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ORIGINAL REPORT

Randomized Trial of Systemic Therapy After Involved-Field Radiotherapy in Patients With Early-Stage Follicular Lymphoma: TROG 99.03

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ABSTRACT

Purpose

Follicular lymphoma (FL) is curable by involved-field radiotherapy (IFRT) in < 50% of patients with stage I to II disease. We hypothesized that adding systemic therapy to IFRT would improve long-term progression-free survival (PFS).

Patients and Methods

A multicenter randomized controlled trial enrolled patients with stage I to II low-grade FL after staging computed tomography scans and bone marrow biopsies. ^{18}F-labeled fluorodeoxyglucose–positron emission tomography (PET) was not mandatory. Patients were randomly assigned to either arm A (30 Gy IFRT alone) or arm B (IFRT plus six cycles of cyclophosphamide, vincristine, and prednisolone [CVP]). From 2006, rituximab was added to arm B (R-CVP).

Results

Between 2000 and 2012, 150 patients were enrolled, 75 per arm. In arm B, 44 patients were allocated to receive CVP and 31 were allocated to receive R-CVP. At randomization, 75% had stage I, the median age was 57 years, 52% were male, and 48% were PET staged. With a median follow-up of 9.6 years (range, 3.1 to 15.8 years), PFS was superior in arm B (hazard ratio, 0.57; 95% CI, 0.34 to 0.95; $P = .033$). Ten-year PFS rates were 59% (95% CI, 46% to 74%) and 41% (95% CI, 30% to 57%) for arms B and A, respectively. Patients in arm B who received R-CVP had markedly superior PFS compared with contemporaneous patients in arm A (hazard ratio, 0.26; 95% CI, 0.07 to 0.97; $P = .045$). Fewer involved regions ($P = .047$) and PET staging ($P = .056$) were associated with better PFS. Histologic transformation occurred in four and 10 patients in arms B and A, respectively ($P = .1$). Ten deaths occurred in arm A versus five in arm B, but overall survival was not significantly different ($P = .40$; 87% and 95% at 10 years, respectively).

Conclusion

Systemic therapy with R-CVP after IFRT reduced relapse outside radiation fields and significantly improved PFS. IFRT followed by immunochemotherapy is more effective than IFRT in early-stage FL.

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INTRODUCTION

Follicular lymphoma (FL), the most common indolent lymphoid malignancy,[1] is highly radiosensitive.[2] Involved-field radiotherapy (IFRT) achieves local disease control in > 90% of patients with localized (stage I to II) disease and is a potentially curative treatment with low toxicity.[3] However, relapse frequently occurs outside irradiated regions. Optimal management of localized FL remains controversial because of the absence of informative randomized controlled trials (RCTs). After 10 years, 40% to 50% of patients treated with relatively low-dose radiotherapy (RT; 24 to 30 Gy) for stage I to II disease remain free from relapse and are probably cured.[3-8] In the remaining patients, disease progression occurs, generally outside RT fields.[3-8] Although recurrent disease usually responds initially to salvage treatment with systemic therapy,[9] most patients eventually die with lymphoma.

Combined modality therapy (CMT) with sequential chemotherapy and RT achieves excellent outcomes in patients with early-stage Hodgkin lymphoma[10] and aggressive lymphomas,[11]

ASSOCIATED CONTENT

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Data Supplement

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including diffuse large B-cell lymphoma (DLBCL). CMT is an attractive but largely unexplored approach for localized FL. It is established that IFRT can reliably control local disease. If systemic therapy could control occult distant disease, improved long-term disease control would be achievable with CMT. A phase II trial from MD Anderson Cancer Center combining IFRT with 10 cycles of multiagent chemotherapy showed 10-year freedom from relapse (73%) and overall survival (OS; 79%) results superior to historical RT outcomes, supporting further investigation of CMT in stage I to II FL.[12,13]

The Trans-Tasman Radiation Oncology Group (TROG) developed an RCT (99.03; ClinicalTrials.gov identifier: NCT00115700) to investigate the hypothesis that IFRT plus systemic therapy could achieve superior PFS in stage I to II FL compared with IFRT. Patients were randomly allocated to IFRT or to IFRT followed by six cycles of cyclophosphamide, vincristine, and prednisone (CVP). From 2006 on, the anti-CD 20 antibody rituximab (R) was added to CVP (R-CVP).[14]

PATIENTS AND METHODS

This randomized, international, multicenter, phase III trial was conducted by TROG, the Australasian Leukaemia and Lymphoma Group, and Princess Margaret Hospital, Toronto, Canada. It was approved by the institutional review board at all centers. After written informed consent, patients were randomly allocated to either arm A (IFRT) or arm B (identical IFRT followed by six cycles of systemic therapy; Fig 1) by the Centre for Biostatistics and Clinical Trials at Peter MacCallum Cancer Centre. Randomization was stratified for center, stage, age (≤ 59 $v \geq 60$ years), and from 2006 on, positron emission tomography (PET) staging, using the minimization technique incorporating a random element. The protocol specified regular post-treatment follow-up visits and annual computed tomography imaging for at least 10 years (Data Supplement).

Sample Size Calculation

The initial target sample size was 200 patients, accrued over 5 years, with a power of 87% to detect a difference in 5-year PFS rates of 60% versus 75%. The sample size was later revised, as described in Results.

Eligibility and Exclusion Criteria

Eligible patients had FL (grade 1, 2, or 3a) diagnosed by surgical or core needle biopsy; Ann Arbor stage I to II; life expectancy $>$ 5 years; assessments by a radiation oncologist and medical oncologist/hematologist; and adequate hematologic and renal function. Computed tomography scanning, bone marrow aspirate, and trephine biopsies were minimum mandatory staging procedures. Staging with ^{18}F-labeled fluorodeoxyglucose–PET was permitted but not mandated. Previous RT or chemotherapy, prior malignancy (excluding nonmelanoma skin cancer), pregnancy, specified infective diseases, or thoracic disease too extensive for safe RT rendered patients ineligible.

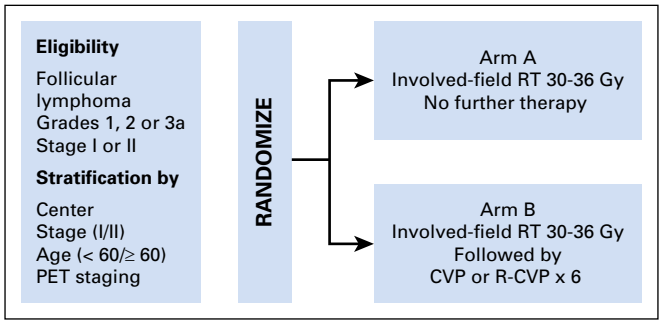

Fig 1. Trial schema. CVP, cyclophosphamide, vincristine, and prednisolone; PET, positron emission tomography; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisolone; RT, radiotherapy.

RT

The RT target volume included all known disease sites and all resected nodal and extranodal disease sites with a margin of at least 1 to 2 cm, depending on anatomic location. A craniocaudal margin of 5 cm was recommended if safely accomplishable. Inclusion of clinically uninvolved next-echelon lymph nodes was permitted. Small conformal treatment volumes were recommended at specified anatomic sites, such as orbit. Nonbulky sites received 30 Gy in 1.5 to 2 Gy fractions. Sites with a transverse diameter $>$ 5 cm received 36 Gy.

Systemic Therapy

Chemotherapy (plus rituximab after protocol amendment) was initiated 4 weeks after completing IFRT, with cycles repeated every 21 days for six cycles. Doses were cyclophosphamide 1,000 mg/m^2, vincristine 1.4 mg/m^2 (maximum 2 mg), and rituximab 375 mg/m^2 intravenously day 1, with prednisolone 50 mg/m^2 orally daily for days 1 to 5. If severe neutropenia occurred, prophylactic granulocyte colony-stimulating factor (pegfilgrastim or filgrastim) was recommended for all subsequent cycles without chemotherapy dose reduction.

Quality Control

The TROG RT quality assurance committee reviewed representative plans from each center. The number of cycles of systemic therapy actually delivered and dose reductions (if any) were recorded for patients in arm B. Although biopsies were submitted for central pathologic review, trial eligibility was based on original pathology reports.

Statistical Methods

Survival curves were analyzed using the Kaplan-Meier method. PFS was compared between arms using the Cox proportional hazards method; the prespecified primary analysis compared arms stratified by the minimization variables, stage, age, and PET. OS was compared using the log-rank test. Analysis of primary and secondary end points was based on intention to treat. Toxicity was scored using National Cancer Institute Common Toxicity Criteria version 2.0[15] and Radiation Therapy Oncology Group Acute and Late Morbidity Scoring Criteria.[16]

RESULTS

Between February 14, 2000, and July 20, 2012, 150 patients from 21 centers in Australia, New Zealand, and Canada were randomly assigned, 75 per arm. Because of slow accrual, an independent data monitoring committee–approved sample size revision was implemented in 2011, on the basis of an evaluation of trial events, blinded to study arm. Accrual ceased at 150 patients after 12.5 years. The resulting power was 71% to detect a PFS difference of 60% versus 75%, with a median follow-up of 5.8 years with a type I error of 0.05 and two-sided testing. The first planned analysis with a minimum potential follow-up of at least 3 years for all patients was performed in July 2016. Patient disposition is shown in the CONSORT diagram (Fig 2).

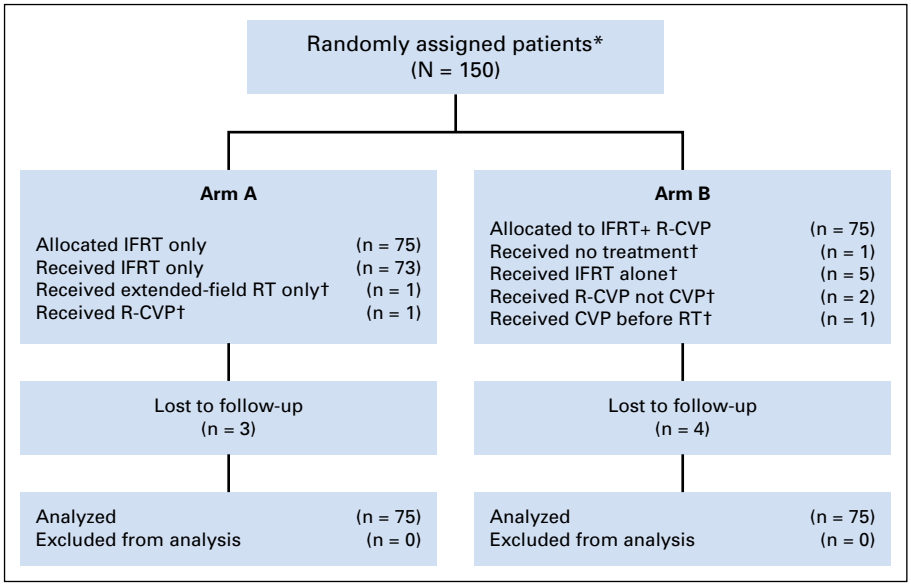

Fig 2. CONSORT diagram. (*) Eligibility infringements were identified postrandomization in three patients, namely, diagnosis established by cytology (arm A; n = 1), previous prostate cancer (arm B; n = 1), and upstaging to stage IIIA by positron emission tomography scan after random assignment (arm A [n = 1], in continuing remission after extended-field radiation). (†) Major deviations from protocol treatment were as follows: found to have more extensive disease after random assignment and received rituximab, cyclophosphamide, vincristine, and prednisolone (R-CVP) but not involved-field radiotherapy (IFRT; [arm A; n= 1]). Received wide-field radiation for extensive disease (arm A; n = 1). Randomly assigned to receive cyclophosphamide, vincristine, and prednisolone (CVP) actually received R-CVP (arm B; n = 2). Had no trial treatment and pursued alternative medicine but was included in follow-up (arm B; n = 1). Refused chemotherapy (arm B; n = 2). Did not receive chemotherapy because of rheumatic fever (arm B; n = 1); had no chemotherapy because of interstitial lung disease (arm B; n = 1); required hernia surgery and received no chemotherapy because of an unhealed wound (arm B; n = 1). Received chemotherapy before IFRT (arm B; n = 1). RT, radiotherapy.

Median potential follow-up time was 9.6 years (range, 3.1 to 15.8 years). Three patients in arm A were lost to follow-up at 8.3, 10.2, and 13.5 years, and four patients in arm B were lost to follow-up at 1.1, 7.4, 9.7, and 10.5 years. Potential prognostic factors, including age, stage, sex, bulky disease, and PET staging, were balanced between arms (Table 1). A higher proportion of grade 1 FL was observed in arm B than arm A. RT quality assurance reviews indicated excellent protocol compliance, with 92.78% of variables classified acceptable. Major and minor protocol variation rates were 1.59% and 1.19%, respectively.

Primary End Point: Progression-Free Survival

Progression-free survival (PFS), adjusted for the minimization variables, stage, PET, and age ≥ 60 years, was significantly superior in the IFRT plus R-CVP arm (arm B); 26 of 75 patients experienced disease progression or died, compared with 38 of 75 patients in the IFRT only arm (arm A; hazard ratio [HR], 0.57; 95% CI, 0.33 to 0.95; $P = .033$; Fig 3). Estimated 10-year PFS was 59% (95% CI, 46% to 74%) for arm B and 41% (95% CI, 30% to 57%) for arm A (PFS curves did not separate until approximately 5 years, and we have therefore quoted 10-year results). An analysis of PFS was performed by treatment period to evaluate the potential effect of rituximab (Fig 4). There was a significant difference in PFS between the 31 patients randomly assigned to IFRT plus R-CVP compared with the 31 patients contemporaneously randomly assigned to IFRT alone ($P = .045$, adjusted analysis; HR, 0.26; 95% CI, 0.07 to 0.97), favoring IFRT plus R-CVP. None of the 26 patients treated with R-CVP with follow-up beyond 3.5 years experienced relapse. In the prerituximab period, the HR was 0.70 (95% CI, 0.39 to 1.27; $P = .24$) for patients treated with RT plus CVP versus RT alone. A test for interaction indicated that these data were insufficient to demonstrate that R-CVP was superior to CVP ($P = .35$). Only two of 148 patients who received IFRT experienced isolated disease progression within the IFRT volume. In seven additional patients, progression was detected simultaneously, both inside and outside the irradiated volume. Of 11 local progressions, one (9.1%) occurred ≥ 5 years from randomization, compared with 14 of 49 (28.6%) distant progressions before 5 years (a difference of 19.5%; $P = .18$; 95% CI, 7.3% to 46.2%). Progression rates for the prerituximab period were one of eight for local and 12 of 38 for distant; for the rituximab period, they were zero of three for local and two of 11 for distant.

Predictors of PFS

Biologic factors associated with significantly superior PFS were fewer sites of nodal involvement ($P = .047$) and extranodal involvement ($P = .02$; Table 2). Extranodal sites were duodenum (n = 5), parotid (n = 2), breast (n = 2), subcutaneous (n = 1), tongue (n = 1), and bladder (n = 1). PET staging was associated with superior PFS (HR, 0.61; $P = .056$). Stage, histologic grade, infradiaphragmatic disease, bulky site, sex, and age were not associated with PFS on univariable analysis.

OS and Causes of Death

There were 10 deaths in arm A and five in arm B (HR, 0.62; $P = .40$; Fig 5). The 10-year OS rate was 86% in arm A and 95% in arm B. In arm A, causes of death were lymphoma (n = 5; one death with neutropenia after salvage chemotherapy), metastatic breast adenocarcinoma (n = 1), upper gastrointestinal adenocarcinoma (n = 1), bowel obstruction and peritoneal adenocarcinoma (n = 1), and unknown (n = 2). In arm B, causes of death were lymphoma (n = 1), myocardial infarction (n = 1), colorectal cancer (n = 1), unknown (n = 1), and myelodysplasia (in remission after IFRT plus CVP; n = 1).

Histologic Transformation

Transformation to aggressive lymphoma had occurred in 14 patients by last follow-up, with 10 and four patients detected in arms A and B, respectively ($P = .1$). In arm A, transformation occurred to DLBCL in nine patients and to Burkitt's lymphoma in

Table 1. Baseline Patient Characteristics

Characteristic	Arm B R-CVP + IFRT	Arm A IFRT only
All patients	(n = 75)	(n = 75)
Period		
Before rituximab amendment	44 (50)	44 (50)
After rituximab amendment*	31 (50)	31 (50)
Sex (P = .71)		
Male	40 (51)	38 (49)
Female	35 (49)	37 (51)
Median age, years	57	57
Stage		
I	56 (50)	57 (50)
II	19 (53)	18 (48)
PET staging		
No	40 (51)	38 (49)
Yes	35 (49)	37 (51)
Involved region		
Supradiaphragmatic	32 (42)	44 (58)
Infradiaphragmatic	43 (59)	30 (41)
Bulky disease (> 5 cm)		
No	65 (50)	64 (50)
Yes	10 (48)	11 (52)
Extranodal disease		
No	68 (49)	70 (51)
Yes	7 (58)	5 (42)
Histologic grade		
1	48 (62)	29 (38)
2-3a	26 (37)	44 (57)
Missing	1 (33)	2 (67)

NOTE. Data presented as No. (%).
Abbreviations: IFRT, involved-field radiotherapy; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisolone.
*All patients randomly assigned to receive rituximab received it.

one patient. In arm B, transformations were to DLBCL (n = 3) or unclassified aggressive B-cell lymphoma (n = 1).

Acute Toxicity of RT

In 148 patients who actually received IFRT, acute grade 1 to 2 toxicities were frequent, but grade 3 to 4 toxicities were rare (2%). Grade 2 toxicities experienced by > 10% of patients were upper gastrointestinal (n = 27; 18%), skin (n = 21; 14%), and mucous membrane (n = 19; 12%). One patient had grade 3 mucositis, and one patient had grade 4 esophageal/pharyngeal mucosal toxicity.

Acute Toxicity of Systemic Therapy

In the 69 patients in arm B who commenced systemic therapy, grade 1 to 2 toxicities were common. Grade 3 toxicities occurred on 35 occasions, and those affecting two or more patients were neutropenia (n = 1; 14%), infection (n = 8; 12%), and diarrhea, elevated gamma-glutamyl transferase, fatigue, and febrile neutropenia (n = 3; 4%) each. Acute grade 3 neuropathy related to vincristine was reported in three patients (4%). There were 10 patients with grade 4 neutropenia (14%).

Late Toxicities

Late toxicities recorded for more than one patient were salivary gland (n = 8; 5%) and skin (n = 4; 3%). Grade 3 lung and menopausal toxicities each affected single patients. Late grade 3 vincristine neuropathy was reported in two patients. One patient diagnosed with grade 3 neuropathy during chemotherapy subsequently progressed to grade 4 neuropathy.

DISCUSSION

To our knowledge, this is the first RCT providing high-level evidence that the long natural history of localized FL can be affected by adding systemic therapy to standard IFRT. In TROG 99.03, the PFS for study arms began to separate at approximately 5 years (Fig 3), which highlights the lack of power of shorter-duration studies. The British National Lymphoma Investigation (BNLI) trial, the only prior RCT ever successfully completed, showed no benefit from adding low-dose chlorambucil to RT.[17] Other RCTs comparing RT with CMT accrued ≤ 28 FL patients.[18-20] The FORT trial (ClinicalTrials.gov identifier: NCT00310167) compared two radiation doses (4 Gy *v* 24 Gy) and showed that 24 Gy provided superior long-term local disease control.[21] A previous large RCT had compared higher- and lower-dose RT in a range of lymphoma subtypes, including FL, and reported that 24 Gy and 40 to 45 Gy provided equivalent disease control.[22] As a result, 24 Gy has become a widely used standard dose, slightly lower than the 30 Gy selected for TROG 99.03, approximately 20 years ago.

During this trial, amendments addressed emerging advances in the treatment of FL. The first was stratification to ensure that ^{18}F-labeled fluorodeoxyglucose-PET staging was balanced between arms. Approximately 30% of patients with stage I to II disease are upstaged to stage III to IV by PET, and in an additional 14% of patients, RT volumes require modification.[23] As expected, PET-staged patients experienced superior PFS, likely related to stage migration. The second major change was to add rituximab to the systemic therapy arm, because rituximab-containing regimens achieved superior OS and PFS[24] in RCTs in advanced-stage FL.

PFS was significantly improved in TROG 99.03 by CMT (P = .033), with an overall difference at 10 years of 18% favoring the systemic therapy arm. However, the effect of systemic therapy was most dramatic in patients treated with R-CVP. At 5 years, PFS was approximately 30% better in the rituximab-containing arm, with a HR of 0.26 compared with contemporaneous patients treated with IFRT alone. No patient treated with R-CVP has yet relapsed beyond 3.5 years. The HR for IFRT plus CVP compared with RT alone was 0.70 (P = .24). A larger sample size would be required to confirm the apparent superiority of IFRT plus CVP over IFRT alone. R-CVP seemed to reduce both early (< 5 years) and late (> 5 years) relapses, whereas CVP only reduced later relapses (Fig 4). Only two patients with isolated in-field progression were recorded of 148 patients treated with IFRT, indicating that the trial dose of 30 Gy was sufficient for local disease control and that the primary effect of systemic therapy was to prevent distant relapse.

The excellent 10-year OS results in both arms (86% and 95% in arms A and B, respectively) were far superior to historical results

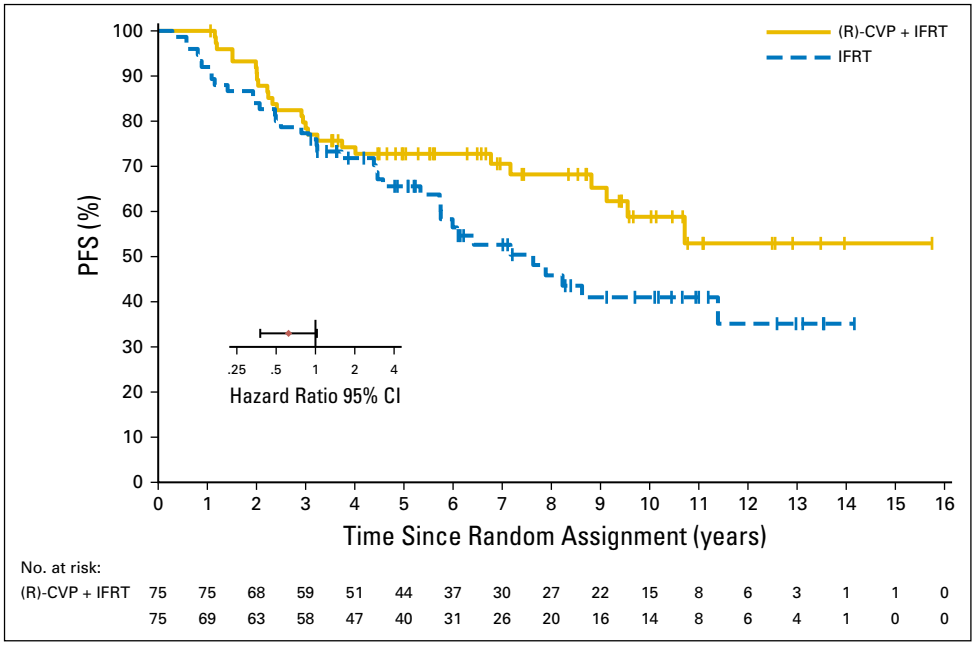

Fig 3. Progression-free survival (PFS) by treatment arm. CVP, cyclophosphamide, vincristine, and prednisolone; IFRT, involved-field radiotherapy; (R)-CVP, rituximab, cyclophosphamide, vincristine, and prednisolone.

(10-year OS was 64% in the 1996 Stanford University series),[4] although the relapse rate after IFRT was similar to earlier series. This could reflect more effective salvage therapies available for relapsed FL. There were twice as many deaths in the IFRT alone arm, but there is no significant difference between the arms to date. Additional follow-up is required to detect late potential differences in OS between the arms. Transformation to aggressive B-cell lymphoma commonly causes death in patients with FL. Bains et al[25] reported a 10-year transformation rate of 18.5% in stage I to II FL. In TROG 99.03, 10 transformations were observed after IFRT alone compared with only four after IFRT plus systemic therapy. A reduced histologic transformation rate in early-stage FL could improve both OS and quality of life.[26] Early and late radiation-related toxicity rates > grade 2 were extremely low, consistent with the known excellent tolerability of IFRT. There was predictably increased toxicity in the systemic therapy arm, especially neuropathy from vincristine, but in most cases, toxicity was mild and transient.

Strengths of this study include its randomized design, prolonged and near-complete follow-up, and the high proportion of PET-staged individuals. Weaknesses include prolonged accrual and the fact that R-CVP is being superseded at some centers by

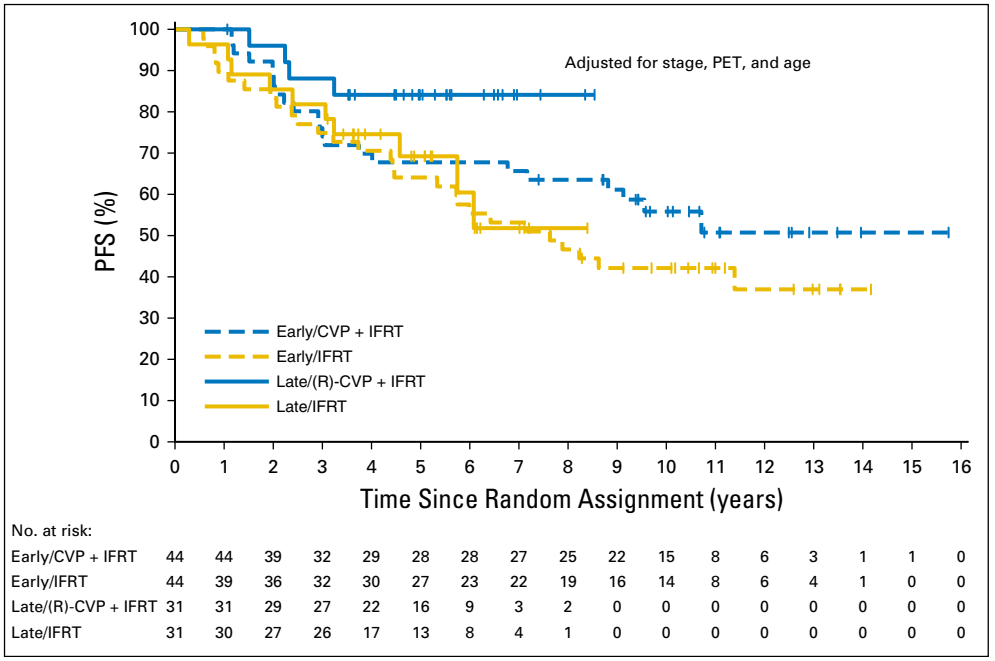

Fig 4. Progression-free survival (PFS) by period and treatment arm. CVP, cyclophosphamide, vincristine, and prednisolone; IFRT, involved-field radiotherapy; PET, positron emission tomography; (R)-CVP, rituximab, cyclophosphamide, vincristine, and prednisolone.

Table 2. Univariable Analyses of Prognostic Factors

Factor	No.	No. of Events	HR	95% CI	*P**	*P*†
Stage						
I	113	44			.17	.18
II‡	37	20	1.44	0.81 to 2.56		
Age					.59	.71
≤ 59	82	37				
≥ 60	68	27	0.87	0.53 to 1.43		
Sex						
Male	78	34			1.00	.90
Female	72	30	1.02	0.62 to 1.66		
Grade						
1	77	31	0.67		.11	.29
2 (excluding 3a)§	63	31	1.49			
Region						
Supradiaphragmatic	76	38	1.54	0.94 to 2.52	.091	.16
Infradiaphragmatic	73	25				
Bulky disease						
1	129	53			.34	.35
2	21	11	1.37	0.66 to 2.83		
No. nodal regions involved						
0	11	1	0.17		.19	.017
1	103	43	1		(trend)	
2-7	36	20	1.38			
Extranodal disease						
No	138	63			.020	.012
Yes	12	1	0.14	0.06 to 0.31		
PET for staging						
No	78	42			.056	.044
Yes	72	22	0.61	0.37 to 1.00		

Abbreviations: HR, hazard ratio; PET, positron emission tomography.
*Unadjusted for arm.
†Adjusted for arm.
‡Stage II includes one stage III.
§Three missing grades; patients with grade 3a (n = 7), all alive and progression free.

more modern regimens, including R-bendamustine, which is more effective than rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in advanced FL.[27]

Currently available approaches for stage I to II FL include watchful waiting, chemotherapy, single-agent rituximab, chemotherapy plus rituximab, radioimmunotherapy, and RT with or without systemic therapy. Although adding rituximab to CVP in TROG 99.03 seemed to increase the efficacy of the systemic therapy, single-agent rituximab is less effective than chemoimmunotherapy in advanced FL. Despite promising retrospective data suggesting that RT plus rituximab is superior to RT alone,[28] an RCT comparing RT plus rituximab with RT plus rituximab plus chemotherapy is required before concluding that chemotherapy should be omitted. Nevertheless, rituximab alone would be reasonable after IFRT for patients unable to tolerate chemotherapy. The 2010 analysis by Pugh et al[29(p3843)] of 6,568 patients from the SEER database with stage I to II FL concluded that "Upfront RT was associated with improved disease specific survival and OS compared with alternate management approaches, a benefit that persisted over time." Despite the efficacy of IFRT, early-stage FL is often treated in the community with chemotherapy and not RT. The results of TROG 99.03 indicate that multiagent chemotherapy, at least with R-CVP, is more toxic than RT and would be less appropriate than RT in stage I to II FL as a single modality.

In conclusion, this trial confirms that single-modality IFRT is safe, tolerable, and can cure a moderate proportion of patients with stage I to II FL. This trial also showed that six cycles of systemic therapy given after IFRT changed the natural history of the disease and significantly improved PFS, especially for patients receiving R-CVP. Longer follow-up is required to determine the effect of systemic therapy on OS. For patients with stage I to II FL who are treated with curative intent, we recommend treatment with IFRT followed by chemoimmunotherapy as a reasonable evidence-based choice for the standard of care. The combination of RT with more effective or less toxic systemic therapy regimens could potentially achieve superior results.

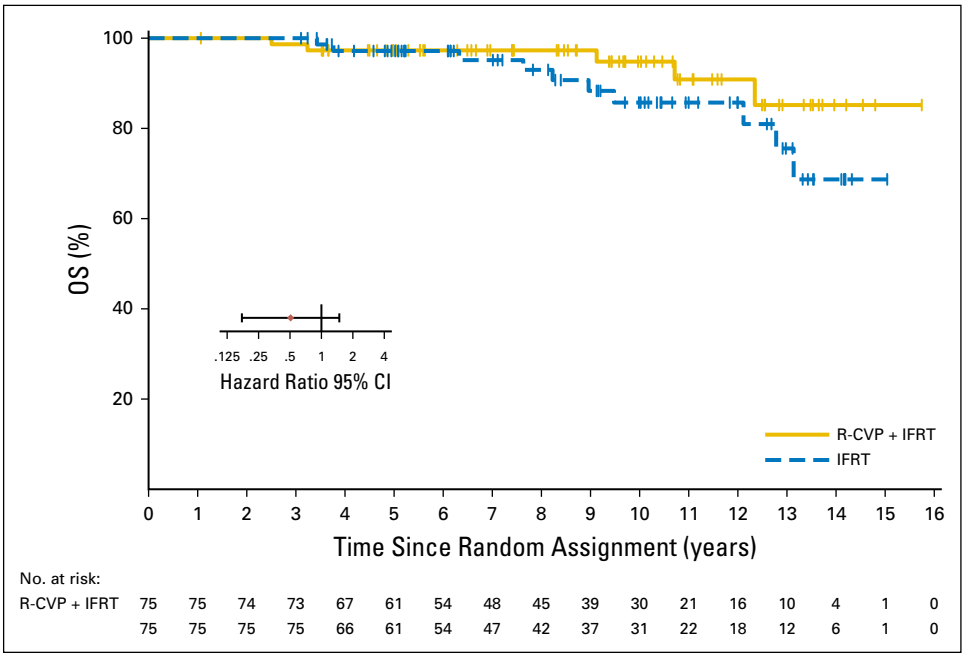

Fig 5. Overall survival (OS) by arm. CVP, cyclophosphamide, vincristine, and prednisolone; IFRT, involved-field radiotherapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Final approval of manuscript: All authors

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REFERENCES

1. Gandhi MK, Marcus RE: Follicular lymphoma: Time for a re-think? Blood Rev 19:165-178, 2005
2. Haas RL: Low dose radiotherapy in indolent lymphomas, enough is enough. Hematol Oncol 27: 71-81, 2009
3. Mac Manus MP, Hoppe RT: Overview of treatment of localized low-grade lymphomas. Hematol Oncol Clin North Am 11:901-918, 1997
4. 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. J Clin Oncol 14:1282-1290, 1996
5. 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 116: 3797-3806, 2010
6. Spry NA, Lamb DS, Vaughan Hudson G, et al: Localized grade I non-Hodgkin's lymphoma: Results of treatment with radiotherapy alone in 88 patients. Clin Oncol (R Coll Radiol) 1:33-38, 1989
7. Bush RS, Gospodarowicz M, Sturgeon J, et al: Radiation therapy of localized non-Hodgkin's lymphoma. Cancer Treat Rep 61:1129-1136, 1977
8. Gospodarowicz MK, Bush RS, Brown TC, et al: Prognostic factors in nodular lymphomas: A multivariate analysis based on the Princess Margaret Hospital experience. Int J Radiat Oncol Biol Phys 10: 489-497, 1984
9. Mac Manus MP, Rainer Bowie CA, Hoppe RT: What is the prognosis for patients who relapse after primary radiation therapy for early-stage low-grade follicular lymphoma? Int J Radiat Oncol Biol Phys 42: 365-371, 1998
10. Kelsey CR, Beaven AW, Diehl LF, et al: Combined-modality therapy for early-stage Hodgkin lymphoma: Maintaining high cure rates while minimizing risks. Oncology (Williston Park) 26:1182-1189, 1193, 2012
11. Verhappen MH, Poortmans PM, Raaijmakers E, et al: Reduction of the treated volume to involved node radiation therapy as part of combined modality treatment for early stage aggressive non-Hodgkin's lymphoma. Radiother Oncol 109: 133-139, 2013
12. Seymour JF, Pro B, Fuller LM, et al: Long-term follow-up of a prospective study of combined modality therapy for stage I-II indolent non-Hodgkin's lymphoma. J Clin Oncol 21:2115-2122, 2003
13. Seymour JF, McLaughlin P, Fuller LM, et al: High rate of prolonged remissions following combined modality therapy for patients with localized low-grade lymphoma. Ann Oncol 7:157-163, 1996
14. Marcus R, Imrie K, Belch A, et al: CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 105:1417-1423, 2005
15. Trotti A, Byhardt R, Stetz J, et al: Common toxicity criteria: Version 2.0. An improved reference for grading the acute effects of cancer treatment: Impact on radiotherapy. Int J Radiat Oncol Biol Phys 47:13-47, 2000
16. Cox JD, Stetz J, Pajak TF: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 31:1341-1346, 1995
17. Kelsey SM, Newland AC, Hudson GV, et al: A British National Lymphoma Investigation randomised trial of single agent chlorambucil plus radiotherapy versus radiotherapy alone in low grade, localised non-Hodgkins lymphoma. Med Oncol 11: 19-25, 1994
18. Nissen NI, Ersbøll J, Hansen HS, et al: A randomized study of radiotherapy versus radiotherapy plus chemotherapy in stage I-II non-Hodgkin's lymphomas. Cancer 52:1-7, 1983
19. Yahalom J, Varsos G, Fuks Z, et al: Adjuvant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy after radiation therapy in stage I low-grade and intermediate-grade non-Hodgkin lymphoma. Results of a prospective randomized study. Cancer 71:2342-2350, 1993
20. Monfardini S, Banfi A, Bonadonna G, et al: Improved five year survival after combined radiotherapy-chemotherapy for stage I-II non-Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 6:125-134, 1980
21. 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 15:457-463, 2014
22. 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 100:86-92, 2011
23. Wirth A, Foo M, Seymour JF, et al: Impact of [18f] fluorodeoxyglucose positron emission tomography on staging and management of early-stage follicular non-Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 71:213-219, 2008
24. Marcus R, Imrie K, Solal-Celigny P, et al: Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 26:4579-4586, 2008
25. Bains P, Al Tourah A, Campbell BA, et al: Incidence of transformation to aggressive lymphoma in limited-stage follicular lymphoma treated with radiotherapy. Ann Oncol 24:428-432, 2013
26. Pettengell R, Donatti C, Hoskin P, et al: The impact of follicular lymphoma on health-related quality of life. Ann Oncol 19:570-576, 2008
27. Rummel MJ, Niederle N, Maschmeyer G, et al: Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: An open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 381:1203-1210, 2013
28. 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 94:783-791, 2016
29. Pugh TJ, Ballonoff A, Newman F, et al: Improved survival in patients with early stage low-grade follicular lymphoma treated with radiation: A Surveillance, Epidemiology, and End Results database analysis. Cancer 116:3843-3851, 2010

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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