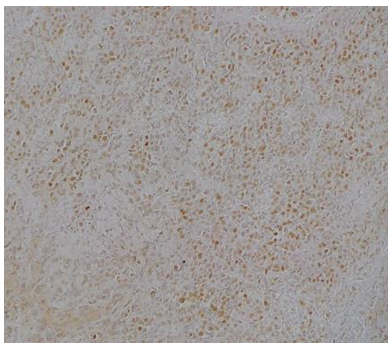
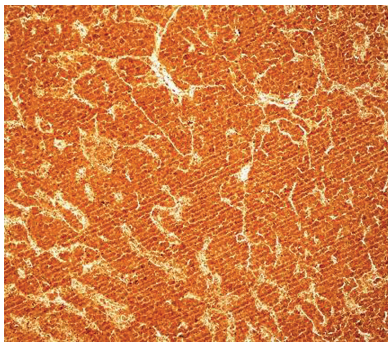
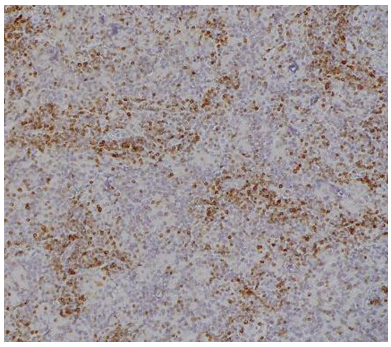
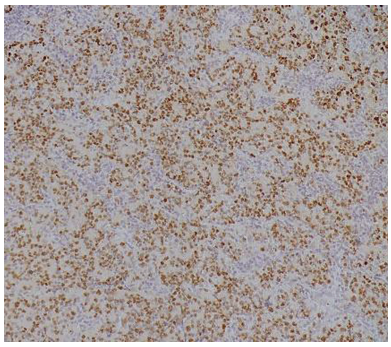
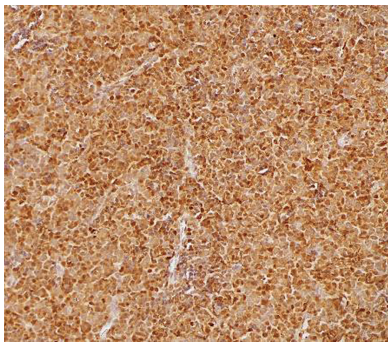
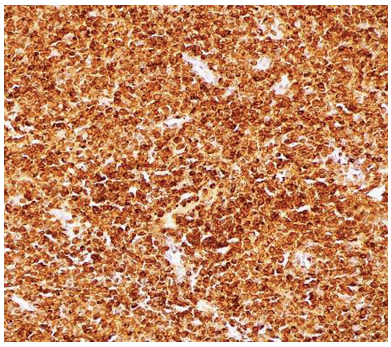
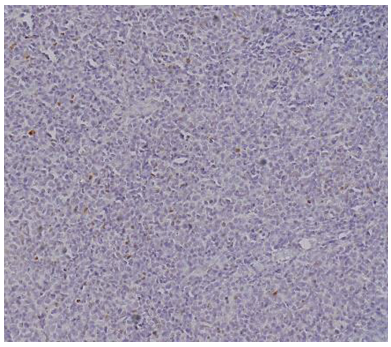
Appendix A. R-CHOP regimen used in this study (given every three weeks)

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

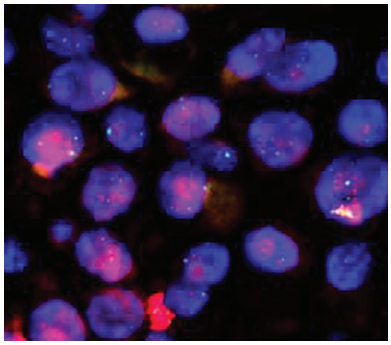
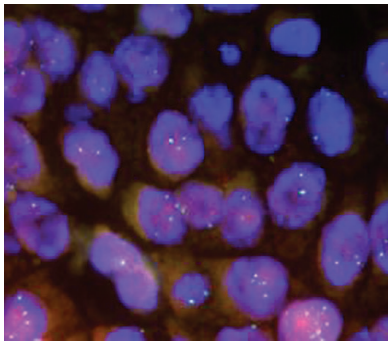
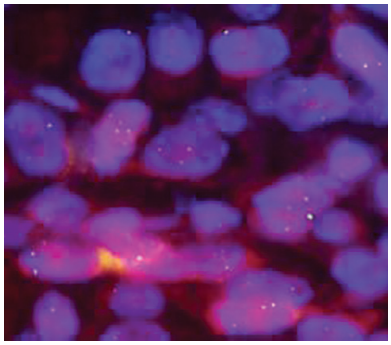
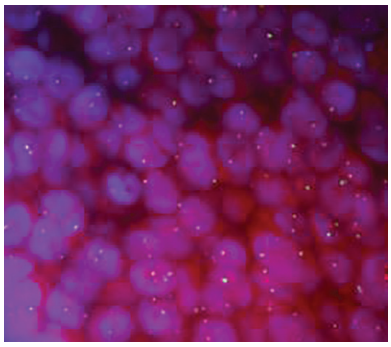
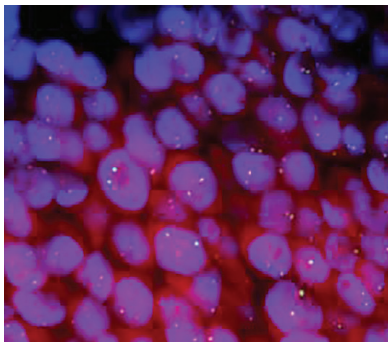
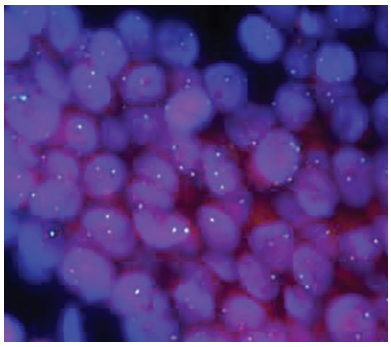
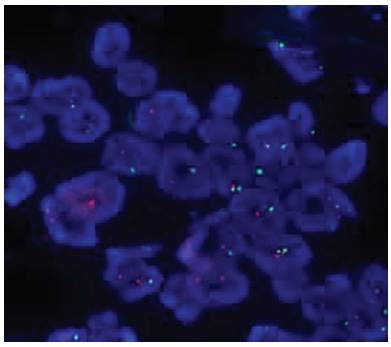
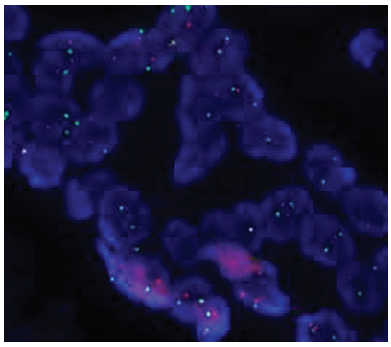
Appendix B. Cells of origin (Hans Algorithm)

	CD10	*BCL6*	*MUM1*	Interpretation
Case 1	 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	Non-Germinal Center B-Cell-Like Subtype
Case 2	 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	Germinal Center B-Cell-Like Subtype
Case 3	 Weak staining in 5% of tumor cells	 No staining seen in tumor cells	 Strong staining in >90% of tumor cells	Non-Germinal Center B-Cell-Like Subtype

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	