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## Salvage Treatment and Survival for Relapsed Follicular Lymphoma Following Primary Radiation Therapy

*A collaborative study on behalf of ILROG*

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Salvage treatment and survival for relapsed follicular lymphoma following primary radiotherapy: A collaborative study on behalf of ILROG

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## Salvage treatment and survival for relapsed follicular lymphoma following primary radiotherapy: A collaborative study on behalf of ILROG

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**Salvage treatment and survival for relapsed follicular lymphoma following primary radiotherapy: A collaborative study on behalf of ILROG**

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**ABSTRACT:**

**Purpose/Objective(s):**

We previously reported ~30% of patients with localized follicular lymphoma (FL) staged by  $^{18}\text{F}$ -FDG-PET-CT (PET-CT) receiving primary radiotherapy (RT) will relapse within 5 years. We sought to report outcomes for those who relapsed.

**Materials/Methods:**

We conducted a multicenter retrospective study of patients who received  $\text{RT} \geq 24\text{Gy}$  for stage I-II FL grade 1-3A FL, with age  $\geq 18$  years, and PET-CT staging. Observation was defined as  $>6$  months without treatment from relapse. Overall survival (OS) and freedom from progression (FFP) were estimated with Kaplan-Meier, and uni- and multivariable analyses (MVA) with Cox regression.

**Results:**

Of 512 patients with median follow up of 52 months, 149 (29.1%) developed recurrent lymphoma at a median 23 months (range, 1-143) after primary RT. Median follow up was 33 months post relapse. 3-year OS was 91.4% after recurrence. OS was significantly worse for those with relapse  $\leq 12$  months from

date of diagnosis versus all others, 88.7% versus 95.8%, respectively ( $p=0.01$ ), and remained significantly worse on MVA (FLIPI-adjusted HR=3.61,  $p=0.009$ ). Histology at relapse included: 93 indolent (grade 1-3A), 3 FL grade 3B/NOS, 18 diffuse large B-cell lymphoma (DLBCL); 35 patients were not biopsied. Of those with follow up  $\geq 3$  months and biopsied ( $n=74$ ) or presumed ( $n=23$ ) indolent recurrence, 58 patients (59.8%) were observed, 19 (19.6%) had systemic therapy, 16 (16.5%) RT, and 4 (4.1%) systemic therapy+RT. For patients with indolent recurrences that were observed, 3-year FFP or freedom from treatment was 56.6% (median, 48 months). For all patients with biopsied/presumed indolent recurrence receiving salvage treatment ( $n=59$ , including 20 initially observed) 3-year FFP was 73.9%.

**Conclusions:**

Prognosis for patients with relapsed FL following primary radiotherapy is excellent supporting the role of primary radiation in the management of early stage disease. Patients with localized FL treated with primary RT who experience early relapse ( $<12$  months) have inferior survival to those with longer disease-free interval.

**INTRODUCTION:**

For patients with localized follicular lymphoma (FL), primary radiotherapy may be curative, with historical cohorts demonstrating freedom from relapse of approximately 40-50% with long term follow up (1). We previously reported that with PET-CT staging, the curative potential of definitive radiotherapy is likely to be higher than previously thought, with 5-year freedom from progression of approximately 74% for stage I and 49% for stage II (2). However, 30-50% of patients will develop relapse, and the optimal management for relapsed follicular lymphoma is not well defined.

Repeat radiotherapy may be an option in the uncommon setting of local recurrence, which occurs <10% of the time after definitive radiotherapy, or for limited relapse, i.e., 'relapse stage I-II'. Clinical judgement is crucial in identifying patients eligible for repeat definitive radiotherapy,  $\geq 24$  Gy, which is reasonable for treatment of local/marginal recurrence or for localized relapse encompassing a limited RT field assuming they responded initially to primary RT (3, 4).

In the vast majority of cases, relapsed FL after definitive radiotherapy occurs distantly (outside of the prescribed dose volume) at which point management is frequently adapted from that of *de novo* advanced stage disease. This may include observation, rituximab monotherapy, and immunochemotherapy (5, 6). Additionally, low dose radiotherapy offers high local control for symptomatic sites



of involvement (7). The challenge in managing these patients lies in identifying those who will have indolently behaving disease appropriate for observation versus those that will have an aggressive course. However, there is mounting evidence that patients with stage III-IV follicular lymphoma who develop progressive disease within 1-2 years after diagnosis have inferior survival compared to others (8, 9). It is not clear if early progression has the same significance in early stage disease treated with RT.

Given limited data, particularly from the rituximab era, we sought to evaluate outcomes following relapse for a large cohort of patients treated with definitive radiotherapy alone for early stage follicular lymphoma.

## **METHODS/MATERIALS:**

### **Patients**

We conducted a multi-institutional retrospective review under the sponsorship of the International Lymphoma Radiation Oncology Group (ILROG). Following individual institutional review board (IRB) approvals, 16 centers submitted de-identified patient cases meeting our prospectively defined inclusion criteria: 1) grade 1-3A follicular lymphoma, 2) stage I-II, 3) staging that included  $^{18}\text{F}$ -fluorodeoxyglucose PET-CT, 4) RT dose equivalent to at least 24 Gy/12 fractions, 5) post-treatment follow up of  $\geq 3$  months, and 6) no prior radiotherapy or systemic therapy. We collected detailed baseline characteristics and primary radiotherapy details as reported previously including the follicular lymphoma

international prognostic index (FLIPI, which includes age, >4 nodal sites, LDH elevation, serum hemoglobin < 12 g/dL, and advanced stage) (2).

### **Relapse, salvage treatment and outcomes assessment**

We collected detailed information at time of relapse, including: method of detection (clinical symptoms, physician exam, radiographic detection), age at recurrence, location of recurrence including relation to radiotherapy volume (local, marginal at or near RT edge, or distant outside of the prescribed dose field), biopsy status and pathology of recurrence, salvage treatment, and response to salvage treatment by clinical and when available radiographic assessment. Limited recurrence was defined as 1-2 sites of involvement (Ann Arbor nodal or extranodal) or extent of disease suitable for radiation monotherapy. Observation was defined as >6 months from relapse without treatment. Progressive disease was scored by clinical, radiographic or pathologic evidence. Lymphoma refractory to initial primary RT was defined as recurrence within the RT prescription dose volume without having achieved clinical or radiographic response within 6 months post-treatment.

### **End points and outcomes assessments**

We measured OS for all patients with relapse from date of recurrence. To evaluate the impact of early relapse, we compared overall survival (OS) for those

experiencing relapse within 12- and 24-months versus all others (8, 9). For this analysis, OS time was measured from date of relapse or 12- and 24-months after pathologic diagnosis to avoid immortal time bias as per methods by Casulo et al. (9). There was no competing risk of death within 24 months from initial diagnosis to progression or relapse event.

For patients with follow up  $\geq 3$  months following diagnosis of relapse, we measured freedom from progression or next treatment as the time interval from date of clinical, radiographic or pathologic recurrence for those observed and date of treatment completion for those receiving salvage treatment.

### **Statistical analyses**

We used the Kaplan-Meier method to measure FFP or time to next treatment and OS with stratification evaluated with the log-rank test. When measuring FFP, only 4 deaths occurred prior to an additional progression event (only 2 prior to 3 years of follow up) representing minimal competing risk with insignificant impact on our estimate of FFP. We did not statistically compare FFP for subgroups receiving observation, lower intensity treatment (rituximab monotherapy or low dose radiation), or intense treatment (definitive radiation or chemotherapy) as full baseline patient factors at time of relapse were not available nor was the justification for selected treatment decision. Univariable and multivariable hazard ratios (HR) were calculated using Cox regression analysis with corresponding Wald 95% confidence intervals (95% CI) and p-values. We conducted

multivariable analyses for patient factors meeting significance of  $p < 0.05$  on univariable analysis without exceeding approximately 1 variable per 10 events in each model. Statistical analysis was performed using SAS version 9.3 (SAS institute, Cary, North Carolina) and R version 3.4 (Vienna, Austria). All p-values were two-sided, and considered significant at  $p < 0.05$ .

## RESULTS:

### Overall survival after relapse

Of 512 patients with median follow up of 52 months, 149 (29.1%) developed relapsed lymphoma at a median 23 months (range, 1-143) after primary RT (**Figure 1**). The 3-year OS for patients with relapse after primary RT was 91.4% (**Figure 2A**, 95% CI=84.9-95.2%) with 16 deaths occurring during follow up (n=8 lymphoma specific deaths, n=3 other causes, and n=5 unknown). Median follow up was 33 months post relapse. 137 (91.9%) recurrences occurred outside of the prescription treatment volume at distant sites. Histology at the time of relapse included: 93 indolent (n=89 follicular lymphoma grade I-IIIa, n=2 primary cutaneous follicle center lymphoma, n=1 nodal marginal zone lymphoma), 3 FL grade 3B/NOS, 18 diffuse large B-cell lymphoma (DLBCL); 35 patients were not biopsied. Thus, we observed that 19 of 149 patients (12.8%) with relapsed lymphoma had biopsy proven large cell transformation to DLBCL (including one patient that initially had low grade recurrence at first relapse).

We compared survival for patients with early relapse versus all others. As demonstrated in **Table 1**, patients with relapse  $\leq 12$  months were more likely to have initial stage II FL ( $p=0.01$ ) and higher ECOG performance score ( $p=0.03$ ) but no difference in age, gender or FLIPI. No patient in this analysis had recurrent lymphoma refractory to initial primary RT (see Methods/Materials section for definition of refractory). As **Figure 2B** demonstrates, 3-year OS was significantly worse for those with relapse  $\leq 12$  months ( $n=28$ ) versus no relapse  $\leq 12$  months ( $n=468$ ) from date of diagnosis, 88.7% (95% CI=69.0-96.2%) versus 97.6% (95% CI=95.4-98.8%), respectively ( $p=0.01$ ). This association persisted for those recurring within 2 years of diagnosis with significantly worse 3-year OS for those with relapse  $\leq 24$  months ( $n=69$ ) versus no relapse  $\leq 24$  months ( $n=377$ ), 91.8% (95% CI=81.4-96.5%) versus 97.0% (95% CI=94.0-97.5), respectively (**Figure 2C**,  $p=0.048$ ).

We next performed univariable and multivariable Cox regression comparing survival for patients with relapse  $\leq 12$  months versus all others. On univariable analysis, FLIPI (HR=1.99, 95% CI=1.13-3.51,  $p=0.02$ ) and relapse  $\leq 12$  months (HR=3.39, 95% CI=1.36-8.47,  $p=0.009$ ) were significantly associated with survival. On MVA, both FLIPI (HR=2.00, 95% CI=1.13-3.52,  $p=0.02$ ) and relapse  $\leq 12$  months (HR=3.61, 95% CI=1.38-9.45,  $p=0.009$ ) significantly associated with survival. We did not observe significant association on univariable analysis between overall survival and gender, initial stage, or ECOG PS. Although we observed similar findings on univariable analysis for patients with relapse  $\leq 24$

months, the FLIPI-adjusted multivariable model showed only trend between relapse  $\leq 24$  months and OS (**Table 2**).

### **Outcomes for patients with indolent relapse and follow up $\geq 3$ months**

97 patients had biopsied (n=74) or presumed (n=23) indolent recurrence and follow up  $\geq 3$  months (median follow up 36.9 months). Notably, only 1 patient who relapsed within 12 months of diagnosis was lost to follow up. Baseline characteristics are summarized in **Table 1** and patients were managed as follows: 58 (59.8%) observation, 19 (19.6%) systemic therapy, 16 (16.5%) RT, and 4 (4.1%) systemic therapy and RT. For many cases, radiographic details provided by individual institutions at time of relapse were limited. For example, as listed in **Table 1**, the total number and location of nodal and extranodal sites involved with relapsed lymphoma were not available for 28.9% of cases.

There was no difference in OS between patients who received immediate salvage treatment versus observation ( $p=0.28$ ). Additionally, there was no significant survival difference for patients who had relapse  $\leq 12$  months who underwent immediate treatment versus those who were observed (log-rank  $p=0.34$ ). As shown in **Figure 3A**, 3-year FFP and/or freedom from treatment was 82.3% (95% CI=64.4-91.8%) for those who received immediate salvage treatment (n=39) and was 56.6% (95% CI=40.5-69.9%) for those selected for observation (n=58). The FFP estimates for the subset of patients with relapse within 12 months were similar: 83.3% (95% CI=27.3-97.7%) for those who

received immediate salvage treatment (n=6) and 42.3% (95% CI=13.8-69.1%) for those selected for observation (n=14). There was no significant difference in age, gender, localized relapses, biopsy status, or symptoms between subgroups (Supplemental Table 1). For those observed, median time to treatment or progression was 48 months (range, 8-56) with 20 receiving salvage treatment at a median of 21 months with continued observation for the remainder.

For all patients with indolent recurrence receiving salvage treatment (n=59), 3-year FFP was 73.9% (95% CI=58.8-84.2%). 35 completed intensive treatment with 3-year FFP of 94.7% (95% CI=68.1-99.2%) (**Figure 3B**). Intensive treatment included the use of definitive radiotherapy for localized recurrence (n=14 with RT $\geq$ 24 Gy), rituximab (R)-chemotherapy (n=2 with 8 cycles R-cyclophosphamide/vincristine/prednisolone [R-CVP], n=5 with 6 cycles R-cyclophosphamide/hydroxydaunorubicin/oncovin/prednisolone [R-CHOP] with maintenance R for n=4, n=1 with R-zevalin, n=1 with 5 doses of anti-CD20 vaccine trial, n=6 with 6 cycles R-bendamustine, n=2 with 6 cycles R-CVP, n=1 with 6 cycles R-lenalidomide), or systemic therapy and RT (n=1 with R-CHOP+39.6 Gy, n=1 with 4 doses of rituximab+30 Gy, n=1 with R-CVP+21 Gy). Only 2 patients who received intensive treatment developed second recurrence during median follow up of 33 months (range 3.3-87.8). 24 patients received more palliative therapy with RT<24 Gy or rituximab alone (n=8 with RT<24 Gy, n=1 with rituximab+4 Gy, and n=15 with rituximab monotherapy with median of 4 doses, range 4-24) with 3-year FFP of 51.7% (95% CI=29.4-70.1%) (**Figure 3B**). There was no significant difference in age, gender, limited recurrences, biopsy

status, or symptoms between subgroups (**Supplemental Table 2**), but there was a significantly lower rate of distant relapse in the cohort receiving intensive treatment corresponding with the small number of patients salvaged with local recurrence ( $p=0.01$ ). We did not observe significant association between age, gender, relapse  $\leq 12$  months, patient symptoms, limited recurrence, or imaging detected recurrence and the outcome FFP (**Supplemental Table 3**).

Of those with localized recurrence, 8 patients had isolated local ( $n=6$  within prior high dose RT field) or marginal ( $n=2$ , at high dose RT field edge) recurrences at a median of 19.2 months following primary RT (range 15-58.9). All 8 patients initially had a complete response either clinically ( $n=2$ ), by CT ( $n=1$ ), or PET-CT ( $n=5$ , all with complete metabolic and size response) within 6 months of completing treatment. 4 were initially observed with 2 ultimately receiving salvage treatment at 9 and 10 months with 24 Gy and 6 cycles R-CHOP, respectively, without further progression. The other 4 patients underwent immediate treatment with radiotherapy alone ( $n=2$ , 36 Gy), radiotherapy (24 Gy) with rituximab, and 6 cycles of R-CHOP. None of the 6 patients who received salvage treatment for local and marginal recurrence had subsequent progression during follow up.

#### **Outcomes for patients with high grade recurrence and large cell transformation and follow up $\geq 3$ months**

2 patients with follow up  $\geq 3$  months developed grade 3B relapsed FL. One was observed with 32 months of follow up without progressive disease and the



other received 6 cycles of R-CHOP with partial response by CT imaging and subsequently received high dose chemotherapy followed by bone marrow transplant 6 months after relapse.

10 patients experienced large cell transformation to DLBCL with follow up  $\geq 3$  months and received salvage treatment (n=5 with 6 cycles of R-CHOP, n=1 with 8 cycles R-CVP, n=1 with 6 cycles of R-CHOP and 4 Gy, n=1 2 cycles R-CHOP and 3 cycles R-etoposide/prednisone/oncovin/cyclophosphamide/hydroxydaunorubicin, n=1 with unknown systemic therapy and 30 Gy, and n=1 enrolled on an anti-CD20 vaccine trial) from which 6 remain disease free with median follow up of 28 months (range, 6.4 – 74.0). 1 patient experienced transformation to DLBCL after initially being observed for biopsy proven low grade relapsed FL for 14 months at which point she received low dose radiotherapy (4 Gy) with transformation occurring 30 months after radiotherapy.

### **Discussion:**

Taken together with our prior report (2), our results demonstrate that a third of patients with predominantly stage I follicular lymphoma will develop relapse after primary radiotherapy but for whom overall survival is excellent in the modern era. The excellent prognosis observed for this relapse cohort emphasizes that primary radiation for localized follicular lymphoma is an excellent treatment option. Although the recently reported randomized TROG 9903 trial showed

progression free survival benefit for patients receiving adjuvant rituximab based chemotherapy after radiation for early stage follicular lymphoma (10), given the excellent prognosis, including that for those with relapse, adjuvant systemic therapy may lead to overtreatment for many patients.

In our cohort, treatment strategy for those with indolent recurrence varied widely and with short follow up, we were unable to detect differences in survival with each approach. Thus, any decision to offer treatment at time of relapse must be weighed with the risk of acute and late adverse effects. Greater than 60% of patients in our cohort with indolent recurrence who underwent salvage treatment received rituximab, likely contributing to the excellent outcomes. However, nearly 60% of patients with indolent recurrence who were observed did not have disease progression nor receive treatment within 3 years. For those with low grade and indolent behaving follicular lymphoma, patients selected for intensive treatment with definitive radiotherapy or immuno-chemotherapy enjoyed a durable response. Although patients in our series had a limited median follow up of ~3 years, large historical cohorts demonstrate the majority of recurrences occur within 3-5 years after salvage treatment (11, 12). Additionally, surrogate endpoints in identifying relapse earlier than clinical or radiographic progression are being investigated for which our data may inform further study design (13).

Large studies investigating management and outcomes for patients with recurrent follicular lymphoma after primary RT in the rituximab era are not available. In a pre-rituximab cohort from Stanford, 70.9% were identified as relapse stage I-II (11), with increasing age,  $\geq 3$  relapse sites associated with

worse FFP. In our series, we were unable to identify patient factors at relapse associated with worse FFP. Rituximab was given to more than half of the patients in our series, which may in part explain why variables such as widespread recurrence ( $\geq 3$  relapse sites) were not associated with subsequent progression. In the Stanford series, increasing age, transformation, and  $\geq 3$  sites were significantly associated with worse OS in multivariable model. Another pre-rituximab era large single institution series showed increasing age and number of prior treatments was associated with worse OS (12). The survival following relapse for patients in our cohort was excellent, 91.4% at 3 years, and did not differ for patients with low grade relapse based on management strategy. Although subset OS for patients with initial stage I FL who relapse in the LymphoCare study is not readily available, our results are consistent with the OS rate for all patients in the LymphoCare cohort with stage I FL who underwent PET-CT staging ( $>90\%$  at 5 years) (14).

Given the indolent nature of FL, observation is typically offered in the de novo advanced stage or relapse setting. In a randomized controlled trial comparing watchful waiting to rituximab monotherapy in patients with low grade and low volume follicular lymphoma, approximately half of those being observed underwent treatment with systemic therapy (4% of which included rituximab monotherapy) or radiotherapy at 3 years of follow up compared with only 12-22% receiving induction or maintenance rituximab (5). Our results are similar. Among the 60% of patients selected for observation in our cohort, only about 1/3 required treatment within 3 years. Additionally, there is evidence that patients

with FL selected for observation do not have a higher rate of transformation compared to those who receive immediate treatment (15). Although our cohort has limited follow up, only one patient experienced large cell transformation following observation and was salvaged with rituximab-chemotherapy. Thus, observation may be a reasonable option for appropriately selected patients with the understanding that treatment may be likely, even during short term follow up.

Despite evidence that an initial observation period for low grade, advanced stage follicular lymphoma, is not associated with a detriment to overall survival, patients with early progression have been found to have inferior survival (6, 16). This finding was also seen in a cohort of patients with FL managed with observation, rituximab monotherapy, and rituximab-chemotherapy, where Mauer et al. reported that patients without relapse within 12 months of diagnosis have mortality equivalent to an age and sex matched general population cohort (8). We also observed that patients in our cohort with early progressive disease from date of diagnosis ( $\leq 12$  or  $\leq 24$  months) had significantly inferior survival to those with longer disease free interval. Our results are similar to the results seen in the LymphoCare study for patients with stage II-IV FL which showed 5 year OS of 50% for those experiencing early progression of disease versus 90% for the reference group (9). We have validated prior evidence suggesting early progression is an adverse prognostic factor following relapse after primary radiation for early stage FL. We do note that the magnitude of our HR=3.39 for relapse  $\leq 12$  and worse survival was smaller than that observed for the cohort from the LymphoCare study (HR=4.86-8.19), likely reflecting the more favorable

patient population in our cohort. Importantly, we found that patients with early progressive disease had no difference in response to salvage treatment. Additionally, given our short follow up, small number of transformation events, and results, it is unclear if immediate or intense treatment translates into a disease specific survival benefit. For patients with stage II-IV FL enrolled in the FL2000 trial, there was event free and overall survival benefit for patients who underwent autologous stem cell transplant at time of first relapse (17).

For the rare cases where patients develop local or marginal recurrence relative to the initial RT field, reirradiation with definitive radiotherapy may be considered. 6 patients in our cohort who underwent reirradiation for marginal or local recurrence all had complete response, similar to results reported by others (3). Additionally, salvage treatment with definitive radiotherapy alone for selected patients with localized recurrence may allow for delay of systemic therapy, including rituximab. This may be potentially advantageous given reports of lower response rate for patients with transformed FL and DLBCL treated with repeat courses of rituximab (18). Results for patients in our series undergoing reirradiation complement the 2014 ILROG guidelines for patients with advanced stage indolent NHL (4).

Our study has several limitations including limited details regarding toxicity, incomplete re-staging at relapse (including lack of biopsy confirmation for 35 patients [23% of those with relapse], LDH, exact number of nodal sites involved by relapse, and hemoglobin), 42 patients without follow up after relapse (28% of patients with relapse), and short follow up. The end point FFP or freedom from

next treatment and the number of patients who did not undergo biopsy of recurrence may over-estimate the percent of patients with progressive FL, particularly those being observed. Although long-term follow up is crucial for assessing outcomes for FL, studies reported prior to implementation of rituximab have shown the majority of recurrences occur within 3-5 years after salvage treatment (11, 12). At the very least, our results are hypothesis generating in providing early outcomes for those with relapsed lymphoma following primary radiotherapy for localized FL.

Our results highlight that patients with stage I-II follicular lymphoma who are treated with curative radiotherapy and experience subsequent relapse have an excellent survival. However, our results also suggest that patients who relapse within 1-2 years have worse prognosis, which may aid in the decision as to whether or not to offer salvage treatment as opposed to observation.

#### **FIGURE LEGENDS:**

**Figure 1. Flow diagram for patient cohort.**

**Figure 2. Overall survival (OS) for patients with relapsed lymphoma following primary radiation for early stage follicular lymphoma.** A. KM curve shows 3-year OS rate of 91.2% for patients with relapsed lymphoma. B. KM curve shows 3-year OS was significantly worse for those with relapse  $\leq 12$  months from date of diagnosis versus others (reference group), 88.7% versus 97.6%, respectively. C. KM curve shows 3-year OS was significantly worse for

those with relapse  $\leq 24$  months from date of diagnosis versus others (reference group), 91.8% versus 97.0%, respectively.

**Figure 3. Freedom from progression (FFP) for patients with indolent recurrence and follow up  $\geq 3$  months stratified by management type.** A. FFP by initial treatment for indolent relapse. B. 3-year FFP was 94.7% for patients selected for intensive salvage treatment, with 3-year FFP 51.7% for those selected for RT  $< 24$  Gy or rituximab monotherapy.

**Table 1.** Patient characteristics for those with and without relapse  $\leq 12$  months

**Table 2.** Uni- and multivariable analysis comparing overall survival for patients with early relapsed follicular lymphoma following primary radiotherapy for localized disease versus all others.

**Table 3.** Patient characteristics for those with follow up  $\geq 3$  months at time of relapse.

**Supplemental Table 1. Comparison of baseline characteristics for patients with indolent relapse after primary RT undergoing observation versus immediate treatment (n=97).**

**Supplemental Table 2. Comparison of baseline characteristics for patients with indolent relapse after primary RT undergoing salvage treatment (n=59).**

**Supplemental Table 3. Univariable analysis of prognostic factors for patients with indolent recurrence and with follow up  $\geq 3$  months at time of relapse.**

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ACCEPTED MANUSCRIPT

**Table 1.** Patient characteristics for those with and without relapse  $\leq 12$  months

Parameter	Relapse $\leq 12$ months (n=28)	No relapse $\leq 12$ months (n=468)	p-value
Median age	62 (35-83)	59 (20-90)	0.29
Male	12 (42.9%)	241 (51.5%)	0.37
Initial stage I	17 (60.7%)	378 (80.7%)	0.01
ECOG PS, median	0 (0-1)	0 (0-2)	0.03
0	21 (75.0%)	431 (92.1%)	
1	7 (25.0%)	35 (7.5%)	
2	0 (0%)	2 (0.4%)	
FLIPI, median	1 (0-3)	1 (0-2)	0.61
0	12 (42.9%)	230 (49.1%)	
1	15 (53.8%)	204 (43.6%)	
>1	1 (3.6%)	34 (7.3%)	

*Abbreviations:* ECOG PS=Eastern cooperative oncology group performance status; FLIPI=Follicular lymphoma international prognostic index.

\* **Continuous variables are shown with range and categorical variables with percentages in parenthesis**

**Table 2.** Uni- and multivariable analysis comparing overall survival for patients with early relapsed follicular lymphoma following primary radiotherapy for localized disease versus all others.

Group		Overall survival		
		Model	≤12 months	≤24 months
No early relapse	Deaths/total		19/468	16/377
Early relapse	Deaths/total		5/28	8/69
	HR	<b>Unadjusted</b>	<b>3.39</b>	<b>2.52</b>
	95% CI		<b>1.36-8.47</b>	<b>1.08-5.91</b>
	p		<b>0.009</b>	<b>0.03</b>
	HR	<b>FLIPI-adjusted (MVA)</b>	<b>3.61</b>	2.20
	95% CI		<b>1.38-9.45</b>	0.92-5.28
	p		<b>0.009</b>	0.08

Abbreviations: HR=Hazard ratio; CI = confidence interval; FLIPI=follicular lymphoma international prognostic index; MVA=Multivariable analysis including FLIPI and relapse ≤12 months.

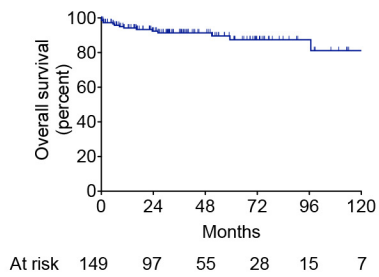
**Table 3.** Patient characteristics for those with low grade recurrence and follow up  $\geq 3$  months from date of relapse.

<b>Parameter</b>	<b>Cohort (n=97)</b>
Median age	61 (26 - 87) years
Male	52 (53.6%)
Biopsy confirmed	
Yes	74 (76.3%)
No (presumed low grade)	23 (23.7%)
Clinical symptoms	25 (25.8%)
Failure relative to RT field	
Local (within RT field)	6 (6.2%)
Marginal (at field edge)	2 (2.1%)
Distant (outside RT field)	89 (91.8%)
Number of relapse sites	
Limited (1 or 2 sites)	45 (46.7%)
Advanced (>2 sites)	24 (24.7%)
Unknown	28 (28.9%)
Initial salvage treatment	
Observation	58 (59.8%)
RT alone	16 (16.5%)
<24 Gy	4 (4.2%)
$\geq 24$ Gy	12 (12.5%)
Rituximab monotherapy	8 (8.3%)
Rituximab + RT (4, 24, 30 Gy)	3 (3.1%)
Rituximab + chemotherapy	11 (11.5%)
R-Chemo + RT (21 Gy)	1 (1.0%)
Median follow up from initial failure	36.9 (4.3 – 150.5) mo.

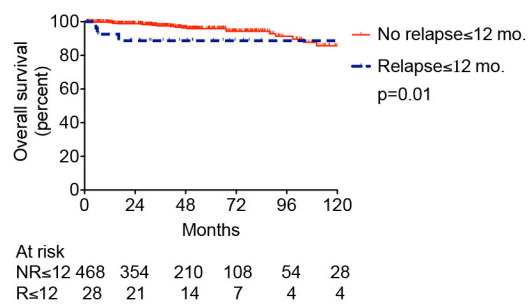
*Abbreviations:* NOS=not otherwise specified., mo.=months

\* **Continuous variables are shown with range and categorical variables with percentages in parenthesis**

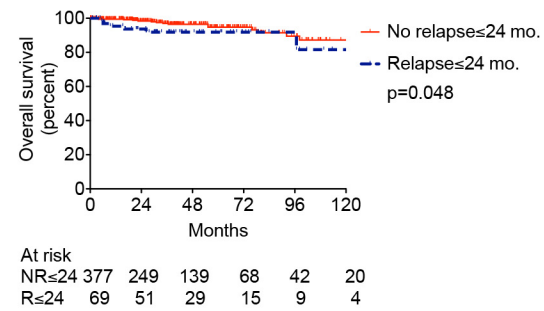
A



B



C

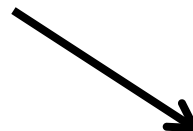
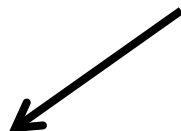




Stage I-II FL staged by PET/CT, n=512



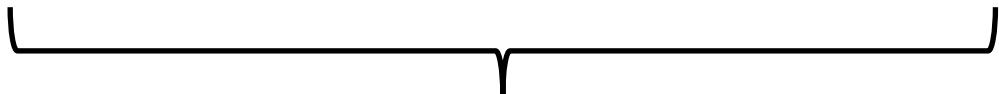
149 pts with relapse:  
n=92 indolent recurrence  
n= 35 un-biopsied  
n=22 transformed



Observation, n=59  
n = 42 indolent  
n = 16 un-biopsied  
(*n = 20 ultimately received treatment*)  
n = 1 transformed

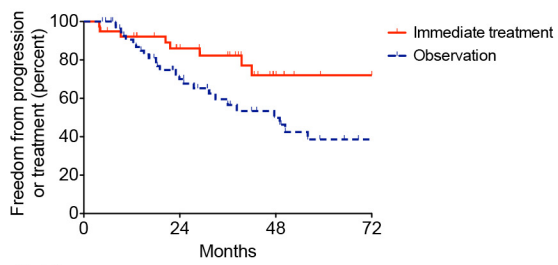
Immediate tx, n=48  
n = 32 indolent  
n = 7 un-biopsied  
n = 9 transformed

Lost to follow up, n=42  
n = 19 indolent  
n = 12 un-biopsied  
n = 11 transformed



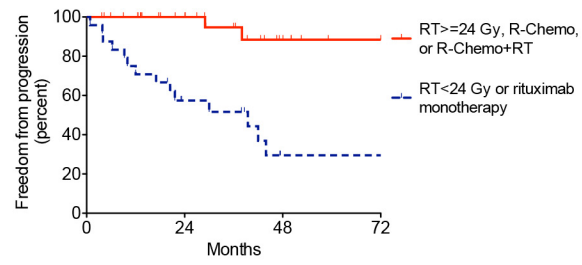
n=59 indolent and received salvage tx

A



At risk				
Obs.	58	31	15	8
Tx	39	26	10	4

B



At risk				
Solid	35	24	10	4
Dashed	24	11	3	3

**SUMMARY:**

In the modern era, survival for patients with relapsed follicular lymphoma after primary radiotherapy for initially localized disease is excellent. Although there are many acceptable treatment strategies for relapse, including observation, patients with recurrent lymphoma less than 12 months from diagnosis after primary radiotherapy appear to have significantly worse OS. Our results may aid in the decision to offer treatment immediately following relapsed lymphoma after primary radiotherapy for localized follicular lymphoma.