

Intensity-modulated Radiotherapy in Patients With Aggressive Extranodal Non-Hodgkin Lymphoma of the Head and Neck

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Abstract. *Background/Aim: Image-guided intensity-modulated radiotherapy (IG-IMRT) is increasingly being used to treat patients with head and neck malignancies. This analysis compared conventional radiotherapy (CRT) and IMRT outcomes for head and neck aggressive extranodal non-Hodgkin lymphomas (EN-NHL). Patients and Methods: Forty-eight patients who underwent irradiation between 2005 and 2019 were identified. Results: The median follow-up was 42 months. Patients treated with IMRT experienced higher overall response rate than patients who received 3DCRT (85% vs. 73%, $p=0.4$). There was non-significant longer survival following IMRT compared with 3DCRT in terms of 5-year OS ($p=0.16$). Complete responders after primary treatments had a significantly higher 5-year progression-free ($p<0.001$) and overall survival ($p=0.003$) in comparison with those without a complete response. Regarding toxicities, IMRT was associated with less acute and chronic adverse events. Conclusion: IG-IMRT following systemic therapy seems to be associated with a favorable survival and toxicity profile in patients with EN-NHL.*

Extranodal non-Hodgkin lymphoma (EN-NHL) is defined as lymphoma arising in an extranodal organ or tissue and accounts for approximately one-third of all NHLs (1, 2). The most common localizations for EN-NHL are the gastrointestinal tract, mediastinum, testis, and central nervous system (CNS). The salivary glands, nasal cavity, paranasal sinuses, and thyroid gland are uncommon sites (2).

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Stage, localization, and histology are essential factors for the decision of treatment modality (2). Radiotherapy (RT) plays a significant role in treating EN-NHL and is frequently used as a consolidation after systemic therapy, salvage treatment, or palliation (1-4). Excellent local control is achieved by RT, resulting in high disease-free and overall survival rates (3). Acute and chronic toxicities of RT are associated with RT dose and rate (1). moreover, irradiated tissue and fraction dose may determine the severity of chronic toxicities (5). Recent dose and volume de-escalation and the increased use of image-guided intensity-modulated radiotherapy (IG-IMRT) in the management of NHL have made it possible to mitigate acute and late toxicities (1-9).

The purpose of this analysis was to examine the effects of different RT techniques on locoregional control (LRC) rates and survival in patients with head and neck EN-NHL. Furthermore, radiation toxicities were investigated with regards to radiotherapy techniques.

Patients and Methods

Patients. In this retrospective study, we collected data regarding clinical features, treatment concepts, and outcomes of patients who were referred for external beam RT between 2005 and 2019. Inclusion criteria for our study were EN-NHL of the head and neck, completion of the treatment course, and a minimum follow-up time of three months. Orbital and CNS lymphomas were excluded due to the different clinical behavior. Common Terminology Criteria for Adverse Events (AEs) was used to assess toxicities. All procedures performed were per the ethical standards of the University Hospital Münster and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Forty-two patients (87%) received chemotherapy, while six patients did not receive chemotherapy due to comorbidities and advanced age (median age was 74 years). RT had been delivered as part of a primary management strategy ($n=46$) or after exhibiting locoregional relapse (LRR) following other treatment modalities

(n=2). At the time of final analysis, 11 (23%) patients had died, while 37 (77%) were alive, and four patients experienced relapse (8%). Five patients (10%) underwent surgical resection of primary EN-NHL.

Radiation technique. Planning CTs were performed with an intravenous contrast approximately two to three weeks before starting RT. Additional PET-CT (n=5) or MRI (n=9) scans were performed on 14 patients for clinical tumor volume (CTV) delineation. Thirty-three patients (69%) received image-guided IMRT (Linear accelerator=23, Tomotherapy=10) and 15 (31%) patients received 3D conformal RT (3DCRT). In this study, patients who received conventional radiotherapy (CRT) were compared with patients who received an IMRT.

Statistical analysis. All statistical analyses were performed with SPSS version 27.0 software (IBM, Armonk, NY, USA). All differences were considered statistically significant at a *p*-value <0.05. Chi-squared or Fisher's exact analyses were conducted to test the relationships between two categorical variables. Overall survival (OS) was calculated from the first day of RT until death, and progression-free survival (PFS) was calculated from RT until relapse or death. Time-dependent event curves were calculated using the Kaplan-Meier method and were compared using the log-rang test.

Results

Patient and disease characteristics. The median age at the start of RT was 63 years (range=33-89 years). The most common histology was diffuse large B-cell lymphoma (n=38; 79%). At the time of diagnosis, the median Hemoglobin value (Hb) was 12 g/dl (range=8-16 g/dl) and the median LDH value was 215 U/l (range=146-593 U/l). At the time of treatment, two-thirds of patients (67%) had an Eastern Co-operative Oncology Group (ECOG) score of 0. Detailed clinical characteristics are summarized in Table I. Approximately half of the patients had stage 1 disease (56%). The median initial radiation dose was 39.6 Gy (range=30-54 Gy). The most common systemic treatments were rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP; n=27) and with addition of etoposide (CHOEP; n=5). Following systemic treatment, RT was applied. Radiation fields included 39 (81%) involved-site radiotherapy (ISRT) and 9 (19%) involved-field radiotherapy (IFRT). The median planning target volume (PTV) was 188 cm³ (range=23-1,297 cm³). The median follow-up time was 42 months. Three patients underwent a second RT course of out-field relapse. The median RT dose of the second course was 45 Gy (range=26-46 Gy).

Outcomes. Following RT, the overall response rate (ORR) was 81% (n=39) with 73% complete response rate (CRR; n=35) and 8% partial response (PR; n=4). In contrast, nine patients (19%) were non-responders to RT. The ORR was higher in patients receiving IMRT (85% vs. 73%, *p*=0.4) than patients who received 3DCRT. At the follow-up period, out-

Table I. Patient and treatment characteristics.

Characteristic	Nr. (% or range)
Patients	48
Med. age	63 (33-89)
Gender	36 M: 12 F
Stage	
I	27 (56%)
II	7 (15%)
III	2 (4%)
IV	12 (25%)
Histology	
DLBCL	38 (79%)
Nasal NK/T-cell lymphoma	6 (13%)
Mantle cell	3 (6%)
Peripheral T-Cell lymphoma	1 (2%)
LDH value	
Normal	24 (50%)
Elevated	19 (40%)
Unknown	5 (10%)
ECOG performance status	
0	32 (67%)
1	13 (27%)
Unknown	3 (6%)
Chemotherapy	
Yes	42 (87%)
No	6 (13%)
Primary tumor site	
Sinonasal/paranasal sinus	22 (46%)
Waldeyer's ring	16 (33%)
Cervical/Thorax aperture	5 (11%)
Mandibula/submandibular	3 (6%)
Other	2 (4%)
Radiation parameters	
Med. RT dose, Gy	39.6 Gy (30-54)
Med. Fraction dose, Gy	1.8 Gy (1.5-2)
Med PTV, cm ³	188 (23-1297)
RT field	
Involved-site	39 (81%)
Involved-field	9 (19%)

LDH: Lactic acid dehydrogenase test; RT: radiotherapy; ECOG: Eastern Co-operative Oncology Group; Med.: median.

of-field recurrences were detected in 3 patients (6%). The 5-year LRC was 83%. In terms of radiation technique, we found a similar LRC in both cohorts (*p*=0.9).

The 5-year PFS and 5-year OS were 67% and 75%, respectively. In terms of 5-year OS, there was a trend towards longer survival following IMRT compared with 3DCRT cohort (100% vs. 69%, *p*=0.16; Figure 1). The 5-year PFS was similar in both cohorts (67% vs. 66%, *p*=0.8). There was no significant impact of RT field size or type of RT technique on PFS or OS (*p*>0.05). Regarding the site of lesions, patients with Waldeyer's ring manifestation had better 5-year PFS (80% vs. 58%, *p*=0.16) and 5-year OS (87% vs. 86%, *p*=0.16) than patients presented with paranasal or maxillary lesions. Patients with complete

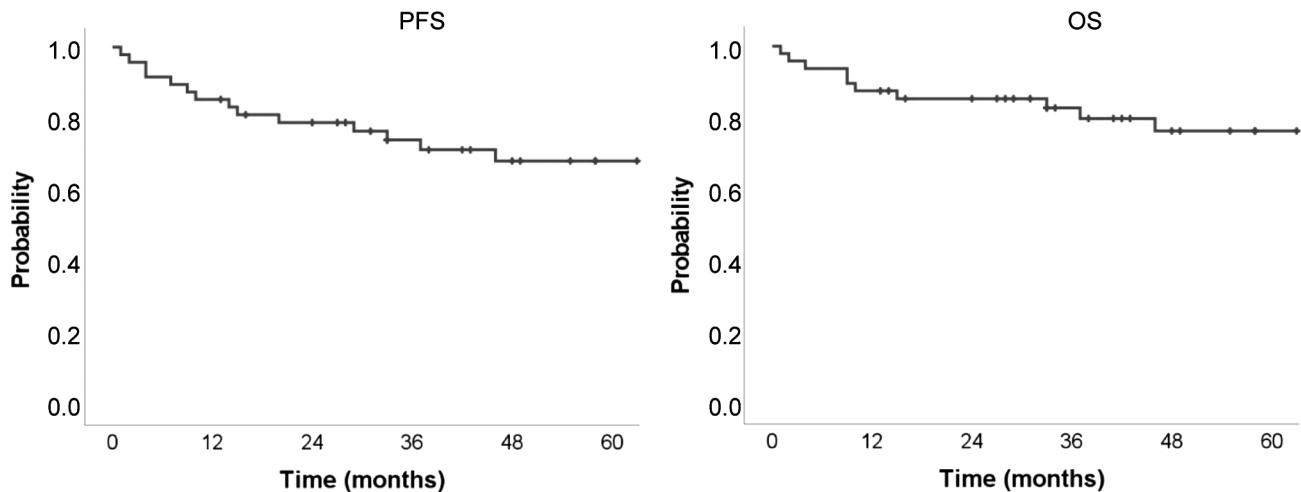


Figure 1. Kaplan-Meier estimates of overall survival of the whole cohort according to radiation technique ($n=48$).

remission (CR) after primary treatments had higher 5-year PFS (80% vs. 17%, $p<0.001$) and OS (83% vs. 58%, $p=0.003$) in comparison with those without CR.

During the initial RT courses, 92% of patients experienced grade 1 AEs, and 23% of patients experienced grade 2 AEs. No grade 3-5 toxicities were observed in our cohort. The most common acute AEs were erythema, xerostomia, and mucositis. Patients treated with IMRT experienced a lower rate of grade 1 toxicities (88% vs. 100%, $p=0.3$) and grade 2 toxicities (18% vs. 33%, $p=0.2$) compared with 3DCRT. In terms of chronic AEs, 12% of patients experienced grade 1 and 2% grade 2. There were no incidences of grade 3-5 chronic AEs. Following IMRT, chronic toxicity incidence was lower than the 3DCRT technique (12% versus 25%, $p=0.3$).

Discussion

In this study, we analyzed the influence of different RT techniques on LRC, survivals, and radiation-related toxicity. The following key findings emerged from this work: 1) There were no survival differences between patients who received IFRT vs. ISRT. 2) We detected a trend towards longer survival and lower toxicities following IMRT compared with 3DCRT. 3) Patients with complete remission after primary therapy had higher 5-year PFS and OS than those without CR.

The benefit of consolidative RT for DLBCL had been analyzed in large clinical trials (3-6). This study showed significant improvements in OS and PFS, if RT was given after R-CHOP chemotherapy (3, 10). A more recent two-institutional study was performed to evaluate the role of RT in the treatment of DLBCL involving the head and neck (11). This analysis showed that prechemotherapy treatment with

R-CHOP followed by modern RT is satisfactory with excellent local control and tolerable toxicity. The advantages of IMRT were also emphasized, particularly for patients with head and neck tumors (11). It is important to mention the importance of additive RT in the treatment modalities of bulky disease in elderly patients with aggressive B-Cell lymphoma. Held *et al.* (12) recommend a consolidative IFRT with 36 Gy in all patients with the bulky disease after analyzing two prospectively treated cohorts from the RICOVER-60 trial. Despite these findings, a clear trend towards RT-free regimens in recent years has been demonstrated in several studies (13), but omitting RT in the treatment of NHL should not be considered outside well-conducted prospective studies. Freeman *et al.* (13) report a large, population-based cohort of 723 DLBCL patients who received 6 to 8 cycles of R-CHOP and underwent end-of-therapy PET-guided RT. 72% of patients had negative PET after R-CHOP with an 83% 3-year time to progression (TTP). However, the progression rate was about 25% in the PET-negative cohort (13). The authors recommend RT omission in selected patients, although this is not a randomized trial and this high rate of relapse is consistent with previously reported data (13, 14). Owing to the inferior prognosis of relapsed DLBCL after primary systemic treatments, consolidative RT remains a valuable modality if not associated with increased toxicity (15). Reduced-dose RT currently seems to be a justifiable treatment approach. Lowry *et al.* (5) did not observe a loss of efficacy when 30 Gy were delivered to aggressive lymphomas compared to 45 Gy.

Due to the exceptionally complicated anatomical positional relationships between tumor and normal tissue in the head-neck area, special attention must be paid to the risk of toxicity effects from radiotherapy. Dysphagia and xerostomia are the main

consequences of radiochemotherapy and negatively affect patients' quality of life (16). The proton therapy or IMRT technique may remedy this challenge, as it has the technical prerequisites to apply high doses of radiation into the target volume and at the same time to protect adjacent tissue and organs (17, 18). Application of these techniques in malignancies of the head and neck seems to improve patients' quality of life, especially in reducing xerostomia and dysphagia (17, 19). A study by Guss *et al.* has compared the IMRT-ISRT (i-ISRT) with the conventional ISRT (c-ISRT) for NHL of the head and neck (n=20). They concluded that with the i-ISRT excellent local control and outspring of the organs at risk (OARs) (7). However, the importance of their study is limited due to their small sample size (n=20). Radiotherapy *via* helical tomotherapy is also advocated for mediastinal lymphoma in a recent French study (8). There, lower acute and late toxicity following IMRT treatment were observed, which is consistent with the results of our study. Important to mention here is also the possibility to minimize the high radiation doses at the OARs, in the heart and lungs, by the tomotherapy application (8). Modern therapy techniques additionally enable advances in image-guided radiotherapy. In the modern use of radiotherapy, correctly applied imaging forms the central pillar of therapy improvement. Recent ILROG guidelines emphasize the critical role of imaging in the management of lymphomas, including guiding, planning, and delivering RT (20). Highlighted are the consensus recommendations for a planning PET/CT before radiotherapy, especially in the ISRT technique, the application of the MRI for diagnostic and planning purposes in the head and neck area, due to its complex anatomy, and the use of image-guided RT, mainly using cone-beam CT (20). Such conclusions propose that PET-CT monitoring after RT guarantees extra investigation as a possible method of identifying subjects who should be referred for further systemic approach (3, 13, 20).

A more recent development represents proton radiotherapy. Proton therapy seems to be a promising treatment modality for dose reduction to OARs and adjacent tissues (17, 21). Therefore, a desirable research approach would be to investigate the dose reduction possibilities of proton therapy in the OARs in the head and neck area.

Our present study has limitations due to its retrospective character, the inhomogeneity of the histological entities, and the relatively small number of cases/patients. Therefore, there is a need for international collaboration to provide a large cohort with more significant evidence in assessing the benefits of IMRT application in patients with head and neck EN-NHL.

Conclusion

IG-IMRT seems to be correlated both with higher locoregional control as well as reduced toxicities. However, more broad studies on the use of IMRT in hematological malignancies are required. Therefore, further research is

needed to improve imaging techniques and implement them even more in future radiotherapy approaches to resolve uncertainties regarding the potential benefit of consolidative modern RT.

Conflicts of Interest

The Authors have no conflicts of interest to report in relation to this study.

Authors' Contributions

Conceptualization, J.E., K.E., and H.T.E.; data curation, J.E., D.R., and I.S.; formal analysis, J.E.; methodology, J.E., K.E.; writing—original draft, J.E. All Authors have read and agreed to the published version of the manuscript.

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