Definitive radiotherapy for localized follicular lymphoma staged by 18F-FDG PET-CT: a collaborative study by ILROG

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Running title:

Definitive radiotherapy for follicular lymphoma

KEY POINTS

Outcome following radiotherapy for stage I and localized stage II follicular lymphoma after PET-CT staging is better than historical series.

More than two-thirds of patients remain in remission at 5 years and most relapses occur in distant sites.

ABSTRACT

Radiotherapy (RT) can be curative in patients with localized follicular lymphoma (FL), with historical series showing a 10-year disease-free survival of 40-50%. As ^{18}F-FDG PET-CT upstages 10-60% of patients compared to CT, we sought to evaluate outcomes in patients staged by PET-CT, to determine if more accurate staging leads to better patient selection and results.

We conducted a multicenter retrospective study. Inclusion criteria were: RT alone for untreated stage I-II FL (grade 1-3A) with dose equivalent $\geq$24 Gy, staged by PET-CT, age $\geq$18 years, and follow up $\geq$3 months. Endpoints were freedom from progression (FFP), local control, and overall survival (OS). FFP and OS were estimated with Kaplan-Meier, and uni- and multivariable analyses of prognostic factors performed with Cox Regression.

512 patients treated from 2000-2017 at 16 centres were eligible for analysis. Median age was 58 years (range 20-90). 410 patients (80.1%) had stage I disease. Median RT dose was 30 Gy (24-52). Median follow up was 52 months (3.2-174.6). 5y-FFP and OS were 68.9% and 95.7%. For stage I, 5y-FFP was 74.1%, vs 49.1% for stage II ($p<0.0001$). 8 patients relapsed infield (1.6%).4 had marginal recurrences (0.8%) resulting in local control rate of 97.6%. On multivariable analysis, stage II (HR=2.11, 95%CI=1.44-3.10) and BCL2 expression (HR =1.62, 95%CI 1.07-2.47) were significantly associated with less favorable FFP.

Outcome after RT in PET-CT staged patients appears to be better than in earlier series, particularly in stage I disease, suggesting that the curative potential of RT for truly localized FL has been underestimated.

INTRODUCTION:

Follicular lymphoma (FL) is the most common form of indolent non-Hodgkin lymphoma (NHL). Patients typically present with advanced stage disease and are generally considered incurable, although with modern chemo-immunotherapy, median overall survival for this patient group is now approaching 15-20 years[1,2].
For the minority with localized stage I or II disease, definitive radiotherapy can be curative, with historical series reporting 10-year disease free survival of 40-50% with few relapses seen beyond this time[3,4].

18 Fluorodeoxyglucose (FDG) Positron emission tomography with computerized tomography (PET-CT) is now considered the gold standard imaging technique for staging FL[5,6]. Over 95% of FL are FDG avid[7-9]. Upstaging occurs in 10-60% of cases compared to conventional CT staging alone.[10-13]

FL is a highly radiosensitive lymphoma. In-field relapse following radiotherapy (RT) is rare, with most relapses occurring distantly[14,15]. This demonstrates that in many cases recurrence is not due to failure of radiotherapy, but instead results from the presence of occult disease outside of the radiation fields.

The aim of this study was to evaluate outcomes of patients staged with PET-CT and treated with RT alone for stage I/II FL. Our hypothesis was that with more accurate staging, patients would be better selected for treatment, with consequent improvement in treatment results.

METHODS

Patients

We conducted a multi-institutional retrospective study including 16 international centers, under the direction of the International Lymphoma Radiation Oncology Group (ILROG). Following individual institutional review board (IRB) approvals (or equivalent in participating institutions), anonymized patient data were submitted to a single data base according to a prospectively agreed protocol. Inclusion criteria were: 1) grade 1-3A follicular lymphoma, 2) stage I-II, 3) staging that included 18F- fluorodeoxyglucose PET-CT, 4) RT dose equivalent to at least 24 Gy/12 fractions, 5) post-treatment follow up of $\geqq$ 3 months, and 6) no prior radiotherapy and no prior or subsequent adjuvant systemic therapy. Pathology was confirmed at each individual institution prior to treatment.

We recorded age, sex, ECOG performance status, race and ethnicity, disease stage and the presence of B symptoms, nodal and extranodal sites of disease, maximum lesion size, histological grade, bone marrow biopsy, Follicular lymphoma international prognostic index (FLIPI) score, and molecular markers when available (BCL2, BCL6, t(14;18)). We also recorded details of radiotherapy including dose, fractionation, field size, modality of treatment and response to treatment.

Treatment, follow up, and outcomes assessment

RT was delivered via 2-dimensional (2D), 3-dimensional (3D) conformal, intensity modulated, and electron beam modalities. Treatment volumes included involved field, involved site, and involved node irradiation.

The time interval until post-RT imaging, (CT or PET-CT imaging obtained within 6 months), was recorded. Post-RT follow up was defined from the end of RT. Post-RT surveillance approaches varied widely and included clinical follow up only, CT alone, PET-CT, or endoscopy for duodenal sites. Post-RT PET-CT imaging was scored according to the Deauville 5-point scale[6].

Treatment related toxicities

Toxicities were graded retrospectively using clinic visit notations according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

End points

The primary end point was freedom from progression (FFP) calculated from the date of RT completion to first progression based on clinical, radiographic, or pathologic evidence. Deaths were considered censor events. The secondary end points were local control, overall survival (OS) and metabolic response rate on PET-CT.

Patterns of failure were recorded with recurrence defined as distant: occurring outside, and local: within the RT target volume. Marginal recurrence was defined as within the same anatomical region but outside the RT target volume. For patients who relapsed method of detection of relapse was recorded.

Statistical analyses

The Kaplan-Meier method was used to measure FFP and OS with stratification evaluated with the log-rank test. Univariable and multivariable hazard ratios (HR) were calculated using Cox regression analysis with corresponding Wald 95% confidence intervals and p-values. The proportional hazard assumption was tested by visualizing log(-log(survival probability)) plots. Patient factors meeting significance $p < 0.05$ on univariable analysis were included in multivariable analysis along with adjustment for other baseline characteristics.

Only 9 patients died without having recurrent disease with competing risk analysis demonstrating nearly identical results (see **Supplemental Figure 1** and **Supplemental Table 1**). For the size of nodal disease, the largest recorded value (on examination or imaging) was used for statistical analysis with imputation of missing values with the mean value. 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

Patient and treatment characteristics

512 patients treated from 2000-2017 at 16 centres were eligible for analysis. As shown in **Table 1**, the majority of patients had stage I disease (n=410, 80.1%), underwent bone marrow biopsy (n=479, 93.6%), and were without B-symptoms (n=507, 99%). Median follow up was 52 months (range 3.2-174.6, average 59 months).

For patients with *stage I disease*, 297 (72.4%) had nodal disease only, including: cervical (which includes supraclavicular, occipital, and pre-auricular nodes) (n=102), axillary/pectoral (n=26), mediastinal (n=2), abdominal para-aortic (n=5), mesenteric (n=15), iliac (n=4), inguinal/femoral (n=140), and epitrochlear/brachial (n=3).
Extranodal sites in 113 patients (26.3%) included: Waldeyer's ring (n=13), parotid gland (n=15), stomach (n=2), bone (n=7), skin (n=10), breast (n=6), thyroid (n=3), orbit (n=5), duodenum (n=26), bladder (n=1), soft tissue (n=14), ileum (n=1), colon (n=1), other salivary gland (n=3), and not otherwise specified (n=6).

For patients with *stage II disease*, nodal sites were involved in all 102 patients and included: cervical (n=40), axillary/pectoral (n=20), mediastinal (n=1), para-aortic (n=9), mesenteric (n=11), iliac (n=26), and inguinal/femoral (n=41). Only 8 patients with stage II disease had non-contiguous nodal sites. Extranodal disease was present in 14 (13.7%) patients with stage II disease and included: Waldeyer's ring (n=3), parotid gland (n=2), bone (n=2), duodenum (n=2), breast (n=2), thyroid (n=1), lacrimal gland (n=1), larynx (n=1).

Treatment was delivered via 2D (n=5), 3D conformal (n=315), intensity modulated (IMRT, n=100), and electron beam modalities (n=15), and was unspecified in 77 patients. Median RT dose was 30 Gy (range 24-36) in median 2 Gy per fraction. The mode (most frequent dose) was 30 Gy with 255 patients (49.8%) receiving 30 Gy.
105 patients received > 30 Gy (20.5%), and as shown in **Table 1**, only a small percent received higher than 36 Gy (5.3%). Treatment volumes included involved field (IFRT, n=256), involved site (ISRT, n=144), and involved node (INRT, n=7), and were unspecified in 105 patients.

Outcomes after definitive RT

For the entire cohort, 5-year FFP was 68.9% (**Figure 1A**, 95%CI=63.9-73.4) and OS was 96.0% (**Figure 1B**, 95%CI=93.2-97.6%). Only 8 pts relapsed in field (1.6%) and 4 had marginal recurrences (0.8%) resulting in local control rate of 97.6%. 137 (91.9%) relapses occurred outside of the irradiated sites. The 5-y FFP for the 33 patients who did not undergo bone marrow biopsy was not significantly different from those who did, but was numerically higher; 81.3% vs 68.1%, respectively ($p = 0.053$).

There was no significant difference in FFP between patients treated according to ISRT or INRT criteria (total 151, 29.4%) compared to patients treated with IFRT (p=0.41). There was a significant difference in outcome by stage. The 5-year FFP for stage I was 74.1% (95%CI=68.5-78.8), vs 49.1% for stage II (95%CI=37.8-59.5, p<0.0001) **(Figure 2A)**.

There was no significant difference in 5-year FFP between nodal and extranodal presentations (**Supplemental Figure 2**, p=0.34) including when stratified by stage (log rank p = 0.63 for stage I and p = 0.92 for stage II). There were no recurrences for the 28 patients with duodenal involvement.

On univariable analysis, stage was significantly associated with higher risk of progression (HR=2.34, 95%CI=1.66-3.30, P<0.0001, **Table 2**). On multivariable analysis, stage II remained significantly associated with higher risk for progression (HR=2.26, 95%CI=1.60-3.19, P<0.0001, **Table 2**) after adjusting for baseline patient characteristics including gender, stage, extranodal status, and FLIPI score.

The majority of patients had molecular marker testing available (n=414, 80.9%). Of those without BCL2 status, 73.5% (72/98) were from a single center that did not collect molecular data as part of their prospective database collection.5- year FFP was significantly worse for patients with BCL2+ expression compared with those without expression (BCL2-), 62.5% (95%CI=55.3-68.9) versus 77.2% (95%CI=67.3- 84.5), respectively (**Figure 2B,** p=0.02).

On univariable analysis BCL2+ was significantly associated with higher risk of progression (HR=1.64, 95%CI=1.09-2.46, P=0.02, **Table 2**). On multivariable analysis, both BCL2+ and stage II remained independently associated with higher risk for progression (**Table 2**) after adjusting for baseline patient characteristics including gender, stage, extra-nodal status, and FLIPI score. There was no significant interaction between stage and BCL2 expression when tested in the multivariable Cox model (**Figure 2C**, interaction p=0.49).

Imaging response to RT

273 (53.3%) patients were assessed with either PET-CT or CT within 6 months following completion of RT. 107 (20.8%) patients underwent a CT scan, performed at a median 2.8 months (range, 0.6-5.8) (IQR =1.9-3.5). 166 (32.4%) had a PET-CT scan to assess response. This was at median 2.9 months from treatment. (range, 0.6-6), (IQR= 1.8-3.5).

143 (86.1%) achieved complete metabolic response (CMR) on PET-CT (Deauville score 1-3). Failure to achieve CMR (n=60, 22.0%) was associated with higher risk of progression (**Figure 3A**, p=0.001). Twenty-three patients did not achieve a CMR, of whom 10 (43.4%) ultimately developed recurrent disease, all occurring distantly to the radiation field. Thirteen (56.5%) patients did not develop recurrent disease; in this group four had subsequent normalization of FDG uptake, seven had stable disease or CR on subsequent CT, and two had no recurrence based on clinical follow up. Failure to achieve CR by size criteria on CT was not significantly associated with a higher rate of progression (**Figure 3B**, p=0.1).

We found no significant difference when comparing time to relapse for those with and without post-RT PET, with median time to relapse of 21.1 months (range, 0.9- 123.9) versus 24.6 months (range, 1.6-142), respectively (log-rank, p=0.25). When comparing the patient characteristics between those with and without post-RT PET performed, we did not find any significant difference between age, sex, stage, extra-nodal status, or size (**Supplemental Table 2**).

Detection of relapse

The first method of detection of recurrent disease (n=149) included: surveillance imaging (n=55, 36.9% of all relapses), patient symptoms (n=34, 22.8% of all relapses), clinical examination (n=11, 7.4% of all relapses), or other/unknown (n=49, 32.9% of all relapses). We found a non-significantly higher rate of relapse detected by imaging for patients with initial abdominal or pelvic (non-inguinal) involvement versus all other sites of involvement, 21.8% (12 of 55) versus 12.7% (12 of 94) (p=0.15).

Toxicity

Acute and late toxicity data were available on 372 pts (72.7%). 85 patients (22.8%) experienced the following grade 1-2 acute toxicities: diarrhea (n=6), abdominal pain (n=1), esophagitis (n=1), radiation dermatitis (n=25), fatigue (n=11), xerostomia (n=8), nausea (n=8), limb edema (n=2), increased urinary frequency (n=2), dry eye (n=1), taste alteration (n=4), mucositis (n=18), dysphagia (n=9), weight loss (n=1), alopecia (n=2), and not otherwise specified (n=9). Grade 3 toxicities were rare and included dysphagia (n=1), dehydration (n=1), and mucositis (n=1). Late toxicities included grade 1 dry mouth (n=1) and grade 2 hypothyroidism (n=1).

Second malignancies occurred in 2.1% (n=11) of patients and included cutaneous melanoma, de-novo metastatic melanoma (n=2), DCIS of the breast, endometrial cancer (n=2), colorectal adenocarcinoma (n=2), neuroendocrine carcinoma,
acute myeloid leukemia, and clear cell renal carcinoma. All except the DCIS of the breast occurred outside of the prescription RT field.

DISCUSSION

This multi institutional study is the largest to evaluate outcomes after RT for patients with stage I and localized stage II FL who underwent modern staging including 18- FDG PET-CT. As PET-CT staging results in more accurate staging and a significant incidence of upstaging from limited stage (I/II) to advanced stage (III/IV), we hypothesized that the improved selection criteria would result in improved outcomes for patients with stage I/II disease.

In this study we included only patients who had a staging PET-CT and were treated with definitive radiotherapy with conventionally fractionated doses $\geq$24Gy. We did not include other patients with stage I or localized stage II who received other or no treatment. The median follow up was 52.3 months. With an estimated 5-year FFP of 68.9% (74.9% for stage I and 49.1% for localized stage II) and overall survival of 96%, treatment results in this study at this time point are considerably better than those reported in historical series from the pre-PET-CT era.

One of the earliest series was from Stanford University and included 177 patients treated between 1961 and 1994[3]. This reported 5- and 10-year freedom from relapse (FFR) of 55% and 44%, with 5 and 10-year OS of 82 and 60% respectively. Staging for these patients included bipedal lymphangiography and bone marrow trephine biopsy, with CT scanning only in the later cases. 25% of patients underwent staging laparotomy.

The Stanford results were in line with a larger study from Princess Margaret Cancer Centre, Toronto. They evaluated 460 patients treated between 1968 and 1999. Relapse free rates at 5 and 10 years post treatment were 62% and 52% respectively, with 5 and 10-year OS of 79 and 62%[14]. Similar outcomes were observed in several other single institution studies published in the nineties and early 2000s[15-17.]

As anticipated, local control post RT in our study was excellent. Fewer than 2% of patients experienced in-field relapse. The great majority of relapses, 91.9%, were at sites beyond the radiotherapy field. This high degree of local control, and relapse pattern is consistent with other reports. In the 24 Gy arm of the FORT study, only 21 out of 299 (7%) of patients progressed in-field with a median follow up of 26 months[18]. In the PMH series, the in-field relapse rate was 5.5%[14], which is almost identical to the Stanford result of 5%[19]. In a retrospective study of 80 patients with stage I-II FL treated 1960-1988 at the MD Anderson Cancer Center, the 15-year local control rate was 100% for tumors <3cm, and 93% for those $\geq$3cm[4].

For patients with stage I disease in our series, outcome after RT was particularly good, with estimated 5-year FFP of 74.9%. In stage II disease, the relapse rate was higher but still half of patients remained disease free at 5 years, with estimated 5- year FFP of 49.1% ($p<0.0001$). OS at 5 years in both groups was 96%.

The proportion of patients with stage II disease in our study is much smaller than in older series. This could be due to the upstaging effect of PET-CT, in that patients previously deemed to being stage II, are found to have stage III/IV disease on PET. In addition, since all these patients were treated since 2000, it is possible that fewer
patients with stage II disease were offered RT in favor of systemic treatment or observation, a trend that has been reported in more recent years[20].

Site of disease, nodal versus extra-nodal did not correlate with risk of relapse, but of note our cohort included 28 patients with FL involving the duodenum. Duodenal FL is increasingly recognized to have a very favorable prognosis, and similar to experiences reported by others, we observed excellent outcomes for these patients, without any recurrences during follow up[21].

In a multivariable model, the only other factor associated with risk of relapse in addition to stage was BCL2 expression. Patients with BCL2 expressing tumors were significantly more likely to relapse. Interestingly, the outcome of patients with stage II FL who were BCL2 negative, was similar to those with stage I disease. However, there were only 23 patients in this group and this may not have provided sufficient power to detect any possible interaction between stage and BCL2.

BCL2 over-expression (BCL2+) is present in approximately 80-90% of cases of FL[16,22-23] and while it confers a poor prognosis in DLBCL, a relationship between BCL2+ and outcome in FL has not been established[24,25]

The incidence of BCL2+ in our study is lower than other series with more advanced disease. Of the 414 patients with known BCL2 status only 281 (68%) were BCL2+. This is likely to be related to the early stage of disease. One other study evaluated patients with stage I and II follicular lymphoma treated with RT, combined modality therapy or chemotherapy alone and reported BCL2+ in 73% of patients, which is more keeping with our results. However they did not identify any relationship between BCL2 status and outcome[26]. The t(14;18) translocation, the hallmark of FL, has also been shown to occur less frequently in early compared to advanced stage disease. In a study of 174 patients with Grade1 -3A FL, those who were t(14;18)
negative were significantly more likely to have localized disease compared to patients with translocation, 62% versus 32%[23]. While we cannot make any firm conclusion regarding the BCL2+ and prognosis of early stage disease treated with
radiotherapy based on this study, we consider the findings to be hypothesis generating and worth of further investigation.

The very high local control after RT and the fact that most relapses are distant suggest the presence of microscopic disease below the threshold of PET detection in a quarter of patients with stage I and half of patients with stage II disease. This raises the question of whether the addition of systemic therapy would improve outcomes further. In a retrospective series from University of Torino, the addition of
rituximab single agent improved results compared to historical controls[27]. A more
recent randomized controlled study testing the addition or chemotherapy or chemoimmunotherapy showed statistically significant improved PFS, although longer follow up is required to evaluate any benefit in OS[28]. Thus, combined modality
therapy may be a useful strategy, particularly for those with stage II disease who are at significantly higher risk of relapse following local treatment.

According to international guidelines PET-CT in lymphoma is used for both initial staging and response assessment[5,6]. 32.4% of our patients underwent response assessment with PET-CT. This was defined as a PET-CT within 6 months of completion of treatment. For this subgroup, achieving a complete metabolic response (CMR), defined as Deauville score 1-3 was strongly associated with a decreased risk of relapse. Patients with incomplete metabolic response were nearly 4 times more likely to relapse than those in CMR. Of the patients who did not achieve a CMR approximately half developed recurrent disease, all failing distantly outside of the radiation field. The other half remained in remission, with subsequent normalization of PET or no evidence of progression on CT or clinically. These results suggest that PET-CT response after RT is worth exploring further to elucidate whether a high-risk subset of patients who might benefit from additional systemic treatment can be identified. Post treatment CT scanning was not found to predict outcome.

Early toxicity data were available for most patients (72.7%), and overall toxicity from RT was minimal, with only 3 cases of G3 toxicity (dysphagia, dehydration, and mucositis). There were no treatment related deaths. These results are not dissimilar to the prospective data from the 24 Gy arm of the FORT trial in which only 2.8% of patients experienced grade 3, and no patients grade 4 toxic effects from treatment[18.]
Late toxicity data collection was limited by the short follow up of the study and its retrospective nature, which is a limitation of this study.

The excellent tolerability of radiotherapy is an important consideration in making treatment decisions, particularly since some have suggested that a watch and wait policy is appropriate for these patients with potentially curable limited stage follicular lymphoma[29]. Our results show that most patients do not experience significant side effects following the relatively low doses and limited radiation fields employed and they benefit from the chance of cure offered only by radiotherapy.

The main limitation of our study is its relatively short follow up for a disease with a long natural history. Data from historical series suggests that further relapse could occur beyond 5 years with an incidence in the order of 10% from 5 to 10 years[3,14,19.]
Longer follow up is required to confirm the long term outcome.

Other limitations are that there was no central pathology or PET-CT review, although all patients in our study were treated in specialist academic centres with significant expertise in treating hematological malignancies. Given the long inclusion period which patients were treated there was variation in RT dose, technique used, and volumes treated (i.e involved field, site and node). We did not identify any relationship between these treatment factors RT and risk of progression. We would however consider the 2014 ILROG guidelines for lymphoma radiotherapy to be the current international standard[30].

A small group (6.4%) of patients in our study did not have a bone marrow biopsy pre- RT as per international guidelines. These patients had similar FFP to those who underwent biopsy. In other studies however, rigorous staging has consistently been shown to be associated with better treatment outcomes[31-33]. We still believe bone marrow biopsy to be standard of care.

The improved outcome seen in this study supports RT as an excellent treatment option for localized FL, particularly those with stage I disease. Several studies, however, suggest that upfront RT is being underutilized in patients with limited stage FL, which contradicts international guidelines. In the LymphoCare study, only 23.4% of patients with stage I disease received RT as their initial treatment[31]. Analysis of data from SEER database for 6568 patients with stage I/II FL diagnosed between
1973 and 2004, showed that only 34% received RT[33]. A more recent study of 35631 patients in the National Cancer Data Base with grade 1-2 localized FL, treated
between 1998 and 2012 showed that RT use had decreased from 37% in 2009 to 24% in 2012[20].

Critics of RT may argue that survival in all groups is high and that there are no randomized data comparing upfront RT with primary chemo-immunotherapy or surveillance, yet the SEER database analysis (6568 patients) showed that initial treatment with RT was independently associated with both improved DSS and OS,
with an absolute benefit of 13% in OS for RT-treated patients[33]. This was also found
in the National Cancer Data Base study (35631 patients) with upfront RT remaining independently associated with improved OS (hazard ratio of death, 0.54; 95% confidence interval, 0.47-0.63 [P<.0001]). The authors of both studies concluded that RT was underused.

Bearing in mind the low toxicity of modern RT, it should be considered as an initial treatment option for patients with limited-stage FL in suitable patients. Our study suggests that it is a highly effective treatment, with nearly three quarters of patients with stage I and approximately half of patients with selected localized stage II disease remaining disease free at 5 years. Whilst longer follow up is clearly needed, it is likely that earlier series in the pre PET-CT era underestimated the value of RT as a curative treatment for stage I/II FL due to limited sensitivity of the staging techniques. Long-term outcome of the addition of systemic therapy to radiotherapy is
eagerly awaited to see if that improves outcome further.

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Nil

AUTHORSHIP CONTRIBUTIONS

JLB as first author designed the study, collected data, analyzed data and wrote the first draft of the manuscript.
MSB as joint first author designed the study, analyzed data, performed statistical analysis and wrote the first draft of the manuscript.
RTH and NGM designed the study, collected data, analyzed data and wrote the manuscript. CH collected data and wrote the manuscript.
MC collected data and wrote the manuscript. KC collected data and wrote the manuscript. AB collected data and wrote the manuscript. ML collected data and wrote the manuscript. ARF collected data and wrote the manuscript. MJ collected data and wrote the manuscript. MM collected data and wrote the manuscript. AW collected data and wrote the manuscript. MO collected data and wrote the manuscript. AKV collected data and wrote the manuscript. TYA collected data and wrote the manuscript. AKN collected data and wrote the manuscript. BMPA collected data and wrote the manuscript. SHC collected data and wrote the manuscript. YK collected data and wrote the manuscript.
SH collected data and wrote the manuscript. GR collected data and wrote the manuscript. HTE collected data and wrote the manuscript. SB collected data and wrote the manuscript. LSC collected data and wrote the manuscript. COS collected data and wrote the manuscript. BD collected data and wrote the manuscript. TCE collected data and wrote the manuscript. DCH collected data and wrote the manuscript. UR collected data and wrote the manuscript. JY collected data and wrote the manuscript.

DISCLOSURE OF CONFLICTS OF INTEREST

JLB has no conflicts of interest to declare MSB has no conflicts of interest to declare MC has no conflicts of interest to declare KC has no conflicts of interest to declare AB has no conflicts of interest to declare ML has no conflicts of interest to declare ARF has no conflicts of interest to declare MJ has no conflicts of interest to declare MM has no conflicts of interest to declare AW has no conflicts of interest to declare MO has no conflicts of interest to declare AKV has no conflicts of interest to declare TYA has no conflicts of interest to declare AKN has no conflicts of interest to declare BMPA has no conflicts of interest to declare SHC has no conflicts of interest to declare YK has no conflicts of interest to declare SH has no conflicts of interest to declare GR has no conflicts of interest to declare HTE has no conflicts of interest to declare SB has no conflicts of interest to declare LSC has no conflicts of interest to declare COS has no conflicts of interest to declare BD has no conflicts of interest to declare TCE has no conflicts of interest to declare DCH has no conflicts of interest to declare UR has no conflicts of interest to declare JY has no conflicts of interest to declare RTH has no conflicts of interest to declare NGM has no conflicts of interest to decla

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TABLES

Table 1. Patient and treatment characteristics.

Parameter	Cohort (n=512)
Median age	58 (20 - 90) years
Female	254 (49.6%)
ECOG PS 0-1	509 (99.4%)
Stage I	410 (80.1%)
Extranodal	113 (22.1%)
B symptoms	3 (0.6%)
Stage II	102 (19.9%)
Extranodal	14 (2.7%)
B symptoms	2 (0.4%)
Grade	
1-2	460 (89.8%)
3a, or 3 NOS	52 (10.2%)
Median RT dose	30 (24 - 52) Gy
24 – 30 Gy	345 (67.4%)
>30 – 36 Gy	140 (27.3%)
>36 Gy	27 (5.3%)
Median pretreatment size	2.8 (0.2 – 10) cm
Unknown	45 (8.8%)
Median follow up	52.3 (3.2 – 174.6) mo.
BCL2 expression:	
Positive	281 (54.9%)
Negative	133 (26.0%)
Unknown	98 (19.1%)

Abbreviations: ECOG PS=performance score, NOS=not otherwise specified, mo.=months
*** Continuous variables are shown with range and categorical variables with percentages in parenthesis**

Table 2. Uni- and multivariable analyses of pretreatment patient characteristics associated with progression after primary RT.

Table 2. Univariable and multivariable analysis (Cox Regression)				
Variable		Progression Univariable	MVA 1 (n=512)	MVA 2 (n=414)
Age	HR 95% CI p	1.00 0.99-1.01 0.99		
Male sex	HR 95% CI p	1.28 0.92-1.77 0.14	1.24 0.90-1.72 0.19	1.25 0.87-1.79 0.23
Extranodal disease	HR 95% CI p	0.83 0.56-1.23 0.35	0.95 0.64-1.42 0.81	1.02 0.65-1.58 0.95
Grade IIIa, or NOS	HR 95% CI p	0.91 0.50-1.64 0.75		
Pretreatment Size, cm	HR 95% CI p	1.06 0.95-1.17 0.29		
Stage II	HR 95% CI p	**2.34** **1.66-3.30** **<0.0001**	**2.31** **1.63-3.27** **<0.0001**	**2.11** **1.44-3.10** **0.0001**
FLIPI	HR 95% CI p	1.04 0.80-1.37 0.75	1.05 0.80-1.38 0.71	1.10 0.81-1.50 0.53
BCL2 positive (n= 414)	HR 95% CI p	**1.64** **1.09-2.46** **0.02**		**1.63** **1.07-2.47** **0.02**
Abbreviations: MVA=Multivariable analysis				

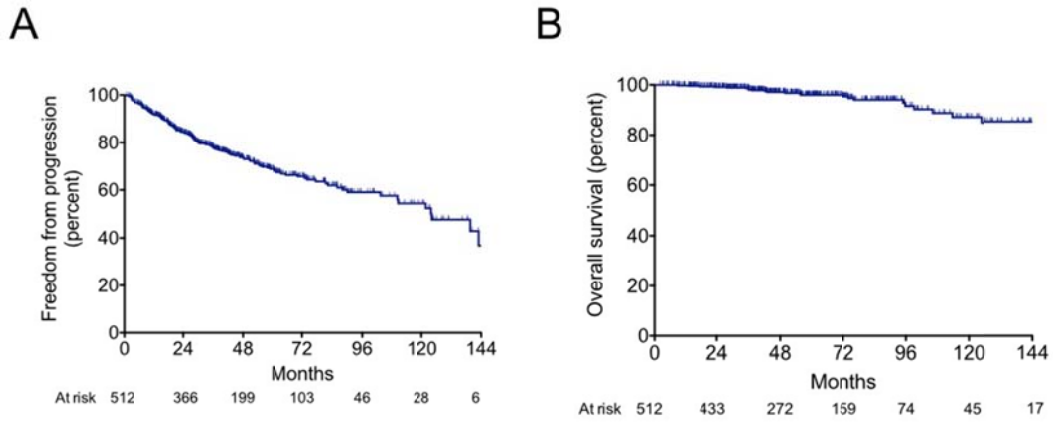

Figure 1. Outcomes after primary RT for the entire cohort. A. FFP with 5-year rate of 68.9%. B. OS with 5-year rate of 96%.

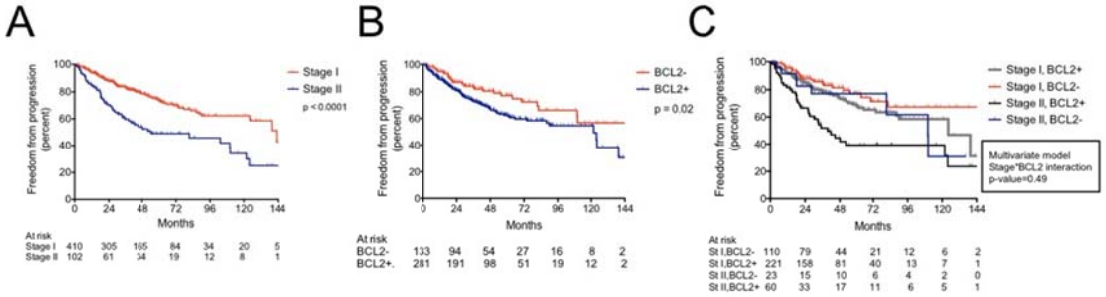

Figure 2. FFP stratified by stage and BCL2 status. A. FFP is significantly worse for patients with stage II disease. B. FFP is significantly worse for pts with BCL2+ expression. C. Stratifying by stage and BCL2 status demonstrates pts with stage II BCL2- disease may have outcomes similar to pts with stage I disease.

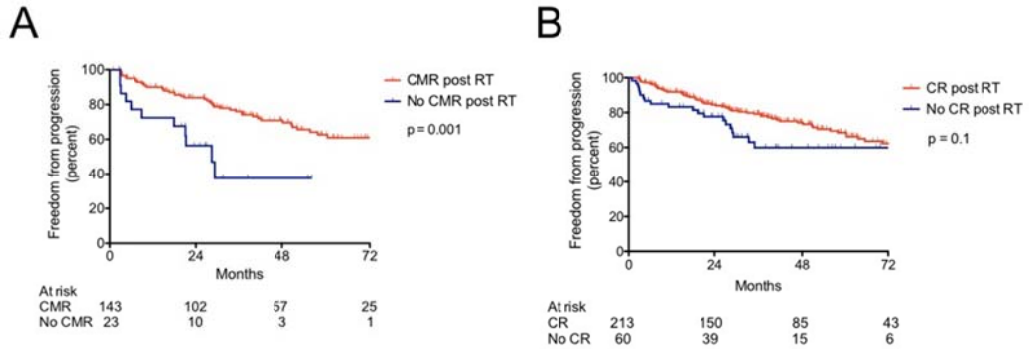

Figure 3. Ability of post-RT imaging to predict recurrence. A. Pts without CMR after primary RT have significantly higher rate of progression. B. Pts without CR after primary RT have non-significantly higher rate of progression.