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ORIGINAL ARTICLE

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The role of local radiotherapy following rituximab-containing chemotherapy in patients with transformed indolent B-cell lymphoma

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Abstract

Objectives: This study aimed to evaluate the outcomes of local radiotherapy (LRT) in patients with histologic transformation (HT) following rituximab-containing chemotherapy.

Methods: We retrospectively analysed 92 patients with biopsy-confirmed HT undergoing rituximab-containing chemotherapy at our institution between 2003 and 2015.

Results: Of the 36 patients with limited-stage disease at diagnosis of HT, 29 (78%) received LRT. The estimated 5-year progression-free survival (PFS) rate was significantly better in patients who underwent LRT than in those who did not (93% and 42%, respectively; $P < 0.05$). Multivariate analyses employing age, sex, performance status, LRT and treatment response demonstrated that LRT was an independent prognostic factor for PFS (hazard ratio [HR]: 11.8; 95% confidence interval [CI]: 1.28-108.1; $P < 0.05$). Of the 32 patients who underwent LRT for HT lesion treatment, 31 (97%) did not show disease progression within radiation fields; among them, 27 patients (84%) survived without disease progression during the follow-up period. One patient developed hypothyroidism due to LRT; the others had no acute or late-onset complications of LRT.

Conclusions: Our data support the recommendation of LRT for HT lesion treatment following rituximab-containing chemotherapy in select patients with localised HT, as a rational treatment approach with potentially limited toxicity.

Novelty Statements: What is the new aspect of your work? This is the first study that evaluated the clinical outcomes of local radiotherapy (LRT) in patients with histologic transformation (HT) who were treated with rituximab-containing chemotherapy. What is the central finding of your work? LRT was beneficial in patients with HT. What is (or could be) the specific clinical relevance of your work? This retrospective study contributes further knowledge on the role of LRT in treating HT lesions including those with MYC/BCL2 rearrangements in the rituximab era.

KEYWORDS
histologic transformation, radiotherapy, rituximab

1 | INTRODUCTION

In patients with indolent B-cell lymphoma, histologic transformation (HT) to aggressive lymphoma has been associated with poor prognosis.[1-5] Although the prognosis of patients with HT has improved in the rituximab era,[6-10] HT is still a critical event in the course of this otherwise indolent disease.

We often encounter patients with locoregional transformation; however, very few studies have focused on the role of local radiotherapy (LRT) in treating HT lesions. In the pre-rituximab era, a retrospective analysis from Stanford University reported that 12 patients with transformed indolent lymphoma who were treated with radiotherapy alone achieved 70% of complete response (CR).[1] Although this retrospective study provided us with clinically useful information in terms of treatment of transformed indolent lymphoma, it was conducted more than 25 years ago with only 12 patients being analysed. The National Comprehensive Cancer Network (NCCN) guideline for B-cell lymphomas version 1.2020 lists LRT as a treatment option for localised HT, without providing explicit references.[11] Because patients with HT are often excluded from clinical trials, there is a paucity of objective data guiding optimal management of HT, especially in patients with localised HT lesions. The role of LRT in treating HT lesions has never been evaluated in prospective clinical trials or retrospective studies, especially in the rituximab era. Therefore, the efficacy of LTR for treating HT lesions remains unclear.

The objective of this study was to evaluate the outcomes in patients with HT who received rituximab-containing chemotherapy followed by LRT.

2 | METHODS

2.1 | Patients

We retrospectively analysed consecutive patients with biopsy-confirmed HT from indolent B-cell lymphoma to diffuse large B-cell lymphoma (DLBCL) diagnosed between 2003 and 2015 at our institution. Histopathologic diagnoses were made by well-experienced hemato-pathologists (authors AMM and HT). In this study, HT was defined as the conversion of a follicular lymphoma (FL) grade 1, 2, 3a or mucosa-associated lymphoid tissue (MALT) lymphoma to DLBCL. Patients with DLBCL, which was histologically converted from initially diagnosed indolent B-cell lymphoma, were categorised into the "sequential group." In contrast, DLBCL, identified with simultaneous evidence of indolent B-cell lymphoma at initial diagnosis, was considered to be a transformation, such as DLBCL and indolent B-cell lymphoma in the same sample or evidence of DLBCL and indolent B-cell lymphoma in distinct locations. Patients with such HT were categorised into the "concurrent group." This study was approved by the Institutional Review Board of the National Cancer Center and was conducted in accordance with the Declaration of Helsinki.

2.2 | Clinical staging

Clinical stage (CS) was determined according to the Ann Arbor classification system. Staging was done at the time of HT diagnosis, regardless of the CS of lymphoma at initial diagnosis. Bone marrow examination and computed tomography (CT) scans of the neck, chest, abdomen and pelvis were routinely performed as staging procedures at our institution. Since gallium-67 scintigraphy and 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT were both available, either of these procedures was performed depending on the treating physicians' choice. Evaluation of clinical staging was routinely performed at initial diagnosis and disease progression, including HT, in all patients.

2.3 | Statistical analyses

Overall survival (OS) was calculated from the date of diagnosis of HT to the date of death from any cause or the last follow-up evaluation. Progression-free survival (PFS) was calculated from the date of diagnosis of HT to the date of disease progression, death from any cause or the last follow-up evaluation. Because the aim of the study was to analyse the outcomes of treatment for HT, OS and PFS were calculated from the date of diagnosis of HT to represent post-HT survival.

Survival curves were calculated using the Kaplan-Meier method, and groups were compared using the log-rank test. We adjusted for the potential confounders in multivariable models that were biologically essential and considered to be associated with the clinical outcomes, including age, sex (male or female), performance status (≤1 or ≥ 2) and treatment response (CR or non-CR). All *P*-values were two-sided, and .05 levels were considered statistically significant. All statistical analyses were performed with EZR, which is a modified version of R commander designed to add statistical functions frequently used in biostatistics[12] by KN, DM and an experienced biostatistician, KiT.

3 | RESULTS

3.1 | Patient characteristics

We recorded the demographic and clinical characteristics of 92 patients with confirmed HT (Table 1), including 42 men and 50 women with a median age of 58 years (range: 26-83), of which

TABLE 1 Patient characteristics relative to histologic transformation

	Sequential group			Concurrent group			Both groups
	With LRT	Without LRT	All	With LRT	Without LRT	All	All
Number of patients	9 (26%)	26 (74%)	35	23 (40%)	34 (60%)	57	92
Median follow-up (mo)	46	24	32	104	77	89	56
Age at transformation							
Median (y)	70	60	60	58	58	58	58
Range (y)	43-72	30-83	30-83	26-83	42-75	26-83	26-83
Sex							
Male	3	11	14 (40%)	13	15	28 (49%)	42 (46%)
Female	6	15	21 (60%)	10	19	29 (51%)	50 (54%)
Subtypes of indolent B-cell lymphoma							
FL grade 1-3a	22	6	28 (80%)	12	31	43 (75%)	71 (77%)
MALT lymphoma	4	3	7 (20%)	11	3	14 (25%)	21 (23%)
CS							
1	5	1	6 (17%)	14	1	15 (26%)	21 (23%)
2	2	2	4 (11%)	8	3	11 (19%)	15 (16%)
3	0	6	6 (17%)	1	10	11 (19%)	17 (18%)
4	2	17	19 (54%)	0	20	20 (35%)	39 (42%)
IPI							
Low	6	6	12 (34%)	20	13	33 (58%)	45 (49%)
Low-Intermediate	2	3	5 (14%)	1	11	12 (21%)	17 (18%)
High-Intermediate	0	11	11 (31%)	1	7	8 (14%)	19 (21%)
High	1	4	5 (14%)	1	3	4 (7%)	9 (10%)
Unkown	0	2	2 (6%)	0	0	0 (0%)	2 (2%)
Bulky (≥10 cm)	2	9	11 (31%)	0	11	11 (19%)	22 (24%)
Staging procedure							
FDG-PET/CT	7	17	24 (69%)	7	23	30 (53%)	57 (62%)
Ga scintigraphy	0	0	0	9	7	16 (28%)	16 (17%)
LRT							
Median (Gy)	36	–	–	40	–	–	40
Range (Gy)	30-46	–	–	30-42	–	–	30-46
Rituximab-anthracycline-based chemotherapy							
Before HT	2	7	9	–	–	–	–
After HT	3	10	13	22	32	54	67 (73%)
Before & after HT	4	3	7	–	–	–	–

Abbreviations: CS, clinical stage; FL, follicular lymphoma; HT, histologic transformation; IPI, International Prognostic Index; LRT, local radiotherapy; MALT, mucosa-associated lymphoid tissue.

35 were in the sequential group and 57 were in the concurrent group (Figure 1). Of 92 patients, 72 (77%) had FL histology at initial diagnosis.

3.2 | LRT to limited-stage disease in both groups

Of 36 patients with limited-stage disease at the diagnosis of HT in both the sequential and concurrent groups, 29 patients (80%) received LRT. The estimated 5-year PFS rate was significantly better in patients with LRT than in those without LRT (93% and 42%, respectively; $P < .05$) (Figure 2). The estimated 5-year OS rate was not significantly different between patients with and without LRT (100% and 93%, respectively; $P = .5$). Multivariate analyses employing age, sex, performance status, LRT and treatment response demonstrated that LRT was an independent prognostic factor for PFS (hazard ratio [HR]: 11.8, 95% confidence interval [CI]: 1.28-108.1; $P < .05$) (Table 2).

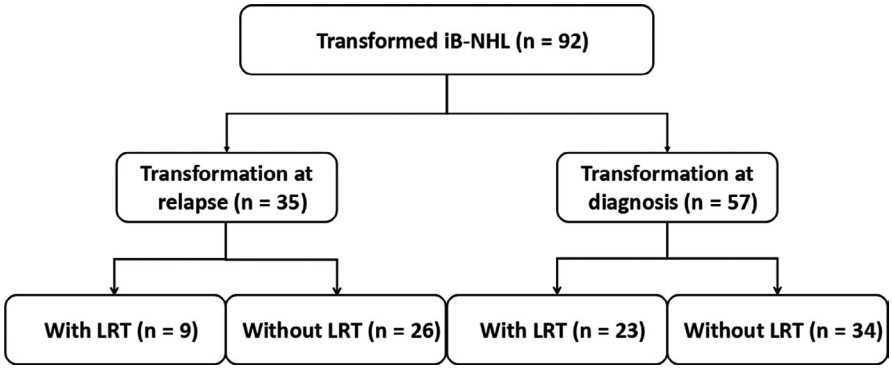

FIGURE 1 Flow chart of patient population selection. Patients were divided into two groups, a sequential and concurrent group, and then further divided into subgroups based on the use of LRT. iB-NHL, indolent B-cell non-Hodgkin lymphoma; LRT, local radiotherapy

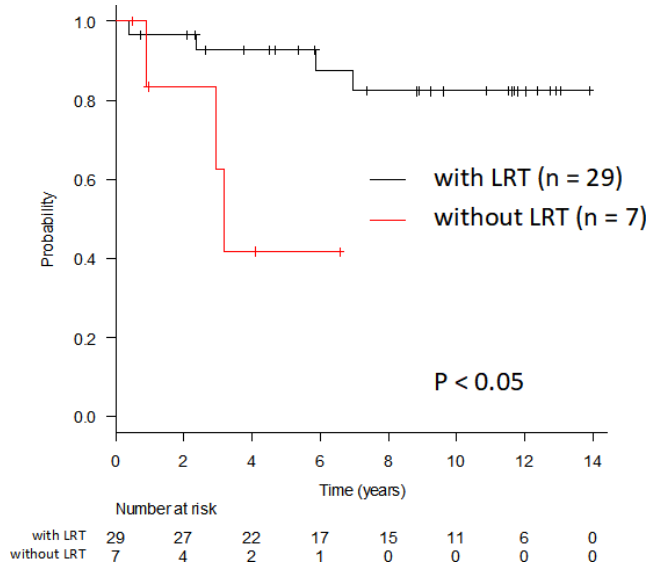

FIGURE 2 Post-transformation PFS in patients with limited-stage disease. Patients who underwent LRT presented significantly better PFS rates than those who did not. LRT, local radiotherapy; PFS, progression-free survival [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Multivariate analysis of patients with limited-stage disease associated with PFS

Factor	Hazard ratio	95% CI	*P*-value
Age	0.96	0.90-1.03	.224
Sex	2.70	0.40-18.29	.310
PS	2.47	0.08-81.08	.611
LRT	11.75	1.28-108.1	.030
Response	14.03	0.90-218.3	.059

Abbreviations: LRT, local radiotherapy; PS, performance status.

3.3 | Local control of LRT in the both groups

Of the 32 patients who received LRT in both the sequential and concurrent groups, 31 patients (97%) did not show disease progression within radiation fields; of these, 27 patients (84%) survived without disease progression during the follow-up period. One patient developed hypothyroidism due to the LRT; the others had no acute or late-onset complications associated with LRT.

3.4 | Sequential group

Among 35 patients in the sequential group, the median age was 60 years (range: 30-83). Subtypes of indolent B-cell lymphoma were FL grade 1-3a in 28 patients (80%) and MALT lymphoma in seven patients (20%). Ten patients (29%) had limited-stage disease and 25 patients (61%) had advanced-stage disease at the time of HT diagnosis. FDG-PET/CT was performed as a staging procedure in 24 patients (69%). Rituximab-anthracycline-based chemotherapy was administered to nine patients before HT diagnosis, to 13 patients after HT diagnosis and to seven patients before and after HT diagnosis.

All 35 patients were treated with rituximab-containing chemotherapy after HT diagnosis, including 20 patients (57%) who received rituximab-anthracycline-based chemotherapy. Nine patients (26%) received LRT to the HT lesions. Seven out of the nine patients (78%) with LRT had limited-stage disease at HT: five patients with CS I and two patients with CS II. The remaining two patients with advanced-stage disease received LRT to biopsy-confirmed HT lesions (bone). Median irradiation dose was 36 Gy (range: 30-46). One patient received autologous stem cell transplantation (ASCT) following chemoradiotherapy. All nine patients who received LRT achieved complete metabolic response (CMR) and did not show disease progression or death within a median follow-up duration of 46 months (range: 9-140) after HT diagnosis. The median follow-up duration in patients without LRT was 24 months (range: 1-109).

The median duration from initial diagnosis to HT was 57 months (range: 3-140) in patients with LRT and 57 months (range: 6-196) in patients without LRT.

Twenty-three of 26 patients (88%) without LRT had advanced-stage disease at HT diagnosis. Of these, 17 patients (65%) achieved CMR, two patients obtained partial response (PR), four patients exhibited stable disease, and three patients had refractory disease after rituximab-containing salvage chemotherapy. Thereafter, two patients received ASCT and eight patients underwent allogeneic stem cell transplantation (allo SCT). In the 26 patients without

LRT, the estimated 5-year PFS and OS rates were 20% and 73%, respectively.

3.5 | Concurrent group

Among 57 patients in the transformation at diagnosis group, the median age was 58 years (range: 26-83). Subtypes of indolent B-cell lymphoma were FL grade 1-3a in 43 patients (76%) including FL grade 3a in 35 patients (62%) and MALT lymphoma in 14 patients (24%). One patient in each subtype group presented composite histology of DLBCL and FL grade 3a or MALT lymphoma at distinct location. Twenty-six patients (46%) had limited-stage disease and 31 patients (54%) had advanced-stage disease at initial diagnosis. FDG-PET/CT and gallium-67 scintigraphy were performed as staging procedures in 30 (53%) and 16 (28%) patients, respectively.

All 57 patients received rituximab-containing chemotherapy, of which 54 patients (95%) had received rituximab-anthracycline-based chemotherapy. Twenty-three of them (40%) received LRT delivered to the HT lesions and the remaining 34 patients were treated without LRT. One patient with LRT received ASCT after the chemoradiotherapy. The median follow-up duration among patients with and without LRT was 130 months (range: 5-169) and 77 months (range: 8-163), respectively.

Twenty-two of 23 patients (96%) with LRT had limited-stage disease at initial diagnosis. Median irradiation dose was 40 Gy (range: 30-42). Twenty patients (87%) achieved CMR and one patient showed PR, whereas one patient had primary refractory disease after initial treatment. Eighteen out of 23 patients (78%) with LRT achieved PFS after a median follow-up duration of 87 months (range: 5-169). For 23 patients with LRT, the estimated 10-year PFS and OS rates were 75% and 87%, respectively.

Thirty of 34 patients (88%) without LRT had advanced-stage disease. Twenty-four patients (70%) achieved CMR and six patients had primary refractory disease after the initial treatment. Four patients without LRT proceeded to allo SCT. In the 34 patients without LRT, the estimated 10-year PFS and OS rates were 46% and 79%, respectively.

3.6 | Patients with FDG-PET/CT in both groups

We performed subgroup analysis for patients who were evaluated by FDG-PET/CT for staging. As mentioned above, 24 out of 35 patients (69%) received PET/CT in the sequential group, and 30 out of 57 patients (53%) received PET/CT in the concurrent group. Among 24 patients in the sequential group, seven patients (29%) received LRT. The estimated 5-year PFS rate was significantly better for patients with LRT than for those without LRT (100% and 14%, respectively; $P < .05$). Among 30 patients in the concurrent group, seven patients (23%) received LRT. The estimated 5-year PFS rate was significantly better for patients with LRT than for those without LRT (100% and 50%, respectively; $P < .05$). Among 18 patients with limited-stage disease in both groups, 13 patients (72%) received LRT. The estimated 5-year PFS rate was significantly better for patients with LRT than for those without LRT (100% and 27%, respectively; $P < .05$).

3.7 | A typical case presentation

A 56-year-old man devoid of any symptoms was referred to our institution for multiple lymphadenopathy. FDG-PET/CT showed increased FDG uptake in the supraclavicular lymph node and clavicle, and mesenteric and para-aortic lymph nodes (Figure 3A,B). Fine-needle biopsy from the left para-aortic lymph node, which was the largest lesion, was performed. Bone marrow examination revealed involvement of low-grade lymphoma cells. He was diagnosed as having FL grade 1 of CS IV with high-tumour burden according to Group d'Etude des Lymphomes Folliculaires criteria[13,14] and underwent bendamustine plus rituximab (BR) therapy as an initial treatment. After three cycles of BR therapy, his lymph node lesions decreased in size and the FDG-PET/CT uptake in these regions had disappeared. However, his clavicle lesion had progressively increased in size and the respective FDG uptake also increased (Figure 3C,D). Biopsy of the clavicle lesion showed DLBCL with double hit (*MYC* break apart and *IGH/BCL2* fusion by fluorescent *in situ* hybridisation), which led to the diagnosis of localised HT with *MYC* and *BCL2* rearrangements. After the diagnosis of HT, he was treated with six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) followed by LRT (38 Gy/18 Fr). Then, his disease achieved CMR (Figure 3E); no evidence of disease progression has been observed more than 3 years after HT.

4 | DISCUSSION

In our study of 92 patients with biopsy-confirmed transformation, we observed good infield disease control and PFS in those who received LRT after rituximab-containing chemotherapy. Among patients with limited-stage disease at the time of HT diagnosis, the PFS rate was significantly better for patients with LRT than for those without LRT. Our study featured a subset of patients with localised HT who received LRT and provided a unique opportunity to learn more about the role of LRT for this population.

In the pre-rituximab era, the prognosis of patients with FL that transformed to DLBCL has been poor, with a median post-transformation OS rate of <2 years.[1-5] Several recent studies have suggested that this may be improved with the use of rituximab to reach a median post-transformation OS rate of approximately 5 years.[6,7]

However, HT remains a significant adverse event in the natural course of indolent lymphomas. A prospective study on patients with newly diagnosed DLBCL who had been treated with immunochemotherapy reported that the rate of indolent lymphoma relapse was higher in patients with concurrent DLBCL and indolent lymphoma than in those with DLBCL alone (7.4% vs 2.1% at 5 years; $P < .01$).[15]

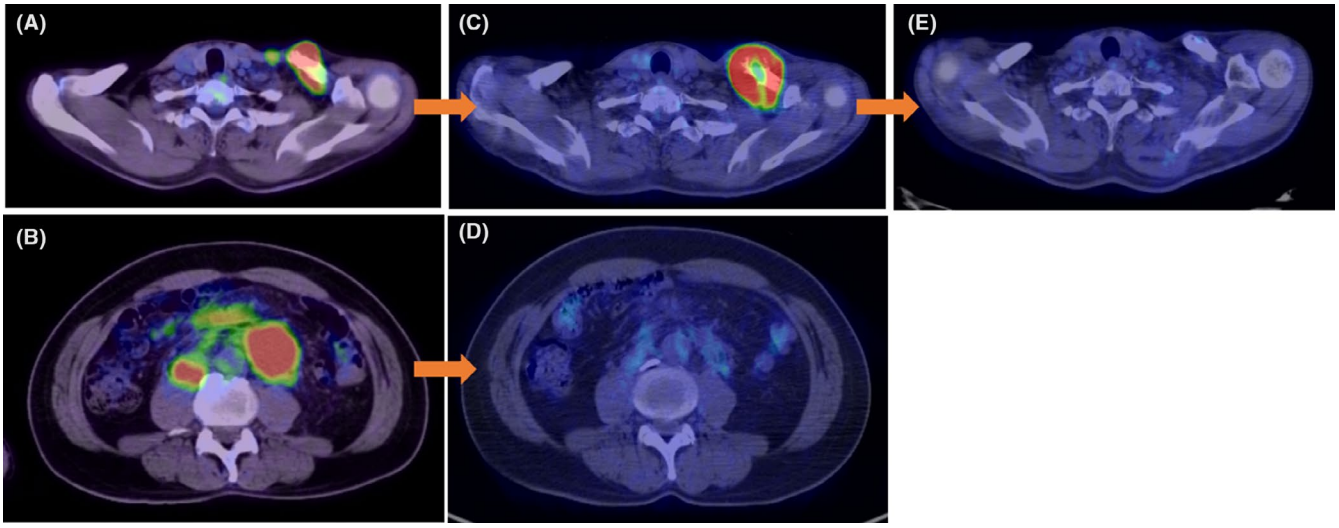

FIGURE 3 FDG-PET/CT scans of a representative patient. A and B, At baseline, FDG uptake in the supraclavicular lymph node and clavicle, mesenteric and para-aortic lymph nodes is observed. C and D, After three cycles of BR, FDG uptake of lymph node lesions disappeared; however, clavicle lesions progressively increased and FDG uptake was increased. E, Six cycles of R-CHOP followed by localised radiotherapy delivered to localised histologic transformation lesions with *MYC/BCL2* rearrangements were effective as seen by the negative signal for FDG uptake. This patient achieved complete metabolic response and no evidence of disease progression has been observed. BR, bendamustine and rituximab; FDG-PET/CT, fluorodeoxyglucose-positron emission tomography/computed tomography; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [Colour figure can be viewed at wileyonlinelibrary.com]

Decisions concerning optimal evidence-based therapy remain challenging because most studies involving patients with HT have comprised small patient numbers and variable follow-up durations. Clinical outcomes of high-dose chemotherapy administration followed by ASCT have been investigated and recent studies have shown that patients achieved a 5-year OS rate of 50%-60%.[9,16] A subset analysis of a National Cancer Institute of Canada Clinical Trials Group LY12 trial (randomised phase 3 trial comparing two salvage chemotherapies before ASCT) reported that patients with relapsed/refractory transformed indolent B-cell lymphoma and de novo DLBCL had similar outcomes to those who had been treated with salvage chemotherapy followed by ASCT.[10]

In this way, patients with HT were often treated with intensive chemotherapy, including SCT, in an attempt to overcome the negative prognostic effect of the disease. In contrast, the role of radiotherapy in HT treatment has never been evaluated in prospective clinical trials and very little is known about the role of radiotherapy in patients with HT, especially in limited-stage disease. In the pre-rituximab era, a retrospective analysis of transformed FL conducted at Stanford University revealed that among 12 patients, those who were treated with radiotherapy alone had higher CR (70% of CR) than patients treated with a standard doxorubicin-containing combination chemotherapy regimen (40% of CR) or other chemotherapy regimen (20% of CR). Of note, eight of 12 patients treated with radiotherapy alone had limited-stage disease at HT.[1] Although it was suggested that radiotherapy may be effective for localised transformed lymphoma, the role of radiotherapy in treating localised HT in the rituximab era has not been well evaluated, even retrospectively.

In our study, among patients in the concurrent group, treatment strategy of rituximab-containing chemotherapy followed by LRT in those with localised HT was extrapolated from the standard of care in de novo DLBCL with limited-stage.[17] Among patients in the sequential group, we observed remarkably good prognosis in the LRT population. Nine patients who received LRT, including seven with limited-stage disease and two with advanced-stage disease, exhibited no disease progression, with a median follow-up duration of 46 months after the diagnosis of HT. Three patients with advanced-stage disease received LRT on the physicians' direction. The patients had local HT lesions and other lesions that were judged to be indolent components. We also presented an example of a typical case of HT with *MYC* and *BCL2* rearrangements that were successfully treated with R-CHOP followed by LRT. Radiotherapy may be effective for transformed lymphoma with respect to controlling the disease within the radiation field and, as a result, reducing aggressive components of the lymphoma. This retrospective study contributes further knowledge on the role of LRT in treating HT lesions including those with *MYC/BCL2* rearrangements in the rituximab era.

This study had several limitations, including the retrospective nature of the analysis and the small number of patients. First, the patients were selected on the basis of receiving LRT, which could have caused a selection bias. The extent of the disease at the time of HT diagnosis in patients who underwent LRT was more limited than in those who did not. Most patients with LRT presented with limited-stage disease at transformation. Therefore, the higher PFS rates in patients who underwent LRT were not solely due to the treatment strategy but also due to their limited-stage disease. Second, the treatment strategy was dependent on the physicians' direction, and there was no uniform treatment protocol. Third, the staging procedure in this study was heterogeneous, especially in FDG-PET/CT. Only 62% of patients underwent FDG-PET/CT for staging. However,

in our subgroup analysis for patients with FDG-PET/CT, similar results regarding the benefit of LRT were observed.

The major finding of this study was that patients with localised HT may achieve good infield disease control and favourable PFS when treated with LRT following rituximab-containing chemotherapy. This alternative treatment approach may benefit selected patients with HT through avoiding more intensive treatment, including aggressive chemotherapy and SCT. Therefore, LRT is an effective treatment option and permits a reduction in the amount of chemotherapy required in selected patients with localised HT, which is a potential advantage with respect to reduced toxicity, especially for elderly patients. This benefit might be gained after successful rituximab-containing chemotherapy in selected patients.

5 | CONCLUSIONS

In conclusion, patients with DLBCL transformed from indolent B-cell lymphoma who received LRT achieved excellent infield disease control and significantly better PFS rates, supporting the administration of LRT to treat HT lesions after rituximab-containing chemotherapy. The administration of LRT to HT lesions in selected patients could be considered as a rational approach of using treatment with limited toxicity for localised transformed indolent B-cell lymphomas. Further investigations are needed to confirm the results of our retrospective study.

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CONFLICTS OF INTEREST

D.M. received research funding and speaker's fees from Chugai Pharma and Eisai. N.Y. received research funding from Ono Pharmaceutical, Celgene, Amgen and Daiichi-Sankyo and paid expert testimony from Takeda. S.M. received honoraria from Celgene, Chugai Pharma, Daiichi-Sankyo, Eisai, Novartis and Takeda. K.I. received research funding and honoraria from Chugai Pharma, Zenyaku Kogyo, Eisai, Kyowa Hakko Kirin and Celgene. K.T. received honoraria from Kyowa Hakko Kirin, Ono Pharmaceutical, Daiichi-Sankyo, Zenyaku Kogyo, Celgene, Takeda, Mundipharma, Chugai Pharma, Yakult, Solasia Pharma, Eisai and HUYA Bioscience International and consulting or advisory roles from Daiichi-Sankyo, Ono Pharmaceutical, HUYA Bioscience International, Celgene, Zenyaku Kogyo, Takeda and Mundipharma. K.N., A.M.M., Ki.T., J.I., T.S., S.Y., T.S., K.T., S.F., W.M., Y.K. and H.T. have nothing to disclose.

AUTHOR CONTRIBUTIONS

KN and DM conceived and designed the study; all authors provided provision of study materials and patients; KN, TS, SY, AMM and DM collected and assembled the data; KN, KiT and DM analysed and interpreted the data; KN and DM wrote the manuscript; all authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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