TO THE EDITOR:

CME Article

Long-term outcomes for patients with limited-stage follicular lymphoma: update of a population-based study

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In light of recent publications from the Trans Tasman Radiation Oncology Group (TROG),[1] the International Lymphoma Radiation Oncology Group,[2] and the Australian Lymphoma Alliance,[3] we sought to update the long-term outcomes of computed tomography–staged limited-stage follicular lymphoma (FL) treated with radiotherapy (RT) alone. The phase 3 TROG study demonstrated that the addition of immunochemotherapy to curative-intent RT improves progression-free survival (PFS), but not overall survival (OS), at the cost of increased acute toxicities.[1] The International Lymphoma Radiation Oncology Group[2] and Australian Lymphoma Alliance studies[3] mandated positron emission tomography (PET) staging and reported excellent intermediate-term outcomes from RT alone. Thus, RT alone remains an attractive treatment option for limited-stage FL; however, given the long natural history, mature follow-up is needed to accurately define relapse risks.

We previously reported the outcomes of limited-stage FL treated with curative-intent RT with a median follow-up of 7.3 years.[4] We demonstrated the safety of reducing RT fields, from conventional involved regional radiotherapy (IRRT) to involved node radiotherapy with margins ≤ 5 cm (INRT≤5cm). These smaller RT fields have since become standard of care, with the intention to reduce the risks of RT-induced toxicities without compromising disease control.

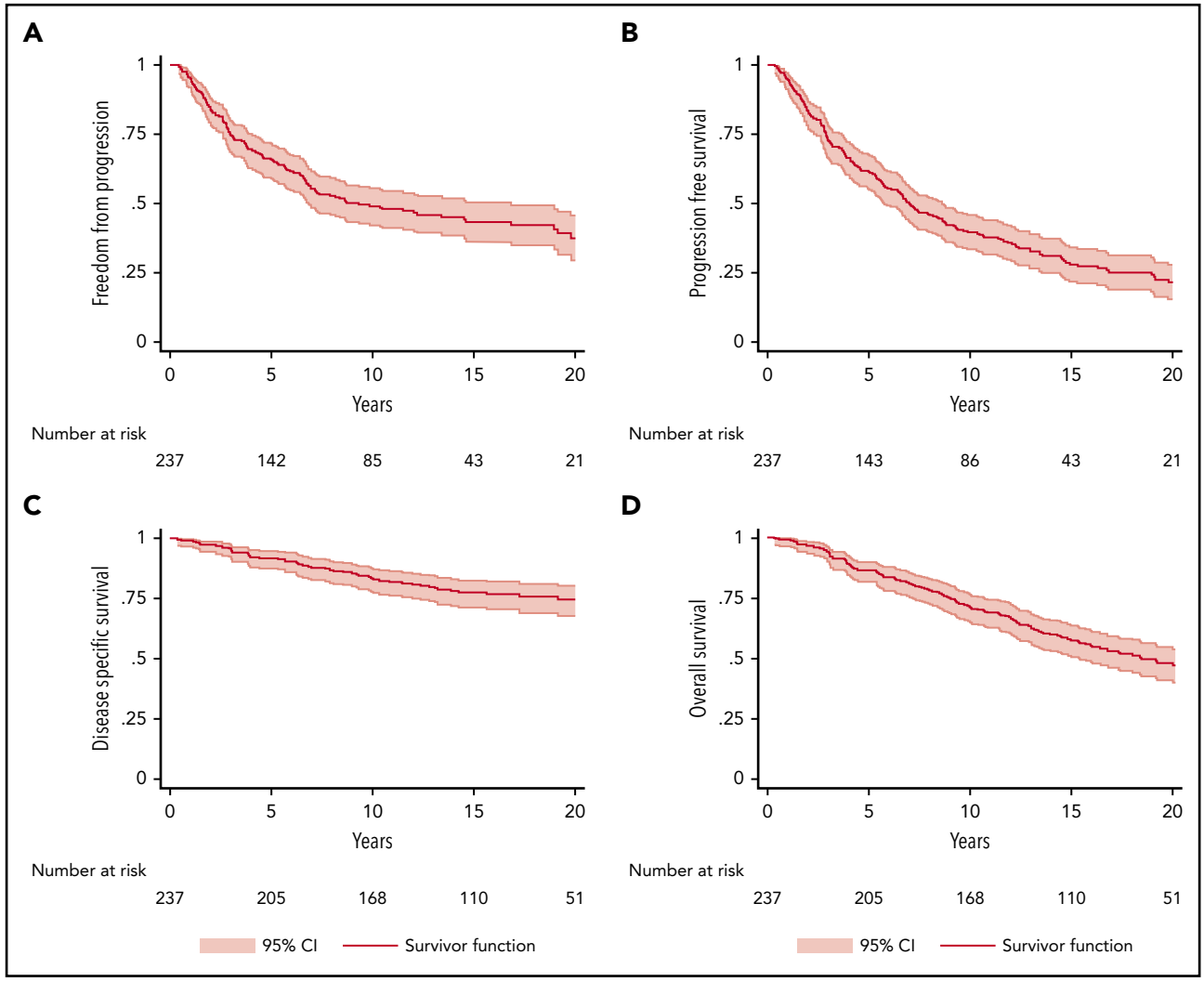

Figure 1. Outcomes for all patients in the study cohort. (A) FFP, (B) PFS, (C) DSS, and (D) OS.

INRT≤5cm was first proposed for the treatment of limited-stage Hodgkin lymphoma,[5] an adaptation of involved node radiotherapy [which encompasses only involved lymph node(s); LN],[6] but with additional margins to account for anatomical and technical uncertainties in defining prechemotherapy disease. In 2013, the term "involved site radiotherapy (ISRT)" was introduced, targeting involved LN(s) with the same additional margins to accommodate for uncertainties. Because INRT≤5cm closely resembles ISRT, it has been renamed accordingly for this article.

We report the updated long-term outcomes of this limited-stage FL cohort, now with a median follow-up of 16.1 years for living patients. Furthermore, the impact of ISRT on patterns of first relapse, freedom from progression (FFP), transformation, and survival are reevaluated.

Ethics approval was obtained from the University of British Columbia–BC Cancer Research Ethics Board, and the work was conducted in accordance with the Declaration of Helsinki. Eligible patients were diagnosed with stage IA/IIA nonbulky (<10 cm) grade 1-3A FL from 1986 to 2006 and received curative-intent RT alone at any of the 4 BC Cancer centers.[4] During this time period, staging included computed tomography, but not PET. From 1986 to 1998, the treatment policy was IRRT, encompassing the involved LN group plus ≥1 adjacent uninvolved LN group(s). From 1998 onward, the treatment policy was ISRT, covering only the involved LN(s) with margins ≤ 5 cm, individualized according to quality and accuracy of pretreatment imaging, physiologic movement, and setup variation. All patients received external beam RT, with a minimum prescribed dose of 20 Gy (range, 20-45).

Survival rates and cumulative incidence of transformation to aggressive lymphoma with standard errors were calculated using the Kaplan-Meier method. For FFP, unrelated deaths were censored, whereas for PFS, all deaths were counted. Other statistical methods were used as previously described.[4]

Of the 237 patients, 48% were male, and 54% were older than 60 years of age at diagnosis. Sixty percent received IRRT, and 40% received ISRT; baseline characteristics are as previously reported (supplemental Table 1).

With a median follow-up of 16.1 years (range, 2.5-33.2) for all living patients (IRRT: median, 16.8; range, 4.0-33.2 and ISRT: median, 14.9; range, 2.5-26.2), outcomes remain very similar

Table 1. Final models for multivariable analyses of FFP, PFS, DSS, and OS

Variable	FFP		PFS		DSS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age >60 vs ≤60y	1.39 (0.95-2.02)	.090	1.73 (1.26-2.37)	.001	2.78 (1.51-5.12)	.001	4.31 (2.81-6.61)	<.0001
Male vs female	1.48 (1.03-2.13)	.034						
ECOG PS 1-2 vs 0							1.42 (0.95-2.12)	.086
Grade 3A vs 1-2								
Stage IIA vs IA	1.51 (1.00-2.26)	.048						
Mass <5 cm vs completely excised	2.86 (1.15-7.13)	.024	1.47 (0.85-2.54)	.165	3.23 (0.76-13.66)	.112		
Mass ≥5 cm vs completely excised	4.01 (1.53-10.49)	.005	2.16 (1.16-4.02)	.015	4.64 (1.04-20.78)	.045		
Extranodal disease vs no extranodal disease	0.63 (0.39-1.03)	.064						
Serum LDH elevated vs normal	1.99 (1.05-3.77)	.035			3.67 (1.68-8.01)	.001		
ISRT vs IRRT								

Empty rows mean that the corresponding variable was not retained in the final model.

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase.

to our previous study[4] (Figure 1): FFP of 66% ± standard error (SE) of 3% at 5 years, 49% ± SE 3% at 10 years, and 43% ± SE 4% at 15 years. Corresponding estimates for PFS were 61% ± SE 3%, 40% ± SE 3%, and 28% ± SE 3%, respectively. Long-term disease-specific survival (DSS) (83% ± SE 3% at 10 years and 78% ± SE 3% at 15 years) was favorable, and OS reflects older age and death due to other causes (71% ± SE 3% and 57% ± SE 3%, respectively). Compared with a population-based cohort of similar age, patients who had not relapsed or died by 10 years had a slightly lower 5-year OS rate and a similar 10-year OS rate (see text section in supplemental Materials).[7]

The cumulative incidence of transformation to aggressive lymphoma was 9% ± SE 2% at 5 years, 17% ± SE 3% at 10 years, and 20% ± SE 3% at 15 years, consistent with our earlier analysis.[8] Forty-two patients have now developed transformed disease, with a median time to transformation of 5.3 years (range, 0.4-20.6), which is longer than our earlier report of 3.6 years.[8] In comparison, a predominantly advanced-stage cohort largely treated with systemic therapy[9] had higher transformation rates. On the other hand, a larger retrospective analysis reported a lower 10-year cumulative hazard of 8% for histological transformation,[10] with it occurring earlier, at a median of 18 months. Possible explanations for this difference include the biopsy-based definition of transformation (vs the clinical- or biopsy-based definition in our previous study[8]), inclusion of only histological transformation occurring as a first event after first-line systemic therapy, and the high proportion of patients treated with rituximab.

Of the 125 relapses (53%), 8 (6%) occurred at between 10 and 15 years, and 4 (3%) occurred beyond 15 years. Other studies with comparable length of follow-up are scarce but have suggested a plateauing of relapse risk beyond 15 years.[11,12] Collectively, these long-term studies confirm the curative potential of RT alone for limited-stage FL.

Our earlier study was the first to apply the modern concept of involved node radiotherapy/ISRT to FL.[4] This update confirms the long-term efficacy of reducing fields from IRRT to ISRT. RT field size was not significantly associated with FFP, PFS, DSS, or OS on univariable analysis (supplemental Table 2) or multivariable analysis (Table 1). Furthermore, of the 95 patients treated with ISRT, only 1 (1%) experienced a first failure that was "regional only" and would have been covered by an IRRT approach. When comparing IRRT and ISRT relapse patterns, in-field relapse alone occurred in 2 (1%) and 2 (2%) patients, distant relapse alone occurred in 71 (50%) and 36 (38%) patients, and concurrent in-field and distant relapse occurred in 8 (6%) and 3 (3%) patients ($P = .19$), respectively.

On multivariable analysis, male gender, stage II, larger mass size, and elevated lactate dehydrogenase (LDH) were associated with an inferior FFP (Table 1). In addition, mass size ≥5 cm was associated with an inferior PFS and DSS, and elevated LDH was associated with a lower DSS. Older age was associated with lower PFS, DSS, and OS. Although grade was adversely prognostic for OS in the original study, its significance is lost with extended follow-up. Subgroup analysis suggests that the presence of both mass size ≥5 cm and elevated LDH confers a higher relapse risk (see text section in supplemental Materials).

Although patients received RT only in our study, the additional value of adjuvant immunochemotherapy is a topical question. Adding adjuvant cyclophosphamide, vincristine, prednisolone,

and rituximab resulted in superior PFS, but not OS, in the TROG study.[1] Importantly, the RT-alone arm only had 2 occurrences of high-grade acute toxicities compared with 45 occurrences with the addition of immunochemotherapy.[1] Efforts to reduce toxicities associated with conventional chemotherapies and improve PFS over RT alone are the subject of a current phase 3 study randomizing patients to ISRT alone vs ISRT with rituximab (NCT01473628).[13] While awaiting evidence of superior outcomes from less toxic regimens, caution should be applied when incorporating immunochemotherapies into upfront treatment of limited-stage FL, particularly in the absence of OS benefit. Previous studies have demonstrated that secondary neoplasm risk may be elevated in patients who receive both alkylators and RT[14,15]; however, modern studies of combined-modality therapy lack sufficient follow-up to assess such risks. Future efforts should focus on individualizing patient care and defining patient subgroups most likely to benefit from adjuvant immunochemotherapy. Our study suggests that mass size ≥5 cm plus elevated LDH are a strong predictor for inferior outcome after RT alone; arguably, increased toxicity risks from immunochemotherapy are likely justifiable in these higher-risk patients.

More recently, PET has been widely adopted into FL staging.[16,17] Because of the effects of PET–computed tomography on stage migration and RT planning, superior outcomes are expected for limited-stage FL patients staged by PET–computed tomography compared with patients staged not using PET. Recent studies have shown, at best, a very modest improvement in intermediate-term outcomes, with 5-year FFP of 69%[2] and 5-year PFS ~ 66%[3] in PET-staged populations compared with 66% and 61% in our cohort not staged with PET, respectively. In the TROG trial, the hazard ratio for PFS was 0.61 for PET staging vs non-PET staging, with borderline significance (95% confidence interval, 0.37-1.00). However, definitions of "limited stage" vary among studies,[18] with some including patients with B symptoms and bulky disease. Longer follow-up is required to uncover the true benefit of PET staging on long-term cure in limited-stage FL treated with RT alone.[18]

Our results confirm the curative potential of RT alone for limited-stage FL in this conventionally staged cohort, with almost half remaining relapse-free beyond 15 years. Reduction of RT field size to ISRT did not impact the long-term risk of relapse or death. Given the excellent outcomes in this population-based analysis, as well as the known low risk of serious RT-induced toxicity, ISRT alone remains a proven, effective, and safe treatment for limited-stage FL.

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Authorship

Contribution: A.C.L., B.A.C., T.P., C.A.-P., L.H.S., J.M.C., and K.J.S. designed and performed research and wrote the manuscript, and A.C.L., B.A.C., and K.J.S. analyzed data.

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Footnotes

The dataset can be requested via e-mail to the corresponding author.

The online version of this article contains a data supplement.

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