Clinical and Translational Radiation Oncology 49 (2024) 100869

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Original Research Article

Maximum disease diameter is associated with outcomes in stage II follicular lymphoma treated with radiation therapy alone

Yi Xu [a], Belinda A. Campbell [b,c,d], Matthew Chan [e,f], Jessica Chan [e,f], Pedro Farinha [g], Christopher P. Venner [a,h,i], David W. Scott [a,h,i], Alina S. Gerrie [a,h,i], Diego Villa [a,h,i], Laurie H. Sehn [a,h,i], Kerry J. Savage [a,h,i], Andrea C. Lo [e,f,i,*]

[a] Department of Medicine, University of British Columbia, 2775 Laurel Street, Vancouver, British Columbia V5Z 1M9, Canada
[b] Department of Radiation Oncology, Peter MacCallum Cancer Center, 305 Grattan Street, Melbourne, Victoria 3000, Australia
[c] The Sir Peter MacCallum Department of Oncology, The University of Melbourne, Grattan Street, Parkville, Victoria 3010, Australia
[d] Department of Clinical Pathology, University of Melbourne, The University of Melbourne, Grattan Street, Parkville, Victoria 3010, Australia
[e] Department of Radiation Oncology, BC Cancer – Vancouver, 600 West 10th Avenue, Vancouver, British Columbia V5Z 4E6, Canada
[f] Department of Surgery, University of British Columbia, 2775 Laurel Street, Vancouver, British Columbia V5Z 1M9, Canada
[g] Department of Pathology and Laboratory Medicine, University of British Columbia, 2211 Wesbrook Mall, Vancouver, British Columbia V6T 2B5, Canada
[h] Department of Medical Oncology, BC Cancer – Vancouver, 600 West 10th Avenue, Vancouver, British Columbia V5Z 4E6, Canada
[i] The Centre for Lymphoid Cancer, BC Cancer – Vancouver, 600 West 10th Avenue, Vancouver, British Columbia V5Z 4E6, Canada

ARTICLE INFO

Keywords:
Lymphoma, Follicular
Radiotherapy
Treatment Outcome
Survival Analysis
Kaplan-Meier Estimate
Prognosis

ABSTRACT

Purpose: The optimal management of stage II follicular lymphoma (FL) is unclear. Radiation therapy (RT) alone has been the gold standard treatment, but a proportion of patients relapse. We sought to characterize outcomes and prognostic factors for stage II FL treated with RT alone to identify a high-risk subgroup of patients who may benefit from treatment intensification.

Methods: This was a population-based, province-wide, retrospective study. Included patients had grade 1–3A, non-mesenteric, stage IIA or IIAE FL diagnosed between 1986 and 2016 and treated with curative-intent (≥20 Gy) RT alone.

Results: 102 patients were included. Median follow-up was 10.4 years (range, 0.3–22.3). Median age was 59 years (range, 33–86). Median greatest disease diameter was 3.6 cm (range, 1.5–11.5). Freedom from progression (FFP) was 60.3% at 5 years and 40.7% at 10 years. Overall survival (OS) was 89.2% at 5 years and 81.8% at 10 years. Greatest disease diameter of >3.6 cm was associated with inferior FFP (10-year FFP 34% vs. 47%, $p = 0.013$) on univariable analysis and inferior FFP (hazard ratio [HR] 1.87, $p = 0.019$) and inferior OS (HR 2.12, $p = 0.027$) on multivariable analysis (MVA). Older age was associated with inferior OS (HR 1.08, unit = 1 year, $p < 0.001$) on MVA.

Conclusions: 40.7% of stage II FL patients treated with RT alone remained disease-free at 10 years. Greatest disease diameter >3.6 cm was associated with inferior FFP and OS, representing a novel prognostic indicator in this population that may help in the decision-making process on whether to complement RT with systemic therapy.

1. Introduction

Contention exists surrounding the optimal management strategy for stage II follicular lymphoma (FL). Radiation therapy (RT) alone represents the traditional gold standard of care for stage I–II disease, with many guidelines, including those from the National Comprehensive Cancer Network (NCCN) [1] and the European Society for Medical Oncology (ESMO) [2], continuing to recommend RT alone as the preferred treatment for non-bulky (<7 cm), contiguous, and low tumour burden stage I–II FL. Emerging data suggest a potential role for the addition of systemic therapy—either immunochemotherapy or immunotherapy alone—to RT for improved progression-free survival (PFS), albeit at the cost of potential additional toxicities and without a clear overall survival (OS) advantage [3,4]. Presently, optimal patient

* Corresponding author at: 600 West 10th Avenue, Vancouver, British Columbia V5Z 4E6, Canada.
E-mail address: andrea.lo@bccancer.bc.ca (A.C. Lo).

https://doi.org/10.1016/j.ctro.2024.100869
Received 19 July 2024; Received in revised form 17 September 2024; Accepted 25 September 2024
Available online 29 September 2024

selection for these approaches remains unclear.

In addition, despite strong evidence that stage II FL patients have inferior outcomes compared to stage I FL patients [5-9], many studies report survival data for stage I and stage II FL together as a group [5,10,11]. Consequently, there is a paucity of outcomes research specifically for stage II FL patients treated with RT alone. In addition, to our knowledge, there has yet to be any investigation into prognostic factors that can be applied specifically to stage II FL patients treated with RT alone. To enable a more individualised management approach for patients with stage II FL currently treated with RT alone, stage-specific data on outcomes and prognostic factors are important. Therefore, this study aims to characterize outcomes and clinical prognostic factors of stage II FL patients treated with standard-of-care RT alone, with the goal to identify a patient subgroup who may be better served by treatment intensification with systemic therapy.

2. Materials and methods

2.1. Patients and treatment

This was a population-based, province-wide, retrospective study. The study was approved by the institutional review board at BC Cancer. Patients were included if they had grade 1–3A, stage IIA or IIAE FL that was diagnosed between 1986 and 2016 and treated with curative-intent (≥20 Gy) RT alone at any of the six BC Cancer tertiary care centres. Patients were staged according to the Ann Arbor Staging Classification [12], with stage II defined as "involvement of 2 or more lymph node regions on the same side of the diagram" and stage IIE defined as "localized involvement of extralymphatic organ or site and of 1 or more lymph node regions on the same side of the diaphragm". Lymph node regions were defined using the Rye Symposium regions [13].

BC Cancer guidelines during this time period recommended RT alone for "limited-stage FL", defined as stage I and II FL (± extranodal involvement), non-bulky disease (≤10 cm) in the absence of B symptoms. Starting in 1990, patients with mesenteric FL were excluded from this approach due to a separate study reporting an increased risk of relapse [14]. Thus, for the present study, any cases with mesenteric involvement were excluded. In addition, the lymphoma was required to be encompassable in an RT field with acceptable toxicity as determined in a multi-disciplinary conference. Patients diagnosed in February 1998 and prior were treated with involved regional RT. Starting in March 1998, patients were treated with smaller field sizes, since re-named involved-site RT [9,15]. Patients were not routinely staged by positron emission tomography / computed tomography (PET/CT). Starting in 2005, PET/CT was used in select patients with indeterminate nodes on computed tomography. Study patients were identified via the BC Cancer Centre for Lymphoid Cancer Database and the BC Cancer Registry Database. Database information and chart review were used to extract patient, disease, and treatment characteristics and outcomes. In determining the greatest disease diameter, clustered nodal masses were considered one mass if the masses were contiguous. If an extranodal mass had a greater diameter than any of the nodal masses, then that diameter was used as the greatest disease diameter. Marginal relapse was defined as disease recurring outside the RT field but within 5 cm beyond the edge of the RT field.

2.2. Statistical analyses

The primary endpoints were freedom from progression (FFP), freedom from transformation (FFT), and OS. For FFP, events were defined as relapsed disease. In the vast majority of cases, relapsed disease was biopsy-proven, and the date of biopsy was used as the date of relapse. In the minority of cases that were not biopsy-proven, the date of the scan that triggered treatment was used. For 1 case, the date of progression was the date of death. Events were defined as transformation for FFT and death from any cause for OS.

To identify the optimal cutoff point for greatest disease diameter for our primary endpoint of FFP with and without consideration of competing events, an iterative process was used to identify a cutoff point which maximized the log likelihood.

Survival curves were generated using the Kaplan-Meier method. A competing risk analysis was performed to assess the impact of death as a competing event for FFP and FFT. Univariable analyses (UVA) were performed using the log-rank test. All factors considered in the UVA were included in the full multivariable model which was reduced using a combination of backward elimination and forward selection method with greatest disease diameter locked in the final model. Akaike's Information Criterion (AIC) values were used to compare full and reduced models. Models with lower AIC values were considered superior to those with higher AIC values. The Fine-Grey subdistribution hazard model was used to perform univariable and multivariable analyses when considering death as a competing event.

To examine how involvement of various lymph node regions impacts outcomes, we first performed a UVA using the log-rank test. MVAs were then performed separately for all associations with a p value of <0.100 using a proportional hazards regression that included age at diagnosis, sex, grade, presence of extranodal disease, greatest disease diameter, ECOG performance status, LDH, and number of lymph node regions. Separate proportional hazards regressions were run to avoid highly correlated independent variables (e.g., patients with inguinal / femoral disease often had iliac disease, patients with inguinal / femoral disease could not have axillary disease).

The chi-squared test was used to investigate the relationship between greatest disease diameter (>3.6 cm vs. ≤3.6 cm) and patterns of failure. The T-test for independent samples was used to investigate the relationship between greatest disease diameter (>3.6 cm vs. ≤3.6 cm) and RT dose. The T-test for independent samples was used to compare the mean greatest disease diameter for patients who were staged with PET and patients who were not staged with PET. The T-test for independent samples was used to compare the mean RT dose for patients diagnosed prior to 2008 and patients diagnosed in 2008 or afterwards. A proportional hazards regression which included the variables in Table 4 was used to assess whether RT dose (≥30 Gy vs. <30 Gy) was associated with outcomes. Results were considered significant if $p < 0.05$. The median follow-up duration was calculated using the reverse Kaplan-Meier method for the FFP and OS outcomes.

3. Results

102 patients were included in the study cohort (Supplemental Fig. 1). The median follow-up duration was 10.4 years (range, 0.3–22.3) for FFP and 17.3 years (range, 4.8–34.5) for OS. The median age at diagnosis was 59 years (range, 33–86). The median greatest diameter of disease was 3.6 cm (range, 1.5–11.5). 17 patients (17%) had stage IIE disease, including 11 patients (11%) who had 1 involved lymph node region plus involvement in 1 extralymphatic organ or site and 6 patients (6%) who had 2 or more involved lymph node regions plus involvement in 1 extralymphatic organ or site. 64 patients (63%) had 2 involved lymph node regions, 19 patients (19%) had 3 involved lymph node regions, and 8 patients (8%) had 4 involved lymph node regions. The median RT dose was 30.0 Gy (range, 20.0–42.0). 8 patients were staged with PET/CT. Table 1 shows the baseline patient, tumour, and treatment characteristics.

Table 2 shows the FFP, FFT, and OS at 5 and 10 years for the entire study cohort. Fig. 1 shows the Kaplan-Meier curves for FFP and OS for the entire cohort. The competing risk analysis showed that considering death as a competing event did not change the 5- and 10-year survival for FFP and FFT (Supplemental Table 1).

Of the 102 patients in the study cohort, 60 patients relapsed. Distant only relapse was the most common pattern of first failure, occurring in 38 patients. Other patterns of first failure were: in-field only in 1 patient; in-field and marginal relapse in 1 patient; in-field and distant (±

Table 1
Baseline characteristics.

Characteristic	Number of Patients (%)
Age at Diagnosis	
<60 Years	53 (52%)
≥60 Years	49 (48%)
Sex	
Female	46 (45%)
Male	56 (55%)
Grade	
1–2	92 (90%)
3A	10 (10%)
Extranodal Disease	
Absent	85 (83%)
Present	17 (17%)
Greatest Disease Diameter	
≤3.6 cm	52 (51%)
>3.6 cm	50 (49%)
Complete Resection	
No	98 (96%)
Yes	4 (4%)
ECOG Performance Status	
0	68 (67%)
1–2	34 (33%)
LDH	
Normal	95 (93%)
Elevated	3 (3%)
Unknown	4 (4%)
Number of Lymph Node Regions	
1–2 regions	75 (74%)
3–4 regions	27 (26%)
Bilateral Disease	
No	53 (52%)
Yes	49 (48%)
Infradiaphragmatic Disease	
No	53 (52%)
Yes	49 (48%)
RT Dose	
20 – <25 Gy	15 (15%)
25 – <30 Gy	21 (21%)
30 – <35 Gy	24 (24%)
≥35 Gy	42 (41%)
Year of Diagnosis	
1986–1996	29 (28%)
1997–2006	30 (29%)
2007–2016	43 (42%)

Abbreviations: ECOG=European Cooperative Oncology Group; LDH=lactate dehydrogenase; RT=radiation therapy.

Table 2
Outcomes after treatment with RT alone for the entire cohort.

Outcome	5 Years	10 Years
Freedom from Progression	60.3% ± SE 5.0%	40.7% ± SE 5.5%
Freedom from Transformation	88.4% ± SE 3.3%	79.2% ± SE 4.7%
Overall Survival	89.2% ± SE 3.1%	81.8% ± SE 3.9%

Abbreviations: SE=standard error.

marginal) relapse in 10 patients; marginal relapse only in 2 patients; marginal and distant relapse in 7 patients; and, unknown relapse site(s) in 1 patient (Supplemental Fig 2). Overall, 55 (93.2%) of the 59 patients who had known site(s) of relapse had involvement of a distant site.

The greatest disease diameter with the highest log likelihood was 10 cm. However, given that only 1 patient in our cohort had a greatest disease diameter >10 cm, we sought to identify a cutoff point that was more clinically applicable to the stage II FL population. The greatest disease diameters with the next highest log likelihoods were 3.4 cm and 3.6 cm (Supplemental Fig. 3). 3.6 cm was selected as the best cutoff point as a bivariate Cox model in which the cutoff was set at 3.6 cm had a lower AIC value (AIC 459.61) compared to the model that had a cutoff point of 3.4 cm (AIC 459.64). The optimal cutoff did not differ when considering death as a competing event for FFP.

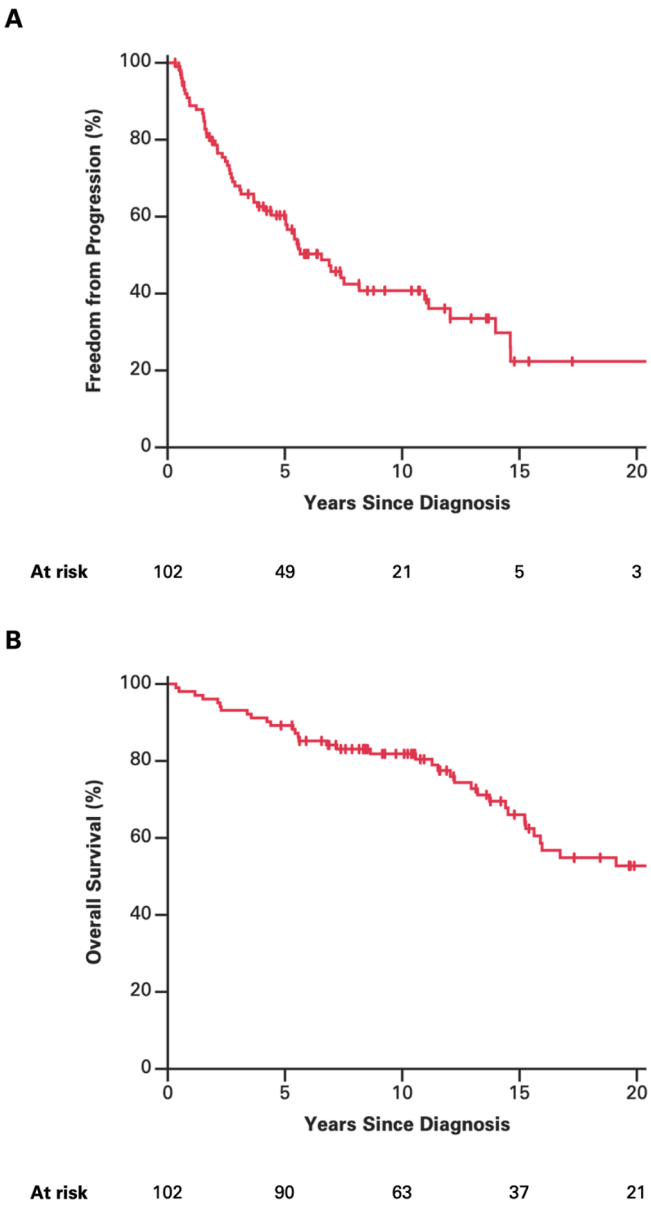

Fig. 1. Outcomes after treatment with RT alone for the entire cohort. Kaplan-Meier curves showing FFP (A) and OS (B) for the entire cohort.

On UVA (Table 3), greatest diameter of disease >3.6 cm was associated with inferior FFP (Fig. 2). The 10-year FFP for patients with greatest diameter of disease of >3.6 cm and ≤3.6 cm were 34% and 47% respectively ($p = 0.013$). Age ≥60 years was associated with inferior FFT and OS. On MVA (Table 4), older age was associated with inferior OS (hazard ratio [HR] 1.08, $p = < 0.001$), greatest diameter of disease >3.6 cm was associated with inferior FFP (HR 1.87, $p = 0.019$) and inferior OS (HR 2.12, $p = 0.027$), and infradiaphragmatic disease was associated with superior OS (HR 0.41, $p = 0.022$). A greater number of involved lymph node regions, bilateral disease, and extranodal involvement did not correlate with worse outcomes on UVA or MVA. When considering death as a competing event, univariable and multivariable analyses were similar for all endpoints compared to when not considering death as a competing event.

Supplemental Table 2 shows a UVA examining the impact of the involvement of various lymph node regions on outcomes. On MVA, patients with disease that involved the inguinal / femoral region had superior OS (HR 0.275, 95% CI 0.125–0.605, $p = 0.001$). Patients with disease that involved the iliac region had superior FFT (HR 0.353, 95%

Table 3
Univariable analyses of oncologic outcomes.

Factor	FFP		FFT		OS	
	10-year FFP	*P* Value	10-year FFT	*P* Value	10-year OS	*P* Value
Age at Diagnosis		.382		.043		<.001
<60 Years	44%		89%		96%	
≥60 Years	37%		67%		66%	
Sex		.140		.584		.647
Female	45%		79%		86%	
Male	38%		79%		78%	
Grade		.356		.187		.886
1–2	42%		82%		82%	
3A	40%		60%		80%	
Extranodal Disease		.361		.740		.116
Absent	44%		79%		84%	
Present	23%		79%		71%	
Greatest Disease Diameter		.013		.228		.208
≤3.6 cm	47%		80%		86%	
>3.6 cm	34%		78%		77%	
ECOG PS		.911		.569		.093
0	41%		79%		85%	
1–2	41%		81%		75%	
LDH		.758		.388		.856
Normal	41%		81%		86%	
Elevated	50%		50%		33%	
Number of Lymph Node Regions		.603		.243		.881
1–2 regions	38%		77%		82%	
3–4 regions	47%		87%		82%	
Bilateral Disease		.323		.325		.622
No	39%		76%		80%	
Yes	43%		81%		84%	
Infradiaphragmatic Disease		.277		.380		.055
No	39%		73%		76%	
Yes	42%		86%		88%	

Abbreviations: FFP=freedom from progression; FFT=freedom from transformation; OS=overall survival; ECOG PS=European Cooperative Oncology Group performance status; LDH=lactate dehydrogenase.

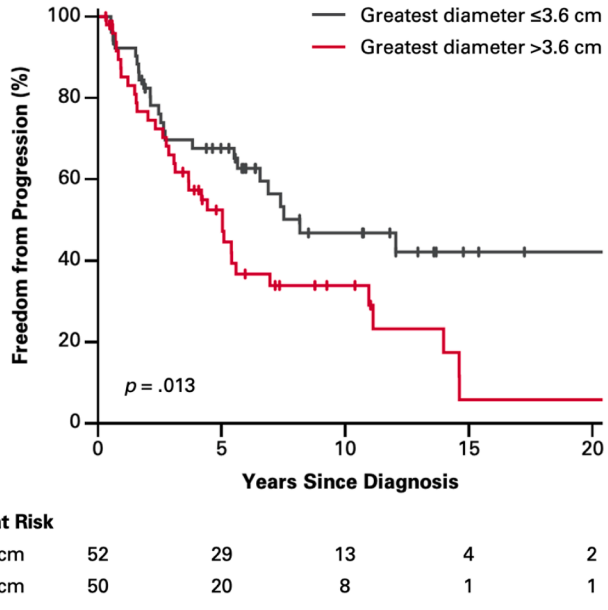

Fig. 2. Greatest disease diameter (>3.6 cm vs. ≤3.6 cm) predicts FFP.

CI 0.131–0.948, $p = 0.039$) and superior OS (HR 0.257, 95% CI 0.098–0.672, $p = 0.006$). Patients with disease that involved the axillary region had inferior OS (HR 4.087, 95% CI 1.554–10.749, $p = 0.004$).

Supplemental Table 3 shows the patterns of failure by greatest disease diameter (>3.6 cm vs. ≤3.6 cm). Greatest disease diameter did not impact patterns of failure. The average RT dose for patients with a greatest disease diameter of >3.6 cm and ≤3.6 cm was 30.5 Gy and 30.7 Gy, respectively ($p = 0.817$).

The mean RT dose for patients diagnosed prior to 2008 was 33.5 Gy while the mean RT dose for patients diagnosed in 2008 or afterwards was 26.0 Gy ($p < 0.001$) (Supplemental Fig. 4). On UVA, RT dose (≥30 Gy vs. <30 Gy) was not significantly associated with FFP ($p = 0.631$), FFT ($p = 0.121$), or OS ($p = 0.259$). On MVA, RT dose (≥30 Gy vs. <30 Gy) was not significantly associated with FFP, FFT, or OS.

There was no significant difference between the mean greatest disease diameter for patients who were staged with PET and patients who were not staged with PET (3.63 ± 1.50 cm vs. 4.18 ± 2.17 cm, $p = 0.480$).

4. Discussion

The optimal management of stage II FL is unclear. RT alone has been the gold standard therapy, but a sizable proportion of patients treated this way (almost 60% according to the present study) experience disease relapse within 10 years. Identification of those patients who are at higher risk of relapse would enable personalization of therapy, including treatment intensification with additional systemic therapy, to improve outcomes. To our knowledge, this present study is the first to attempt to identify a high-risk subgroup of stage II FL patients treated with RT alone.

Our study demonstrates that for stage II FL patients treated with RT alone, greatest disease diameter >3.6 cm is associated with inferior FFP and OS, but not inferior FFT, on multivariable analysis. Previous studies that investigated the prognostic potential of disease diameter were based on study cohorts that were not stage II specific, making them less applicable to the present population [15,16,17]. Other existing prognostic tools for FL are also not as applicable to the present population. For instance, FLIPI and FLIPI-2 are well known prognostic tools in FL [16,18]. However, only a small proportion (22% and 32%, respectively) of study patients were stage I–II, likely explaining the mixed results regarding their reliability as prognostic tools for stage I–II FL [10,19]. There have also been attempts to identify molecular predictors of outcomes [20,21,22]. While promising, these tools are currently inaccessible to the vast majority of patients, even at major academic centres. On the contrary, greatest diameter of disease is an easy-to-apply and accessible prognostic variable that may distinguish stage II FL patients treated with RT alone who are at higher risk of recurrence and shortened survival.

Identifying those at the greatest risk of inferior outcomes following RT alone is important in considering the optimal treatment strategy for these patients. The question then becomes whether additional benefit may be gained from intensification of the treatment approach for these higher-risk patients. The TROG trial demonstrated that adding adjuvant cyclophosphamide, vincristine, prednisolone, and rituximab to RT results in superior PFS, but not OS, and at the cost of increased acute toxicity rates [3]. Therefore, given that RT alone is associated with low rates of toxicities [23], it remains unclear whether the benefits outweigh the drawbacks of adding immunochemotherapy. More recently, the addition of rituximab to RT for stage I–II FL has been shown to improve PFS without the toxicities typically associated with chemotherapy [4,24,25], representing a strategy that may be worthwhile for patients with a higher risk of recurrence. This study's identification of greatest diameter of disease as a prognostic factor for stage II FL patients treated with RT alone may provide a helpful aid in the decision-making process on whether to complement RT with rituximab.

This study also adds to the very limited body of knowledge on stage II-specific outcomes. Traditionally, the optimal management approaches for stage I and II FL have not been distinguished. Existing publications have typically reported outcomes for stage I–II FL as a

Table 4
Final models for multivariable analyses of oncologic outcomes.

Factor	FFP		FFT		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at Diagnosis (Continuous; Unit = 1 Year)			1.03 (1.00–1.07)	0.070	1.08 (1.05–1.11)	<0.001
Sex (Male vs. Female)	0.70 (0.41–1.19)	0.184			0.68 (0.36–1.26)	0.222
Grade (3A vs. 1–2)						
Extranodal Disease (Present vs. Absent)					1.86 (0.79–4.36)	0.152
Greatest Disease Diameter (>3.6 cm vs. ≤3.6 cm)	1.87 (1.11–3.16)	0.019	2.45 (1.00–6.02)	0.050	2.12 (1.09–4.12)	0.027
ECOG PS (1–2 vs. 0)						
LDH (Elevated vs. Normal)						
Number of Lymph Node Regions (3–4 vs. 1–2)					2.11 (1.00–4.46)	0.050
Bilateral Disease (Yes vs. No)						
Infradiaphragmatic Disease (Yes vs. No)			0.49 (0.20–1.18)	0.112	0.41 (0.19–0.88)	0.022

Abbreviations: FFP=freedom from progression; FFT=freedom from transformation; DSS=disease-specific survival; OS=overall survival; ECOG PS=European Cooperative Oncology Group performance status; LDH=lactate dehydrogenase.

group, rarely reporting analyses specific to the stage II subgroup [7,8,17,26]. Despite common management strategies presently used for these two stages of disease, there is strong evidence that patients with stage II FL have inferior outcomes compared to those with stage I FL following RT [5,6,7,8,9], suggesting that stage II FL has a clinical trajectory that is distinct from that of stage I FL. With a median follow-up duration greater than 10 years, this present study adds robust, long-term data to the limited body of knowledge on stage II-specific outcomes in FL treated with RT alone and sheds light on the unique clinical trajectory of stage II FL.

With an FFP of 40.7% at 10 years, this study demonstrates that RT alone is an effective treatment for stage II FL patients. Previously published data from our institution showed that for stage IA/IIA FL together, recurrences beyond 10 years were rare [9,15], suggesting that RT alone was potentially curative for this population. However, in the current analysis limited to the stage II subgroup in isolation, we have observed no clear plateau in the survival curve after the 10-year mark (Fig. 1**A**), consistent with findings from a different series [7]. These results suggest that stage II FL may have a different clinical trajectory than stage I FL, with recurrences continuing to occur even after the 10-year mark. Taken together with our finding that the vast majority (93%) of recurrences in stage II FL involved a distant site, our study suggests that stage II FL has a much higher propensity to involve distant microscopic sites of disease compared with stage I FL.

Interestingly, although FFP does not appear to plateau for stage II FL patients as a whole or for those with a greatest disease diameter >3.6 cm, it appears to plateau at 44% for patients with a greatest disease diameter ≤3.6 cm (Fig. 2). However, given that there are relatively few patients at risk after 10 years for both subgroups, it is difficult for the present study to make definitive conclusions. Further research is needed to assess this potential trend. Whether or not outcomes plateau is an important clinical question as it has implications for management (e.g., follow-up duration) and prognosis.

Despite strong evidence from the present study and previous studies showing that RT alone is an effective management approach for suitable patients with stage II FL, management practices are not uniformly reflective of this [5,9]. While comparing outcomes between treatment modalities is limited without randomized trials, systemic therapy alone does not result in superior OS compared to management with RT alone, and is associated with greater side effects [3,10,27]. Nevertheless, a substantial proportion of patients—ranging from 32.5% to 69.0% according to two studies—are managed with systemic therapy only, which is notably higher than the proportion of patients managed with RT alone (5.6% to 19.3%) [5,28]. In addition, the utilization of RT alone has decreased over time, from 24.3% in 1998–2002 to 19.3% in 2008–2012 [5]. Our study shows that RT alone is an effective management approach for stage II FL. Given that RT alone leads to comparable outcomes to systemic therapy alone with fewer side effects, it should be strongly considered when selecting first-line therapy modality for stage II FL.

Interestingly, our study found that 1–2 vs. 3–4 lymph node regions was not prognostic in stage II FL patients treated with RT alone. There has been limited research investigating the prognostic value of this variable, with all of the studies involving cohorts that were not stage II-specific [3,10,16,26,29,30]. These studies showed mixed results regarding the prognostic value of the number of involved lymph node regions. Thus, at present, there is insufficient evidence to support treatment intensification based on the number of involved nodal regions in patients with stage II FL. Although one would expect more widespread disease to be associated with worse outcomes, our finding is likely a reflection of the fact that many patients in both subgroups had distant microscopic disease which were not covered by the RT fields and therefore, were untreated. Based on our results, it appears that disease diameter is a better predictor of the presence of distant microscopic disease than the number of involved nodal regions.

This study also investigated whether location or general distribution of disease were associated with outcomes. We found that bilateral disease was not associated with inferior outcomes. Infradiaphragmatic disease was predictive of superior OS, with this effect being driven primarily by the inguinal / femoral and iliac lymph node regions, rather than the paraaortic region. The inferior OS associated with supradiaphragmatic disease was primarily driven by the axillary region. There has been limited research looking at the predictive value of infradiaphragmatic disease, with all of the studies involving cohorts that were not stage II-specific [3,17,31]. These studies showed mixed results regarding the predictive value of infradiaphragmatic disease. Further research is needed to confirm our findings on the impact of anatomic location on OS and determine the mechanism for these associations.

In the past 13 years, a few trials have looked at whether reducing the RT dose affects outcomes in FL. The Lowry et al. trial compared 40–45 Gy with 24 Gy and found no difference in PFS or OS [32]. The FORT trial further compared 4 Gy with 24 Gy and found that treatment with only 4

Gy led to increased risk of local progression, leading the study authors to conclude that 24 Gy should remain as the standard of care [23]. In our cohort, the mean RT dose decreased from 33.5 Gy (prior to 2008) to 26.0 Gy (2008 and afterwards). On MVA, there was no difference in outcomes between patients who received a higher dose (≥30 Gy) and those who received a lower dose (<30 Gy). Thus, our real-world data supports the finding in the Lowry et al. trial that a reduction in RT dose to 24 Gy did not lead to inferior outcomes. Although the FORT trial found that 4 Gy was inferior to 24 Gy, there are ongoing efforts to study 4 Gy in combination with obinutuzumab [33].

This study had some limitations. First, this was a retrospective study. Second, given the relatively small cohort size, further research is required to validate 3.6 cm as a threshold for risk stratification for greatest diameter of disease. Third, positron emission tomography (PET) staging was not mandatory, and thus, there may be some differences in our patient cohort compared to a PET-staged stage II cohort, including the possibility of patients who had additional, undetected sites of disease which, if had been detected, would have resulted in either more extensive stage II FL or FL of a higher stage [26,30,34]. However, a study with a PET-staged cohort revealed similar outcomes and a similar outcome trajectory for stage II FL treated with RT alone [7].

In conclusion, 40.7% of stage II FL patients selected to receive RT alone were disease-free 10 years after treatment. Greatest diameter of disease was associated with inferior FFP and OS, representing a novel prognostic indicator in this population that may help in the decision-making process on whether to complement RT with systemic therapy. Further research is required to validate 3.6 cm as a threshold for risk stratification for greatest disease diameter in stage II FL patients treated with RT alone.

Data availability statement

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

Funding

This research was supported by the BC Cancer Research Studentship from the BC Cancer Foundation and a BC Cancer Radiation Oncology Grant from the BC Cancer Foundation.

CRediT authorship contribution statement

Yi Xu: Investigation, Data curation, Methodology, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Belinda A. Campbell:** Writing – review & editing. **Matthew Chan:** Writing – review & editing. **Jessica Chan:** Writing – review & editing. **Pedro Farinha:** Data curation, Writing – review & editing. **Christopher P. Venner:** Writing – review & editing. **David W. Scott:** Writing – review & editing. **Alina S. Gerrie:** Writing – review & editing. **Diego Villa:** Writing – review & editing. **Laurie H. Sehn:** Writing – review & editing. **Kerry J. Savage:** Conceptualization, Writing - Review & Editing. **Andrea C. Lo:** Conceptualization, Methodology, Writing - Review & Editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: David W. Scott has received grants from Roche. Alina S. Gerrie has received grants from Abbvie, AstraZeneca, Janssen, and Roche Canada, consulting fees and honoraria from Abbvie, AstraZeneca, BeiGene, and Janssen, and support for travel expenses from Janssen. Diego Villa has received grants from Roche and AstraZeneca and honoraria from Roche, Merck, BMS/Celgene, Kite/Gilead, Janssen, AstraZeneca, Abbvie, BeiGene, and Novartis. Laurie H. Sehn has received grants from F. Hoffmann-La Roche Ltd, Genentech, Inc., and Teva, and consulting fees and honoraria from F. Hoffmann-La Roche Ltd, Genentech, Inc., AbbVie, AstraZeneca, BMS/Celgene, Gilead Sciences, Janssen, Incyte, Kite Pharma, Merck, Seagen, Teva, and TG Therapeutics. Kerry J. Savage has received grants from Roche and Bristol Myers Squibb, has received consulting fees and honoraria from Bristol Myers Squibb, AbbVie, and Seagen, participates on the data safety monitoring board of Regeneron, and participates on the steering committee of Beigene and AstraZeneca. Yi Xu, Belinda A. Campbell, Matthew Chan, Jessica Chan, Pedro Farinha, Christopher P. Venner, and Andrea C. Lo report no disclosures.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100869.

References

[1] Zelenetz AD, Gordon LI, Abramson JS, et al. NCCN Guidelines – B-Cell Lymphomas – Version 2023;4:2023.
[2] Dreyling M, Ghielmini M, Rule S, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2021;32:298–308.
[3] MacManus M, Fisher R, Roos D, et al. Randomized trial of systemic therapy after involved-field radiotherapy in patients with early-stage follicular lymphoma: TROG 99.03. JCO 2018;36:2918–25.
[4] Herfarth K, Borchmann P, Schnaidt S, et al. Rituximab with involved field irradiation for early-stage nodal follicular lymphoma: results of the MIR study. Hemasphere 2018;2:e160.
[5] Vargo JA, Gill BS, Balasubramani GK, et al. What is the optimal management of early-stage low-grade follicular lymphoma in the modern era? Cancer 2015;121:3325–34.
[6] Dinnessen MAW, Van der Poel MWM, Tonino SH, et al. Stage-specific trends in primary therapy and survival in follicular lymphoma: a nationwide population-based analysis in the Netherlands, 1989–2016. Leukemia 2021;35:1683–95.
[7] Brady JL, Binkley MS, Hajj C, et al. Definitive radiotherapy for localized follicular lymphoma staged by 18F-FDG PET-CT: a collaborative study by ILROG. Blood 2019;133:237–45.
[8] Mac Manus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. JCO 1996;14:1282–90.
[9] Lo AC, Campbell BA, Pickles T, et al. Long-term outcomes for patients with limited-stage follicular lymphoma: update of a population-based study. Blood 2020;136:1006–10.
[10] Tobin JWD, Rule G, Colvin K, et al. Outcomes of stage I/II follicular lymphoma in the PET era: an international study from the Australian Lymphoma Alliance. Blood Adv 2019;3:2804–11.
[11] Ahmed N, Owen TE, Rubinger M, et al. Early stage W.H.O. grade I and II follicular lymphoma treated with radiation therapy alone. PLoS One 2013;8:e65156.
[12] Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on hodgkin's disease staging classification. Cancer Res 1971;31:1860–1.
[13] Armitage JO. Staging non-hodgkin lymphoma. CA Cancer J Clin 2005;55:368–76.
[14] Gospodarowicz MK, Sutcliffe SB, Clark RM, et al. Outcome analysis of localized gastrointestinal lymphoma treated with surgery and postoperative irradiation. Int J Radiat Oncol Biol Phys 1990;19:1351–5.
[15] Campbell BA, Voss N, Woods R, et al. Long-term outcomes for patients with limited stage follicular lymphoma: Involved regional radiotherapy versus involved node radiotherapy. Cancer 2010;116:3797–806.
[16] Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. JCO 2009;27:4555–62.
[17] Wilder RB, Jones D, Tucker SL, et al. Long-term results with radiotherapy for stage I-II follicular lymphomas. Int J Radiat Oncol Biol Phys 2001;51:1219–27.
[18] Solal-Céligny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258–65.
[19] Sha F, Okwali M, Alperovich A, et al. Clinical outcomes with use of radiation therapy and risk of transformation in early-stage follicular lymphoma. Blood Cancer J 2022;12:29.
[20] Cerhan JR, Wang S, Maurer MJ, et al. Prognostic significance of host immune gene polymorphisms in follicular lymphoma survival. Blood 2007;109:5439–46.
[21] Huet S, Tesson B, Jais J, et al. A gene-expression profiling score for prediction of outcome in patients with follicular lymphoma: a retrospective training and validation analysis in three international cohorts. Lancet Oncol 2018;19:549–61.
[22] Pulsoni A, Starza ID, Cappelli LV, et al. Minimal residual disease monitoring in early stage follicular lymphoma can predict prognosis and drive treatment with rituximab after radiotherapy. Br J Haematol 2020;188:249–58.
[23] Hoskin PJ, Kirkwood AA, Popova B, et al. 4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial. Lancet Oncol 2014;15:457–63.

[24] Ruella M, Filippi AR, Bruna R, et al. Addition of rituximab to involved-field radiation therapy prolongs progression-free survival in stage I-II follicular lymphoma: results of a multicenter study. Int J Radiat Oncol Biol Phys 2016;94:783–91.
[25] Cencini E, Puccini B, Rigacci L, et al. Radiotherapy plus rituximab as first-line regimen for localized follicular lymphoma. Leuk Lymphoma 2018;59:1420–6.
[26] Ng SP, Khor R, Bressel M, et al. Outcome of patients with early-stage follicular lymphoma staged with 18F-Fluorodeoxyglucose (FDG) positron emission tomography (PET) and treated with radiotherapy alone. Eur J Nucl Med Mol Imaging 2019;46:80–6.
[27] Sancho JM, García O, Mercadal S, et al. The long term follow-up of early stage follicular lymphoma treated with radiotherapy, chemotherapy or combined modality treatment. Leuk Res 2015;39:853–8.
[28] Friedberg JW, Taylor MD, Cerhan JR, et al. Follicular lymphoma in the united states: first report of the national lymphocare study. J Clin Oncol 2009;27:1202–8.
[29] Besa PC, McLaughlin PW, Cox JD, et al. Long term assessment of patterns of treatment failure and survival in patients with stage I or II follicular lymphoma. Cancer 1995;75:2361–7.
[30] Metser U, Dudebout J, Baetz T, et al. [18F]-FDG PET/CT in the staging and management of indolent lymphoma: a prospective multicenter PET registry study: PET/CT in Indolent Lymphoma. Cancer 2017;123:2860–6.
[31] Barzenje DA, Småstuen MC, Liestøl K, et al. Radiotherapy compared to other strategies in the treatment of stage I/II follicular lymphoma: a study of 404 patients with a median follow-up of 15 years. PLoS One 2015;10:e0131158.
[32] Lowry L, Smith P, Qian W, et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase III trial. Radiother Oncol 2011;100:86–92.
[33] König L, Dreyling M, Dürig J, et al. Therapy of nodal Follicular Lymphoma (WHO grade 1/2) in clinical stage I/II using response adapted Involved Site Radiotherapy in combination with Obinutuzumab (Gazyvaro) - GAZAI Trial (GAZyvaro and response adapted Involved-site Radiotherapy): a study protocol for a single-arm, non-randomized, open, national, multi-center phase II trial. Trials 2019;20:544.
[34] Luminari S, Biasoli I, Arcaini L, et al. The use of FDG-PET in the initial staging of 142 patients with follicular lymphoma: a retrospective study from the FOLL05 randomized trial of the Fondazione Italiana Linfomi. Ann Oncol 2013;24:2108–12.