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Treatment outcome of diffuse large B-cell lymphoma involving the head and neck

Two-institutional study for the significance of radiotherapy after R-CHOP chemotherapy

Yoo-Kang Kwak, MD[a], Byung-Ock Choi, MD[b], Sung Hwan Kim, MD[a], Joo Hwan Lee, MD[a], Dae Gyu Kang, MS[a], Jong Hoon Lee, MD[a,*]

Abstract

This study was performed to analyze the treatment outcome for diffuse large B-cell lymphoma (DLBCL) involving the head and neck and to evaluate the role of radiotherapy in the rituximab era. Fifty-six patients diagnosed with DLBCL involving the head and neck were assessed. All patients were treated with 6 cycles of rituximab, cyclophosphamide, adriamycin, vincristine, and prednisolone (R-CHOP). After chemotherapy, radiation was delivered to the head and neck area in a median dose of 36 Gy. Radiation was delivered using 3-dimensional radiotherapy (n = 25) or intensity-modulated radiotherapy (n = 31). Primary endpoints were relapse-free survival (RFS), overall survival (OS), and local control rate. After median follow-up time of 45 months, the 5-year RFS and OS rates were 72% and 61%, respectively. Fourteen (25%) of 56 patients relapsed; 1 had a local relapse, 11 had distant relapses, and 2 had both local and distant relapses. The final local control rate after radiotherapy was 94%. Age, performance status, international prognostic index score, and radiotherapy response were significant prognostic factors for both RFS and OS in the multivariate analysis. Incidence of acute grade 3 and 4 hematologic toxicity was 9% and 4%, respectively. Grade 3 nonhematologic toxicity occurred in 2 (4%) patients, and there was no grade 4 nonhematologic toxicity for the irradiated patients. Excellent local control and survival rates can be achieved with R-CHOP followed by radiotherapy in patients with DLBCL involving the head and neck. Treatment-related toxicity after the introduction of modern radiotherapy was acceptable and limited.

Abbreviations: CR = complete response, IFRT = involved-field radiotherapy, IMRT = intensity-modulated radiotherapy, IPI = international prognostic index, ISRT = involved-site radiotherapy, LDH = lactate dehydrogenase.

Keywords: head and neck, lymphoma, radiotherapy, rituximab

1. Introduction

Lymphoma is classified into Hodgkin lymphoma and non-Hodgkin lymphoma. Non-Hodgkin lymphoma is further categorized according to specific cell types. The most common type of non-Hodgkin lymphoma is diffuse large B-cell lymphoma (DLBCL), which comprises about 30% of all lymphomas.[1] The characteristic of DLBCL is its fast growing and aggressive feature. Staging of DLBCL, like other lymphomas, is done using the Ann Arbor staging system,[2] which classifies the disease according to the extent of the disease since it can develop in any location throughout the body. Among the lymph node groups, the head and neck region contains rich lymphatic chains and blood supplies in a relatively confined area. Although it is unusual to categorize DLBCL according to anatomical sites, we had a question whether the distinguishing anatomical features of the head and neck will influence the clinical features and treatment outcomes of the disease.

Standard treatment for early-stage DLBCL is an abbreviated course (3 cycles) of chemotherapy followed by radiotherapy. In the advanced stage, a full course (6 cycles) of chemotherapy is the main treatment with optional radiotherapy to the initial bulky mass. However, the role of radiotherapy has been controversial and the results of reported studies are conflicting.[3–7] With the introduction of rituximab, the treatment outcomes of DLBCL improved, and the use of radiotherapy is gradually decreasing due to the increased treatment-related toxicity. Actually, the use of combined-modality therapy has significantly decreased after a peak of 47% in 2000 to 32% in 2012 at North America.[8] Three-dimensional conformal radiation therapy (3DCRT) employs several numbers of beams that are shaped to cover the target volume, and it uses conventional beam modifiers (eg, wedges, blocks, and compensating filters) to enhance the radiation conformity. Intensity-modulated radiotherapy (IMRT) can achieve even greater conformity by optimally modulating the intensity of individual beams and more homogeneous dose distribution with sharper fall-off of dose at target boundaries thereby sparing adjacent normal tissues. In terms of radiotherapy technique, the use of IMRT has become generalized recently. In

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[a] Department of Radiation Oncology, St. Vincent's Hospital, [b] Department of Radiation Oncology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.

[*] Correspondence: Jong Hoon Lee, Department of Radiation Oncology, St. Vincent's Hospital, 442-723, 93-6, Ji-dong, Paldal-gu, Suwon, Kyeonggi-do, Seoul, Republic of Korea (e-mail: koppul@catholic.ac.kr).

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this IMRT era, radiotherapy has become feasible with tolerable toxicity. IMRT is especially effective for treating lesions in the head and neck with acceptable toxicity.

Based on the above subjects, we selected patients with DLBCL of the head and neck and analyzed the clinical features and treatment outcomes. Also, the role of radiotherapy in the treatment of head and neck DLBCL in the rituximab era was examined.

2. Methods and materials

2.1. Patients

The study included data of patients who were diagnosed with DLBCL of the head and neck treated with chemotherapy followed by radiotherapy from January 2006 to March 2015 at 2 tertiary institutions. Inclusion criteria were age ≥20 years, pathologically confirmed DLBCL, and receipt of radiotherapy in the head and neck area. We excluded the patients who did not receive chemotherapy prior to radiotherapy, had immunodeficiency virus infection, and had a history of other malignancies. For diagnosis and clinical workup, history taking, physical examination, complete blood counts, blood chemistry, bone marrow biopsy, tissue biopsy, and imaging studies including neck, chest, abdomen, and pelvis computed tomography (CT), and positron emission tomography (PET) CT were evaluated. All patients were staged according to the Ann Arbor staging system. A total of 56 patients were enrolled. This study was approved by the institutional review boards of each institution.

2.2. Treatment

All patients received 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) chemotherapy (rituximab: 375 mg/m^2, cyclophosphamide: 750 mg/m^2, doxorubicin: 50 mg/m^2, vincristine: 1.4 mg/m^2, and prednisolone: 100 mg orally, day 1–5).

Radiotherapy simulation was performed in the supine position, and head and shoulder s-frame mask was used for immobilization. Enhanced neck CT was obtained in 3-mm slices. Radiation was delivered using 3-dimensional radiotherapy (n = 25) or IMRT (n = 31). Radiotherapy technique was chosen upon each clinician's policy. In South Korea, national health insurance program covered IMRT technique after July 2011 since IMRT could decrease the toxic effect such as mucositis and xerostomia in head and neck cancer patients. IMRT has been used broadly in the recent time. Thirty-four patients received involved-field radiotherapy (IFRT), and 22 patients received involved-site radiotherapy (ISRT) according to the clinician's policy. ISRT delivers a radiation only to the involved nodes or sites in the prechemotherapy CT images. IFRT covers the whole adjacent lymphatic regions of involved nodes or sites. Therefore, IFRT includes a wider region compared to ISRT, which increases the risk of radiation toxicity but can decrease the risk of locoregional recurrence. Radiation was administered in a median dose of 36 Gy (range, 24–54 Gy) at 1.8 to 2 Gy per fraction, once daily, 5 times a week. Median treatment time was 25 days (range, 14–43 days).

2.3. Assessment

Enhanced neck CT and PET-CT were used for treatment response assessment. According to the response criteria for malignant lymphoma,[9] complete response (CR) was defined as disappearance of all evidence of disease with Deuville score 3 to 5.[10] Partial response (PR) was defined as regression of measurable disease and no new sites. Progressive disease (PD) was defined as any new lesion or increase by ≥50% of previously involved sites from nadir. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. International prognostic index (IPI) consisted of age, stage, Eastern Cooperative Oncology Group performance status, extranodal involvement, and lactate dehydrogenase level, and it was scored from 0 to 5. In our study, upper normal limit of lactate dehydrogenase level was 230 IU/L.

Patients were interviewed weekly during the treatment, monthly for 3 months after the treatment, and every 3 months thereafter. Overall survival (OS) was defined as the period from the date of pathologic diagnosis to death from any cause. Relapse-free survival (RFS) was defined as the period from the date of pathologic diagnosis to the date of any relapse or death. Local control (LC) was defined as absence of tumor regrowth in the irradiated area. Adverse effects of radiotherapy were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Incidence of toxicity grade ≥2 was recorded.

2.4. Statistical analyses

Primary endpoints of this study were OS, RFS, and local control rate. Secondary endpoints were toxicity caused by multimodality therapy and pattern of relapse after radiotherapy. Kaplan–Meier analysis with the log-rank test was used for the univariate survival analysis. To evaluate the prognostic factors related to recurrence and survival, multivariate analysis was performed with the Cox regression method. A P-value $<.05$ was considered as a statistically significant one. Factors with P-value $<.05$ in the univariate analysis were entered for multivariate analysis. All statistical analyses were performed using R software version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org).

3. Results

Table 1 shows characteristics of the enrolled patients. Median age was 57 years. Among these 56 patients, 46 patients (82%) had a low and low-intermediate IPI score. Patients were further classified according to the location involved; 52% of patients had lesions in Waldeyer ring, 14% of patients had lesions in lymph nodes, 20% of patients had lesions in the nasal cavity and paranasal sinuses, and 14% of patients had lesions in other sites such as the submandibular gland, thyroid, and lacrimal sac (Fig. 1). Nodal disease was defined as lesions involving lymph nodes and Waldeyer ring. Thus, 37 patients (66%) had nodal diseases. Initial Ann Arbor stages III and IV were found in 11 patients (20%); these patients had residual or relapsed disease in the head and neck area only after chemotherapy.

3.1. Treatment response

Median time interval for radiotherapy and response evaluation was 2 months. After chemotherapy, 39 patients (74%) achieved CR, 6 patients (11%) had PR, and 8 patients (15%) had PD. After radiotherapy, 38 patients maintained CR; 1 patient showed distant relapse. Among the 6 patients with PR after chemotherapy, 3 patients achieved CR, 2 patients had PR, and 1 patient had PD. Among the 8 patients with PD, 3 patients achieved CR, 2 patients showed PR, and 3 patients still had PD (Fig. 2).

Table 1

Patient characteristics (n = 56).

Characteristics	No	%
Age, y		
≤60	36	64
>60	20	36
Gender		
Male	38	68
Female	18	32
ECOG performance status		
0	25	45
1	26	46
2	5	9
IPI score		
Low	40	71
Low-intermediate	6	11
High-intermediate	6	11
High	4	7
Lactate dehydrogenase		
Normal	35	63
Elevated	21	38
Disease site		
Nodal	37	66
Extranodal	19	34
Stage		
I–II	45	80
III–IV	11	20
Radiation dose, Gy		
≤36	31	55
>36	25	45

ECOG = Eastern Cooperative Oncology Group, IPI = international prognostic index.

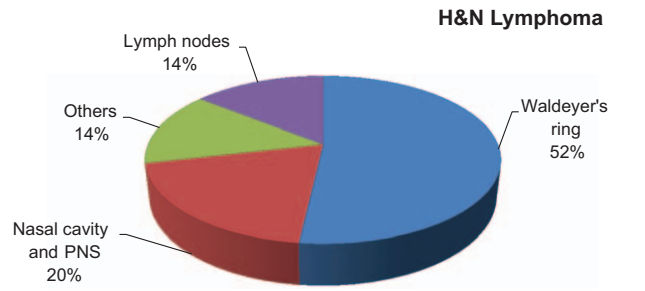

Figure 1. Pie graph describes the proportion of patients according to the involved site. *Other sites: thyroid, lacrimal sac, submandibular gland. PNS = paranasal sinus.

3.2. Recurrence and survival

The median follow-up time was 45 months (range, 11–110 months). The RFS (Fig. 3A) and OS (Fig. 3B) rates at 5 years in all patients were 72% and 61%, respectively. There were 14 (25%) relapsed cases. One patient had a local relapse after radiotherapy, 11 had distant relapses, and 2 had both local and distant relapses. The final local control rate after radiotherapy was 94%.

Prognostic factors for RFS and OS are shown in Table 2. In the univariate analysis, age ($P = .05$), performance status ($P = .01$), stage ($P = .01$), IPI score ($P < .01$), chemotherapy response ($P = .04$), radiation dose ($P = .05$), radiation response ($P = .01$), and radiation modality ($P = .03$) are prognostic factors for RFS. Age ($P = .02$), performance status ($P = .01$), stage ($P < .01$), IPI score ($P < .01$), chemotherapy response ($P < .01$), and radiation response ($P < .01$) are prognostic factors for OS. In the additional multivariate analysis, age ($P = .03$), performance status ($P = .03$), IPI score ($P = .02$), and radiotherapy response ($P = .01$) showed a statistical significance for RFS. Regarding OS, age ($P = .01$), performance status ($P < .01$), stage ($P < .01$), IPI score ($P < .01$), and radiotherapy response ($P < .01$) were statistically significant factors. There were no significant differences in recurrence and survival with respect to tumor location, chemotherapy response, radiation dose, modality, and field in the multivariate analysis.

3.3. Toxicity

Table 3 describes acute hematologic and nonhematologic toxicity. Severe grade 3 or 4 hematologic toxicities occurred in 7 patients (13%). Two patients (4%) suffered from grade 3 nonhematologic toxicities such as oral mucositis and generalized weakness. There was no grade 4 nonhematologic toxicity. Grade

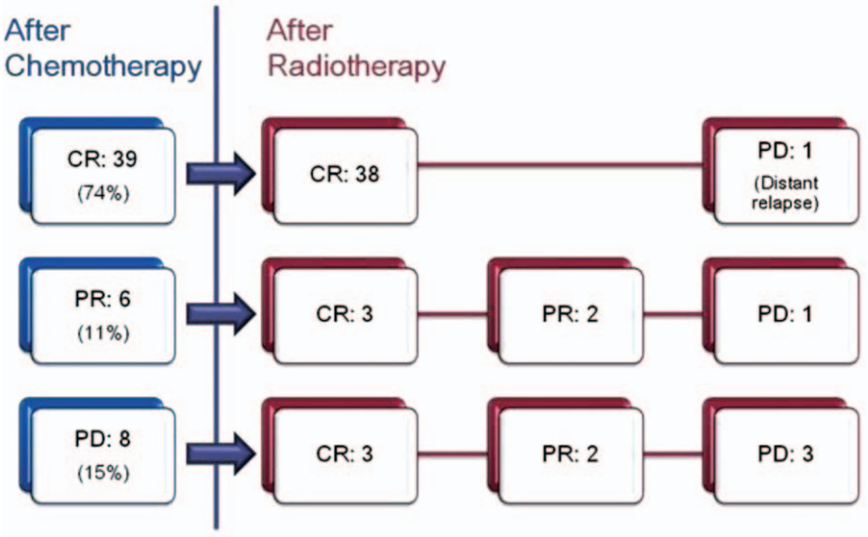

Figure 2. Diagram shows treatment response after chemotherapy and radiotherapy. CR = complete response, PD = progressive disease, PR = partial response.

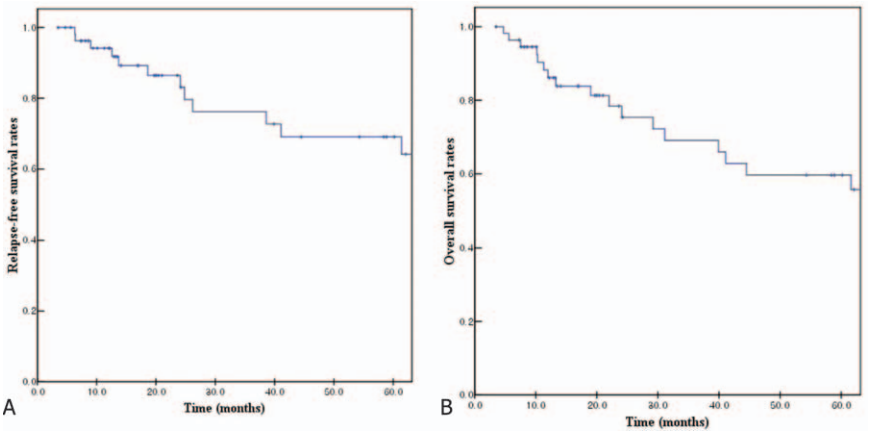

Figure 3. Kaplan–Meier estimates of relapse-free (A) and overall (B) survival rate.

Table 2

Prognostic factors for relapse-free and overall survival.

	Relapse-free survival			Overall survival		
Factors	**Univariate (*P*)**	**Hazard ratio (95% CI)**	**Multivariate (*P*)**	**Univariate (*P*)**	**Hazard ratio (95% CI)**	**Multivariate (*P*)**
Age, y (≤60 vs >60)	.05	**6.3 (1.7–24.0)**	**.03**	0.02	**15.6 (1.8–136.2)**	**.01**
Gender (male vs female)	.13			0.30		
ECOG (0–1 vs 2–3)	.01	**54.5 (1.4–105.6)**	**.03**	0.01	**27.7 (16.1–63.2)**	**<.01**
LDH (normal vs elevated)	.22			0.16		
Stage (I–II vs III–IV)	.01	2.4 (0.2–24.0)	.45	<0.01	**40.9 (4.4–82.7)**	**<.01**
Tumor location (nodal vs extranodal)	.55			0.61		
IPI score (0–2 vs 3–5)	<.01	**12.9 (2.8–58.8)**	**.02**	<0.01	**51.3 (13.7–121.6)**	**<.01**
Chemotherapy response (CR vs non-CR)	.04	0.5 (0.1–3.5)	.46	<0.01	1.0 (0.3–3.9)	.98
Radiotherapy dose, Gy (≤36 vs >36)	.05	2.4 (0.2–28.1)	.50	0.19		
Radiotherapy response (CR vs non-CR)	.01	**5.3 (1.4–20.3)**	**.01**	<0.01	**36.6 (4.0–137.8)**	**<.01**
Radiotherapy modality (IMRT vs conventional RT)	.03	3.3 (0.1–87.3)	.47	0.21		
Radiotherapy field (IFRT vs ISRT)	.88			0.92		

Numbers in bold represent statistically significant values in the multivariate analysis. CI = confidence interval, CR = complete response, ECOG = Eastern Cooperative Oncology Group, IFRT = involved-field radiotherapy, IMRT = intensity-modulated radiotherapy, IPI = international prognostic index, ISRT = involved-site radiotherapy, LDH = lactate dehydrogenase, RT = radiotherapy.

2 or 3 nonhematologic toxicities occurred in 13 patients (23%) and 2 patients (4%), respectively. Dry mouth, oral mucositis, and esophagitis were the most common signs of nonhematologic toxicity. Most of the acute toxicities resolved after 1 or 2 months of radiation completion. In 2 patients, toxicity was observed after 3 months of radiotherapy; 1 had pulmonary fibrosis, and the other had grade 2 dry mouth.

Table 3

Grade 2 or higher acute adverse effects.

	Grade 2	Grade 3	Grade 4
Hematologic			
Leucopenia	10	4	1
Anemia	2	0	0
Thrombocytopenia	1	1	1
Total	13 (23%)	5 (9%)	2 (4%)
Nonhematologic			
Dry mouth	2	0	0
Oral mucositis	3	1	0
Esophagitis	7	0	0
General weakness	1	1	0
Total	13 (23%)	2 (4%)	0

4. Discussion

This study assessed the patients with head and neck DLBCL treated with chemotherapy followed by radiotherapy. The results showed an excellent local control rate with acceptable toxicities. Only 1 patient suffered from grade 4 toxicity (leucopenia and thrombocytopenia), and the patient recovered after G-CSF administration and transfusion. Since the recommended dose of radiotherapy in lymphoma is relatively low (30–36 Gy in CR and 40–50 Gy in PR) and with the generalized use of IMRT and conformal radiotherapy, tolerable toxicity was achieved in our study. The local control rate was 94%. Since the patient cohort in this study received both chemotherapy and radiotherapy, we could not completely exclude the effects of chemotherapy, but we assume that radiotherapy contributed more to local control since radiotherapy is local therapy whereas chemotherapy contributes more on systemic control.

To the best of our knowledge, there are no studies reported on head and neck DLBCL. Compared to other randomized trials for non-Hodgkin lymphoma in the pre-rituximab era, survival outcomes were better with additional radiotherapy.[3,5,6] In the modern chemotherapy and rituximab era, there is an ongoing debate about the use of consolidative radiotherapy in non-

Hodgkin lymphoma and its usage is actually diminishing. A study by Vargo et al[8] with 59,255 DLBCL patients demonstrated that the use of combined-modality therapy declined from 47% in 2000 to 32% in 2012 with a statistical significance ($P < .01$). In their study, only 39% of patients received combined-modality therapy, but overall survival was significantly better in the combined modality arm compared to the chemotherapy alone arm (hazard ratio, 0.66; 95% confidence interval, 0.61–0.71; $P < .01$). Several retrospective studies for DLBCL in single institution were performed in the rituximab era, and the results showed positive effects of adding radiation after chemotherapy in all stages.[11–14]

In the preretuximab era, the treatment results of some studies that assessed patients with DLBCL treated with chemotherapy alone and combined-modality treatment reported 5-year RFS of 56% to 64% and 61% to 73%, respectively.[5,6,15] These studies also proved benefits of combined-modality treatment compared to chemotherapy alone. In the rituximab era, a subgroup analysis of the RICOVER-60 trial, which was a prospective assessment in the 2 cohorts, treated with R-CHOP with optional IFRT (36 Gy) to bulky disease, was performed and it provided strong support for adding radiation to sites of bulky disease in aggressive B-cell lymphoma.[4] Another prospective phase III trial by the German High-Grade Non-Hodgkin Lymphoma Study Group, named UNFOLDER21/14 trial, randomized patients to either R-CHOP 21 or R-CHOP 14, with secondary randomization to RT or observation.[16] On the planned interim analysis, patients who did not receive radiation had significantly inferior event-free survival than patients who received a combined-modality treatment. Consequently, the 2 arms without radiation were closed early. The final results of UNFOLDER21/14 trial could provide a strong evidence for the supportive role of radiation for DLBCL even in the rituximab era.

There are some limitations to our study. First of all, the retrospective nature of this study caused inevitable selection and observer biases.[17] Eleven (20%) patients with initially advanced stage III–IV were included in our study. In stages III and IV, it is not appropriate to classify the disease as head and neck DLBCL. However, the included patients had an initial bulky mass in the head and neck area only and were disease-free at sites other than the head and neck after chemotherapy. In this study, patients who received only a combined-modality treatment were included. Thus, a direct comparison of oncologic outcomes between combined modality and chemotherapy alone groups was not available.[18,19] To verify our results, future multicenter trials are needed that will compare chemotherapy alone and chemotherapy plus radiotherapy methods for the treatment of DLBCL involving the head and neck.

In conclusion, treatment outcomes of DLBCL involving the head and neck treated with R-CHOP followed by radiotherapy were satisfactory with excellent local control and tolerable toxicity. With the recent advances in radiotherapy technology, radiation could be more practicable in patients with the head and neck DLBCL even in the rituximab era.

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