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Radiotherapy with rituximab may be better than radiotherapy alone in first-line treatment of early-stage follicular lymphoma: is it time to change the standard strategy?

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Abstract

Early-stage follicular lymphoma (FL) has traditionally been treated with involved-field radiotherapy (RT). Rituximab (R) is a low-toxic, efficient systemic therapy for FL, but there are no data about its clinical impact in early FL. We retrospectively analyzed 93 patients with stage I–II indolent FL treated with RT ($n = 65$) or RT + R ($n = 14$) or R alone ($n = 14$). Median follow-up was 5.0 years for patients with RT, 2.8 years for the RT + R subgroup and 2.5 years for patients treated with R. The complete response rate was 92%, 100% and 86% (not significant) and the median PFS was 3.3 years, not reached and 4.9 years ($p = 0.035$) for the RT, RT + R and R arms, with no impact on overall survival. R combined with RT seems to give better results in terms of global FL control, but longer follow-up and prospective comparison are needed to verify these results.

Keywords: Follicular lymphoma, rituximab, radiotherapy

Introduction

Follicular lymphoma (FL) is the most frequently diagnosed subtype of indolent non-Hodgkin lymphoma (NHL), which is considered to be an incurable disease with relapsing behavior, with the majority of patients being diagnosed at an advanced stage. Nevertheless, nearly 25–30% of cases present with early-stage disease (I or II) [1,2]. Even if a wide range of treatment approaches exist, early-stage FL has traditionally been treated with involved-field radiotherapy (IF-RT), which seems to be able to cure a significant proportion of patients [3–7]. FL is one of the neoplasms with the highest radiosensitivity, and with efficacy observed even at low doses (4 Gy) [8,9]. In spite of these observations, nearly half of patients with early-stage FL relapse within 10 years, almost exclusively in distant non-irradiated areas. A limitation of local therapy alone also supports the fact that, regardless of negative histology, t(14;18)-positive cells can be detected by polymerase chain reaction (PCR) in the blood and/or bone marrow in a majority of patients with early-stage FL at the time of diagnosis and also after the end of IF-RT [10–12]. On the other hand, it needs to be noted that detectable t(14;18)-positive cells may not always represent a residual malignant clone, and can be derived from non-neoplastic lymphocytes [13].

The concept of avoiding distant relapses is long established. The combination of RT and chemotherapy was more effective than RT alone in a study with low-grade lymphoma, but this approach was accompanied by therapy-related myelodysplasia and secondary malignancies [14]. The 10-year risk of transformation is about 18% after IF-RT, which is substantially lower in comparison to chemotherapy (about 30%) [15].

Rituximab (R; anti-CD20 antibody) is a low-toxic, first targeted therapy to be developed for the treatment of CD20-positive lymphoma, and has been widely adopted. R has been confirmed to be efficient systemic therapy for FL, leading to

significant improvements in clinical outcome [16]. Moreover, *in vitro* models provide evidence of significant synergism between R and RT [17,18]. Albeit local control of early-stage FL is quite good with IF-RT alone, it seems highly logical to combine low-toxic systemic R therapy with locally efficient IF-RT. At present, there are no clinical data available comparing the clinical benefit of adding R to IF-RT in the early stages of FL.

The Czech Lymphoma Study Group (CLSG) database is a disease-specific, prospective registry that enrolled approximately 1700 patients with newly diagnosed FL between 1999 and 2012 from 14 practice sites (including six university hospitals) in the Czech Republic. With long-term follow-up, we have analyzed the outcomes of patients with stage I and II FL, specifically comparing the use of IF-RT alone (RT) vs. IF-RT with R (RT + R) vs. R only (R) in the early stages of FL.

Methods

Patients

From 1999 to 2012, through the prospectively maintained multicentric CLSG database, consecutive patients with newly diagnosed FL were recruited at participating sites. Patients signed informed consent regarding data collection and analysis. The pathology diagnosis was established in reference pathology centers, and moreover the reports were reviewed by a central pathologist (V.C.) in accordance with World Health Organization (WHO) guidelines. Inconclusive or incomplete reports were excluded, as well as FL with grade 3B according to the WHO classification.

Treatment and outcomes including response, time to progression and survival were collected annually. Follow-up data were actively inputted from every participating site at the time of clinical follow-up. Enrolled patients were monitored until their death, withdrawal of consent or loss of follow-up.

Patient stage was determined by the treating physician according to Ann Arbor criteria, and more recently CLSG staging recommendations were also used [19,20]. Initial rigorous staging included at least a thoracic and abdominal computed tomography (CT) scan, and unilateral bone marrow biopsy. Patients with no or non-conclusive bone marrow biopsy results were excluded from this analysis. No central review of bone marrow biopsy was performed. Positron emission tomography (PET) or PET/CT has only been used in recent years. A complete blood count and lactate dehydrogenase (LDH) level analysis were performed and recorded in the database. The Follicular Lymphoma International Prognostic Index (FLIPI) score was calculated based on individual parameters. Patients were retrospectively divided into three subgroups according to initial therapy (RT alone, RT + R, R alone). Patients receiving any current or consecutive chemotherapy/immunochemotherapy were not included.

R (four doses at 375 mg/m^2) was administered prior to the start of RT in the combined arm. The total number of doses of R varied between 4 and 8 at 375 mg/m^2 in the R monotherapy subgroup as well as in the combined arm. The administered IF-RT radiation dose varied between 24 and 45 Gy. IF-RT was defined as a field encompassing the involved disease including a margin up to one neighboring nodal group proximally and distally.

Response to therapy was evaluated within 6–12 weeks after the last dose of therapy. Restaging procedures consisted of at least a CT scan of the involved region; more recently also PET or PET/CT was used. Post-treatment monitoring was based on clinical examination of all peripheral lymph node sites or radiologically if appropriate, and laboratory tests (complete blood count and biochemistry including LDH). The frequency of clinical examination was dependent on the individual participating center's decision; however, it was performed at least once annually. No data concerning toxicity of RT or R were collected; also there are not sufficient data concerning the cause of death in the CLSG registry.

Because of the substantial costs of R therapy, it should be mentioned that no socio-economic factor could play a role in the selection of patients for R therapy; R is fully covered by health insurance in the Czech Republic.

Statistical analysis

Baseline factors were compared across treatment groups using Pearson's χ^2 test (categorical data) and the Kruskal–Wallis test (continuous data). Progression-free survival (PFS) and overall survival (OS) were estimated by means of the Kaplan–Meier method. OS was defined as the time from first-line treatment initiation to death due to any cause. PFS was defined as the time from first-line treatment initiation to first progression/relapse or death due to any cause. The statistical significance of differences in Kaplan–Meier estimates was assessed using the log-rank test. All point estimates were accompanied by 95% confidence interval (CI). The standard level of significance $\alpha = 0.05$ was used.

Results

For the study period, 1686 patients with FL were identified in the CLSG database; 1477 patients with FL had completed staging procedures, and the proportion of FL with stage I or II was 386/1477 (26%). We analyzed 344/386 patients; 42 had to be excluded (15 patients with FL grade 3B, and 28 with insufficient data; both of these conditions were identified in one patient). Retrospectively, 344 patients were divided into treatment subgroups: chemotherapy + immunotherapy ($n = 91$; R, $n = 90$ and ofatumumab, $n = 1$), chemotherapy alone ($n = 60$), chemotherapy + RT + R ($n = 36$), chemotherapy + RT ($n = 32$) and no therapy ($n = 32$). The remaining 93 patients with stage I–II FL (grade 1–3A) were treated with R and/or RT and were included in the analysis. Sixty-five patients were treated with RT alone, 14 patients were treated with R alone and 14 patients received R and RT. Detailed baseline characteristics of all treatment groups are summarized in Table I.

Patient management varied significantly over the time period; the use of R or RT + R increased over the last 5 years (Table II). Also, the recent inclusion of PET in lymphoma staging in the latter years led to differences in PET-staged patients, with 11% vs. 36% in RT vs. RT + R and R subgroups ($p = 0.035$), respectively. In restaging, PET or PET/CT was used in 29% of patients treated with RT + R or R and in 24% cases managed by RT only; the difference was not significant.

Table I. Baseline characteristics: all treatment groups.

	CT + R (n = 91)	CT only (n = 60)	CT + RT + R (n = 36)	CT + RT (n = 32)	No therapy (n = 32)	RT only (n = 65)	RT + R (n = 14)	R only (n = 14)
Gender, n (%)								
Males	35 (38.5)	20 (33.3)	17 (47.2)	14 (43.8)	15 (46.9)	26 (40.0)	5 (35.7)	6 (42.9)
Females	56 (61.5)	40 (66.7)	19 (52.8)	18 (56.3)	17 (53.1)	39 (60.0)	9 (64.3)	8 (57.1)
Age at diagnosis (years)								
Median (min–max)	59 (32–84)	57 (33–81)	58 (37–82)	54 (32–77)	60 (33–87)	59 (30–85)	53 (30–76)	52 (30–66)
Diagnosis according to WHO, n (%)								
FL	13 (14.3)	19 (31.7)	8 (22.2)	10 (31.3)	2 (6.3)	8 (12.3)	0 (0)	3 (21.4)
FL1	34 (37.4)	16 (26.7)	8 (22.2)	8 (25.0)	11 (34.4)	29 (44.6)	4 (28.6)	5 (35.7)
FL2	29 (31.9)	18 (30.0)	9 (25.0)	10 (31.3)	16 (50.0)	27 (41.5)	5 (35.7)	5 (35.7)
FL3A	15 (16.5)	7 (11.7)	11 (30.6)	4 (12.5)	3 (9.4)	1 (1.5)*	5 (35.7)*	1 (7.1)*
Nodal involvement, n (%)	85 (93.4)	58 (96.7)	32 (88.9)	27 (84.4)	30 (93.8)	54 (83.1)	13 (92.9)	11 (78.6)
Extranodal involvement, n (%)	13 (14.3)	12 (20.0)	7 (19.4)	5 (15.6)	4 (12.5)	11 (16.9)	2 (14.3)	2 (14.3)
Presence of B-symptoms, n (%)	19 (20.9)	5 (8.3)	8 (22.2)	2 (6.3)	1 (3.1)	1 (1.5)	0 (0)	1 (7.1)
Biggest size of tumor, n (%)								
Up to 1.9 cm	5 (5.5)	7 (11.7)	3 (8.3)	2 (6.3)	8 (25.0)	16 (24.6)	4 (28.6)	1 (7.1)
2.0–4.9 cm	35 (38.5)	29 (48.3)	13 (36.1)	15 (46.9)	20 (62.5)	31 (47.7)	8 (57.1)	10 (71.4)
5.0 cm and more	44 (48.4)	17 (28.3)	18 (50.0)	11 (34.4)	2 (6.3)	6 (9.2)	2 (14.3)	0 (0)
Unknown	7 (7.7)	7 (11.7)	2 (5.6)	4 (12.5)	2 (6.3)	12 (18.5)	0 (0)	3 (21.4)
Clinical stage, n (%)								
I	19 (20.9)	17 (28.3)	16 (44.4)	18 (56.3)	20 (62.5)	53 (81.5)	12 (85.7)	9 (64.3)
II	72 (79.1)	43 (71.7)	20 (55.6)	14 (43.8)	12 (37.5)	12 (18.5)	2 (14.3)	5 (35.7)
Performance status, n (%)								
0	57 (63.3)	34 (58.6)	19 (54.3)	18 (58.1)	24 (75.0)	48 (75.0)	12 (85.7)	13 (92.9)
1	27 (30.0)	19 (32.8)	14 (40.0)	10 (32.3)	8 (25.0)	14 (21.9)	2 (14.3)	1 (7.1)
≥2	6 (6.7)	5 (8.6)	2 (5.7)	3 (9.7)	0 (0)	2 (3.1)	0 (0)	0 (0)
LDH above upper limit, n (%)	28 (30.8)	13 (21.7)	8 (22.2)	7 (21.9)	7 (21.9)	10 (15.4)	3 (21.4)	3 (21.4)
Hemoglobin, median (min–max)	133 (14–169)	137 (106–169)	140 (97–174)	142 (90–167)	139 (118–165)	139 (106–178)	144 (131–172)	140 (117–158)
FLIPI, n (%)								
Low risk	72 (80.0)	46 (82.1)	30 (83.3)	25 (80.6)	27 (84.4)	56 (87.5)	11 (78.6)	11 (84.6)
Intermediate risk	16 (17.8)	10 (17.9)	6 (16.7)	5 (16.1)	4 (12.5)	8 (12.5)	3 (21.4)	2 (15.4)
High risk	2 (2.2)	0 (0)	0 (0)	1 (3.2)	1 (3.1)	0 (0)	0 (0)	0 (0)
First-line treatment terminated, n (%)	91 (100)	60 (100)	36 (100)	32 (100)	—	65 (100)	14 (100)	14 (100)
Best response to first-line treatment, n (%)								
CR	65 (71.4)	39 (65.0)	24 (66.7)	25 (78.1)	—	60 (92.3)	14 (100)	12 (85.7)
uCR	7 (7.7)	8 (13.3)	5 (13.9)	2 (6.3)	—	1 (1.5)	0 (0)	0 (0)
PR	11 (12.1)	5 (8.3)	4 (11.1)	2 (6.3)	—	3 (4.6)	0 (0)	0 (0)
SD	1 (1.1)	3 (5.0)	3 (8.3)	1 (3.1)	—	0 (0)	0 (0)	1 (7.1)
PD	2 (2.2)	4 (6.7)	0 (0)	1 (3.1)	—	0 (0)	0 (0)	1 (7.1)
Not evaluated	5 (5.5)	1 (1.7)	0 (0)	1 (3.1)	—	1 (1.5)	0 (0)	0 (0)

WHO, World Health Organization; FL, follicular lymphoma; LDH, lactate dehydrogenase; FLIPI, Follicular Lymphoma International Prognostic Index; CR, complete response; uCR, unconfirmed complete response; PR, partial response; SD, stable disease; PD, progressive disease; CT, chemotherapy; R, rituximab; RT, radiotherapy.
*Significant difference.

Table II. Year of first-line therapy initiation: all treatment groups.

Year of start of first-line therapy, n (%)	CT + R (n = 91)	CT only (n = 60)	CT + RT + R (n = 36)	CT + RT (n = 32)	No therapy (n = 40)	RT only (n = 65)	RT + R (n = 14)	R only (n = 14)
Before 2005	4 (4.4)	53 (91.4)	7 (19.4)	30 (93.8)	2 (25.0)	22 (33.8)	0 (0)	0 (0)
2005	9 (9.9)	0 (0)	7 (19.4)	2 (6.3)	1 (12.5)	6 (9.2)	1 (7.1)	0 (0)
2006	10 (11.0)	1 (1.7)	2 (5.6)	0 (0)	1 (12.5)	7 (10.8)	2 (14.3)	1 (7.1)
2007	7 (7.7)	1 (1.7)	6 (16.7)	0 (0)	1 (12.5)	10 (15.4)	1 (7.1)	1 (7.1)
2008	14 (15.4)	1 (1.7)	7 (19.4)	0 (0)	0 (0)	0 (0)	1 (7.1)	3 (21.4)
2009	8 (8.8)	0 (0)	5 (13.9)	0 (0)	2 (25.0)	4 (6.2)	3 (21.4)	2 (14.3)
2010	22 (24.2)	1 (1.7)	1 (2.8)	0 (0)	0 (0)	9 (13.8)	2 (14.3)	3 (21.4)
2011	12 (13.2)	1 (1.7)	1 (2.8)	0 (0)	1 (12.5)	4 (6.2)	1 (7.1)	2 (14.3)
2012	5 (5.5)	0 (0)	0 (0)	0 (0)	0 (0)	3 (4.6)	3 (21.4)	2 (14.3)

CT, chemotherapy; R, rituximab; RT, radiotherapy.

The median time from diagnosis to initial therapy was 2.2 months (0–17) for RT, 2.4 months (0–7) for RT + R and 1.0 month (0–6) for the R arm, respectively ($p = 0.036$).

The median follow-up of the whole cohort was 3.7 years from the start of initial therapy, and 37/93 (40%) patients relapsed. According to the separate subgroups, the median follow-up from the start of initial therapy was as follows: 5.0 years for the RT arm, 2.8 years for patients with RT + R and 2.5 years for patients treated with R alone. There were no differences in age, performance status, FLIPI or proportion of bulky or extranodal tumors among the treatment subgroups. In the subgroup treated with RT + R there was a higher proportion of FL grade 3A in comparison with arms with R or RT alone (35.7% vs. 7.1% vs. 1.5%; $p = 0.007$). The complete response rate was 92% in the RT arm, 100% in the arm with RT + R and 86% in the group treated with R alone; differences did not reach statistical significance. The median PFS was 3.3 years in the RT group, not reached in the RT + R arm and 4.9 years in patients treated with R alone. The 3-year PFS was 57.4% for the RT arm, and 85.7% and 91.7% for the RT + R and R arms (Table III). Differences were statistically significant ($p = 0.035$), but with no impact on overall survival (Figure 1). Because both R-containing arms seem to lead to better PFS than RT alone, we therefore analyzed the RT + R and R arms together versus RT and observed a significant difference ($p = 0.011$) (Figure 2).

Discussion

To our knowledge, this is the first published series of prospectively enrolled patients with early-stage FL evaluating the addition of R to RT.

Early-stage FL is potentially curable with regional or IF-RT, which results in excellent complete response rates and long-term local control rates >90% [3,5,21–24]. The literature describing outcomes of early-stage FL treated with RT alone consists of retrospective accounts of selected patients from single institutions treated in the era before modern chemotherapy, R and modern staging procedures. These series generally included patients with not only FL, and used various doses of RT (between 30 and 45 Gy) with heterogeneous field sizes, including extended RT. Until now, the guidelines have recommended RT as a standard treatment approach for early-stage FL, based on these selected retrospective studies [25]. Even if the relative improvement in outcomes for patients treated with and without RT has never been tested in randomized trials, in a large retrospective study including 6568 patients, upfront RT was associated with improved disease-specific survival (DSS) and OS [6]. Watchful waiting with administration of salvage therapies on progression/relapse does not compensate for inadequate initial definitive treatment. Analysis did not adjust for FLIPI, and radiation was not controlled for dose or field [6].

In early-stage FL, the main objective is to cure the disease or at least to maintain long-term remission. However, the lengthy OS of patients with FL despite active disease encourages minimizing treatment toxicity as much as possible. Moreover, approximately half of patients with stage I or II disease relapse within 10 years, and lymphoma remains the leading cause of death in these patients [3]. Although recent data show that R monotherapy significantly prolongs the period without the need for any new anti-lymphoma treatment in patients with asymptomatic, advanced-stage, low-tumor burden FL, there are currently no long-term data suggesting the curative potential of R as a single agent [26]. Despite that, R represents an ideal systemic low-toxic therapy, which is able to eliminate circulating lymphoma cells as well as distant subclinical involvement. R alone or R added to RT seems to be a reasonable choice, with minimal real risk for patients and with potential benefit [27,28]. Unfortunately,

Table III. Progression-free survival and overall survival from first-line treatment initiation.

	Median value (95% CI)	At 2 years (95% CI)	At 3 years (95% CI)	Log-rank p-value
PFS				
RT	3.3 years (2.3–4.4)	68.1% (55.6–80.7)	57.4% (43.7–71.1)	0.035
RT + R	Not reached	100%	85.7% (59.8–99.9)	
R	4.9 years (2.8–7.1)	91.7% (76.0–99.9)	91.7% (76.0–99.9)	
OS				
RT	Not reached	98.0% (94.1–99.9)	95.6% (89.5–99.9)	0.647
RT + R	Not reached	100%	85.7% (59.8–99.9)	
R	Not reached	100%	100%	

PFS, progression-free survival; RT, radiotherapy; R, rituximab; OS, overall survival; CI, confidence interval.
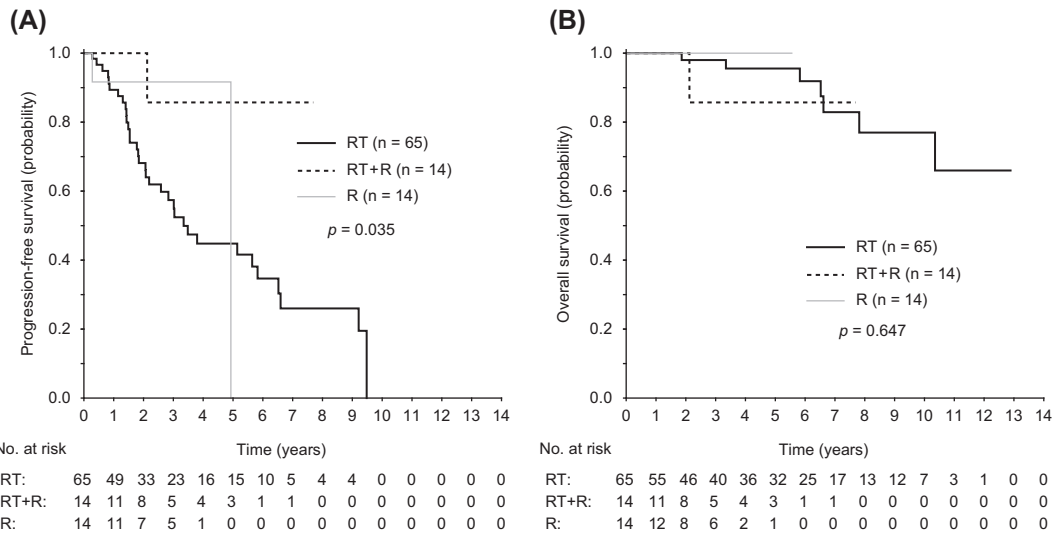
(A)

(B)

Figure 1. PFS (A) and OS (B) from first-line treatment initiation: RT vs. RT + R vs. R.

there are no data to establish the combination of RT with R as a new strategy. Some previous experience of combined modality treatment of early-stage FL is limited to small studies from single institutions that did not use R [14,29].

Only a few studies have evaluated alternative or combined modalities in a comparative setting. One retrospective analysis published by Michallet *et al.* analyzed the impact of current therapies on early-stage FL. A total of 145 patients were retrospectively divided into six treatment groups: watch and wait strategy, RT alone, chemotherapy alone, chemotherapy + R, R alone and RT + chemotherapy. A treatment group including R + RT was not present in this cohort of patients. The demographic structure of the study population in terms of median age and stage of disease was similar to our cohort. The global median follow-up in this study was longer (about 7 years vs. 4.6 years), but the outcome concerning PFS of the RT arm in 5 years was about 48%, which is comparable to our observation. PFS at 7.5 years was 19% vs. 60% and not reached, for RT alone vs. chemotherapy + R vs. R alone [30]. Although this relatively small, retrospective

single-institution study has some limitations, the results support our observation of the efficacy of systemic treatment including R in early-stage FL. Diverse treatment approaches were analyzed by the National Lymphocare Study, which included 206 patients with FL of stage I only [31]. There was a median follow-up of 57 months with 21% relapsed patients; in our study the median follow-up was 44 months with 40% relapsed patients. Again, there was a comparison of RT alone vs. chemotherapy vs. RT + chemotherapy vs. observation vs. R monotherapy; an RT + R arm was not included. Also in this study, R + chemotherapy or RT + chemotherapy were superior to RT alone in terms of PFS. Therapy modality seems to have no influence on OS in published studies and also in our analysis.

It must be emphasized that there are some limitations of our study, due to the observational and retrospective design of analysis. We are aware of several methodological factors potentially influencing result interpretation. Our analysis was focused on the RT vs. RT + R and R comparison, but patients treated with chemotherapy more frequently had
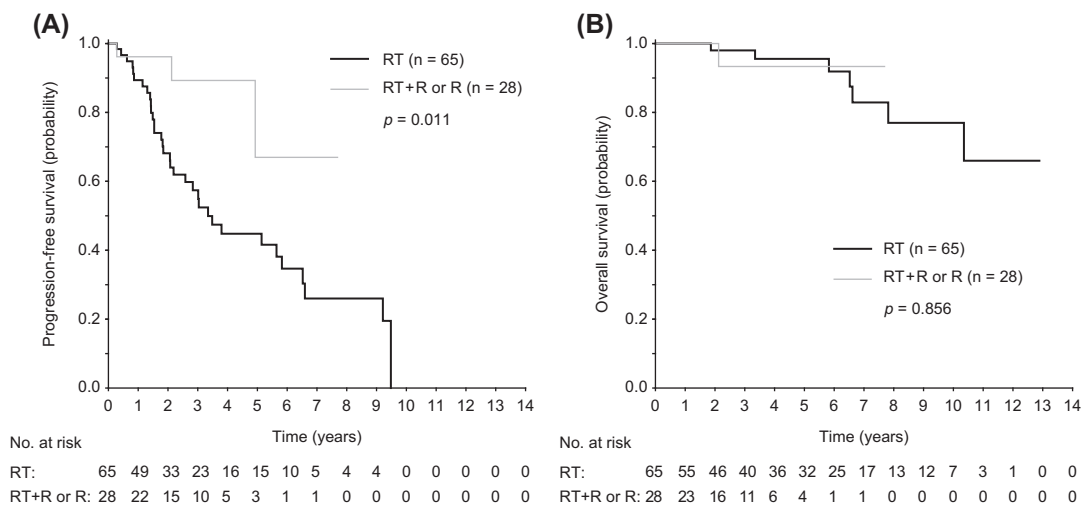
(A)

(B)

Figure 2. PFS (A) and OS (B) from first-line treatment initiation: RT vs. RT + R or R.

B-symptoms, tumor size above 5 cm and stage II disease, and therefore some selection bias cannot be excluded. There were also substantial imbalances among the RT, RT + R and R subgroups. PET, which has the potential to upstage and thereby alter management in FLs, was used less in the RT vs. R-based subgroup (11% vs. 36%) [32,33]. The median time from diagnosis to initial therapy varied slightly among subgroups ($p = 0.036$), and the follow-up was evidently shorter for R-treated patients (2.8 and 2.5 years vs. 5.0 years for the RT arm). These differences may also influence the outcome.

Although there was no significant difference in age among subgroups (RT vs. RT + R vs. R alone), the RT-treated population seemed to be a little bit older compared to the R-containing arms (59 vs. 53 years; $p = 0.072$). Nevertheless, we consider this statistical difference not clinically relevant, because an age of ≥ 60 years at diagnosis is associated with reduced OS, but does not affect PFS in early-stage FL [34].

The PFS of the RT subgroup was lower in our study compared to similar results reported in the literature [3,4,31]. One explanation could be the inherent limits of the retrospective setting. Another potential aspect of uncertainty about the accuracy of PFS data is that CT scanning was only rarely part of the post-treatment monitoring. However, our results concerning PFS in the RT arm were very similar to the observation published by Michallet *et al.* [30]. The discrepancy in PFS could also be caused by the different design of previously published studies. Lowry *et al.* published a prospective randomized trial of a mixture of indolent NHL with 59% FL, but also with a significant proportion of marginal zone lymphoma (19%), which is the most indolent lymphoma of all, having the best long-term prognosis, especially in early stages. Moreover, a significant proportion of patients were treated with RT and previous/contemporaneous chemotherapy (20–23%) [4]. In an article published by Guadagnolo *et al.*, again about 24% of patients with stage I or II FL received RT combined with chemotherapy [3]. A large study published by Friedberg *et al.* presented retrospective Lymphocare registry data focused on the subset of patients with stage I FL only. Moreover, Friedberg *et al.* also described that more than half of the patients had not undergone the complete recommended staging [31].

The available data, including the data presented here, suggest that a randomized comparison of RT vs. RT plus R would undoubtedly be preferred, but such a trial is difficult to perform because of the rarity of the early-stage of FL, quite good survival results, long natural history and sufficient follow-up. Despite this, one such phase II study evaluating R with IF-RT in prospective design was started, but no results have been published as yet [35]. In the absence of randomized data, the results of retrospective and pooled analysis are the only tool to guide a physician's decision-making.

Conclusions

Despite that IF-RT is considered to be a good initial treatment for early-stage FL, R alone or, better, in combination with RT could be a reasonable option, and seems to give better results in terms of global control of the disease. Our preliminary results should be confirmed with prospective randomized studies, and a longer follow-up is needed to verify or disprove the real impact of R in the early stages of FL. The role of systemic therapy in early-stage FL still remains to be defined.

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