Survival by first-line treatment type and timing of progression among follicular lymphoma patients: A national population-based study in Sweden

Caroline Weibull (caroline.weibull@ki.se)
Karolinska Institutet https://orcid.org/0000-0001-8231-8183
Tove Wästerlid
Lymphoma Unit, Department of Hematology, Karolinska University Hospital Solna
Bjorn Wahlin
Division of Hematology, Department of Medicine Huddinge, Karolinska Institutet and Department of Hematology, Karolinska University Hospital
Per-Ola Andersson Andersson
Medicine
Sara Ekberg
Division of Clinical Epidemiology, Department of Medicine Solna, Karolinska Institutet
Sandra Lockmer
Karolinska Institutet
Gunilla Enblad
Uppsala University Hospital https://orcid.org/0000-0002-0594-724X
Michael Crowther
Red Door Analytics
Eva Kimby
Institution of Medicine https://orcid.org/0000-0003-3078-6131
Karin Ekstrom Smedby
Karolinska Institutet

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Title page

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Running head: Treatment, progression and survival in follicular lymphoma

Caroline E. Weibull[a] (PhD), Tove Wästerlid[a,b] (MD, PhD), Björn Engelbrekt Wahlin[b,c] (MD, PhD), P-O Andersson[d] (MD, PhD), Sara Ekberg[a] (PhD), Sandra Lockmer[b,c] (MD, PhD), Gunilla Enblad[e] (MD, PhD), Michael J. Crowther[f,g] (PhD), Eva Kimby[c] (MD, PhD), Karin E. Smedby[a,b] (MD, PhD)

[a] Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

[b] Department of Hematology, Karolinska University Hospital, Stockholm, Sweden

[c] Unit of Hematology, Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden

[d] Section for Hematology, Oncology and Lung medicine, Södra Älvsborg hospital, Borås, Sweden

[e] Department of Immunology, Genetics and Pathology, Experimental and Clinical Oncology, Uppsala University, Uppsala, Sweden

[f] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

[g] Red Door Analytics, Stockholm, Sweden

Corresponding author:

Caroline Weibull

Department of Medicine Solna, Karolinska Institutet

Clinical Epidemiology Division T2, Karolinska University Hospital

SE-171 76 Stockholm, Sweden

E-mail: caroline.weibull@ki.se

Telephone: +46 70 984 14 55

Personal Twitter handle: @carolineweibull

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ABSTRACT

In follicular lymphoma (FL), progression of disease ≤24 months (POD24) has emerged as a prognostic marker for overall survival (OS). We aimed to investigate OS broadly by timing of progression and treatment in a population-based setting. A total of 948 stage II-IV indolent FL patients, diagnosed 2007-2014 and treated with first-line systemic therapy, were identified in the Swedish Lymphoma Register and followed through 2020. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated by first progression of disease at any time during follow-up (POD) using Cox regression. OS was predicted by POD using an illness-death model. During a median follow-up of 6.1 years (range: 0-10), 414 patients experienced POD (44%), of which 270 (65%) occurred ≤24 months. Compared with patients in remission, POD increased all-cause mortality across treatment groups, but less so among patients treated with rituximab(R)-single (HR=4.54, 95% CI: 2.76-7.47) than R-chemotherapy (HR=8.17, 95% CI: 6.09-10.94). The negative impact of POD on survival remained for progressions up to five years after R-chemotherapy, but was restricted to the first two years after R-single. To conclude, progression of disease beyond 24 months is associated with worse survival, illustrating the need for individualized management for optimal care of patients with FL.

INTRODUCTION

Follicular lymphoma (FL) is the most common indolent lymphoma type, accounting for about 20% of all lymphomas.(1) FL is predominantly incurable, with the exception of limited-stage disease which may be cured with radiotherapy (RT).(2) In recent years, the heterogeneity of FL has become increasingly recognized, both regarding tumor molecular characteristics and clinical course. Due to the incurability of advanced-stage FL even with modern therapy, and the fact that early therapy has not been shown to prolong survival, many patients with indolent FL are managed with an initial watch and wait approach.(1, 3, 4) However, some patients require immediate systemic treatment due to rapidly progressing or symptomatic disease. During recent decades, both progression-free and overall survival (PFS/OS) have improved following the introduction of monoclonal anti-CD20 antibody therapy (mainly rituximab, R), and improved supportive care.(5-7) Treatments of choice include R as a single agent or in combination with chemotherapy (e.g., with bendamustine, BR) or in cases where a more prompt tumor reduction is needed, R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone).(1, 3) Still, some patients suffer from rapidly progressive disease and risk of transformation to diffuse large B-cell lymphoma.(8)

Factors that determine early disease progression and need for treatment are not yet entirely defined. Currently, patients with FL are risk stratified using FLIPI, FLIPI2, and m7-FLIPI, which take into account clinical and laboratory characteristics and molecular features in the latter,(9-11) but these are still not sufficient to predict need for treatment and risk of progression, why novel scoring methods are being developed.(12) Several studies have found that FL patients in need of initial systemic treatment and subsequent early re-treatment within 2 years of diagnosis (POD24) have a particularly bad prognosis.(13-18) The impact of POD24 on prognosis was initially established for patients treated with R-chemotherapy,(13, 16, 19, 20) but has since been demonstrated to predict prognosis also among patients managed with immunotherapy only.(14, 21, 22)·(23) However, the majority of reports on the impact of POD24 have been performed on patients from clinical trials or from single centers, and comprehensive real-world evaluations of the impact of progression are lacking. Also, the proportion of patients that experience POD24 appears to vary by treatment, as does the association of POD24 with

risk for transformation.(15, 22) For example, lower rates of POD have been reported for BR-treated patients, but with a concomitantly higher risk of transformation among BR-treated patients who do experience POD24.(16, 24) In contrast, the risk of experiencing POD24 appears to be higher among patients managed with immunotherapy only,(14, 21, 22) but was not significantly associated with survival among patients managed with immunotherapy or radiotherapy only in one study.(15)

In the current study, we aimed to investigate the impact of timing of first progression on survival more broadly beyond the POD24 time point and by first-line systemic treatment type in a large Swedish population-based cohort of FL patients diagnosed 2007-2014 in Sweden and followed through 2020.

MATERIAL AND METHODS

Data sources and data collection

Patients registered with a first diagnosis of indolent FL between 2007 and 2014 were identified through the Swedish Lymphoma Register (SLR). Discordant and primary cutaneous FL patients were not included. The SLR was initiated in 2000 and has a coverage above 95% compared to the nationwide Swedish Cancer Register.(25) The SLR records detailed data on patient- and clinical characteristics at diagnosis, first-line treatment, and progression. For this study, the register data was validated and supplemented with data on progression, transformation, and second-line therapies from a medical chart review. Informed consent was enquired for all patients alive by 2018-10-18, except in two Swedish regions where the ethical permission allowed for complementary data collection without active consent (Skåne and Uppsala). For deceased patients, no informed consent was needed from next-of-kin. The medical chart data collection was initiated in 2018 and finalized in 2020.

Study population

A total of 2 079 registered patients were identified as eligible for the study and the medical chart review could be completed for 1 844 FL patients (89%). Non-completion was primarily due to lack of active consent, missing medical records, and cases found to be discordant (transformed) at diagnosis although registered as indolent. Patients who were managed with watch-and-wait only during the entire follow-

73 up period (n=412), had grade 3B (n=72), were stage I or limited stage II and treated with curative
74 intended RT (n=304), were stage III-IV disease and treated with RT only (n=42), and patients who
75 experienced a transformation prior to first-line treatment initiation (n=66) were excluded. The final
76 study population comprised 948 patients (Figure 1).
77
78 *Definition of treatment groups*
79 Patients were classified as treated first-line with either R-chemotherapy (R-chemo), R-single, or other
80 treatments. The R-chemo group included R-CHOP, BR, R-CVP (cyclophosphamide, vincristine,
81 prednisone), and R-FC (fludarabine, cyclophosphamide). The "other" group consisted of patients
82 treated with chemotherapy (CHOP/B/CVP/FC) without R, oral treatments such as chlorambucil,
83 trophosphamid or lenalidomide, and patients with missing information on type of systemic treatment.
84
85 *Definition of progression of disease (POD)*
86 POD was defined as either progressive disease as best response to first-line therapy, initial response but
87 later relapse/progression as indication for second-line therapy, or transformation. Patients not (yet)
88 fulfilling any of these criteria were considered progression-free (PF). Date of POD was subsequently
89 defined as date of first-line evaluation, second-line treatment initiation date, or date of first
90 transformation (after first-line treatment). POD24 was defined as fulfilling the above criteria within 24
91 months after start of first-line treatment.
92
93 *Statistical methods*
94 Frequencies and proportions of demographical, clinical, and follow-up characteristics were calculated
95 by type of first-line treatment. Chi2-tests were used to test difference in distribution between categorical
96 variables. Among patients with POD, the proportion of patients where POD (and POD24) was
97 represented by a transformation was calculated by first-line treatment. Follow-up ended at date of death
98 due to any cause, or end of study period, whichever came first. End of study period depended on when
99 the data collection was performed, and varied between December 31st, 2018, and December 31st, 2020.
100 Follow-up was restricted to the first 10 years following diagnosis.

The prognostic impact of POD was analyzed in two ways. To estimate the relative effect of POD on all-cause mortality by first-line treatment, Cox regression models were fitted treating POD as a time-varying exposure. Both univariable (adjusted for time since first-line treatment) and multivariable models (adjusted for age and calendar year of diagnosis, sex, and FLIPI) were fitted. Interaction effects between POD and treatments were tested using Wald tests. To further estimate the prognostic value of progression as a function of time of POD/PF since first-line treatment on the absolute risk scale, and hence quantify the impact of timing of POD on survival, the 5-year OS conditional on either being PF or having experienced POD at different time points during follow-up was estimated. This was done using an illness-death model(26) with three states: diagnosed and treated for FL and still PF and alive (initial state), progressed and alive (POD state), and deceased (DEAD state) (Supplementary Figure 1). Transition rates from the initial state to the POD and DEAD state, and from POD to DEAD, were modelled using flexible parametric models. Time since initiation of first-line treatment was used as the underlying time scale, and the transition from POD to DEAD was additionally adjusted for time of POD (i.e., semi-Markov). Lastly, POD24 was assessed. Follow-up started at date of progression among POD24 patients, and at 24 months after treatment initiation among patients who were progression-free (PF) as in previous studies (19, 27-29). In the PF patient group, patients dying (n=74) or being censored due to end of study period (n=6) within 24 months were excluded from this analysis (n=80). OS was estimated using the Kaplan-Meier method by POD24 for the different treatment groups.

RESULTS

In the final cohort of 948 patients, 519 (55%) were treated with R-chemo, 273 (29%) with R-single, and 156 (16%) with other treatments (Figure 1, Table 1). The "other" treatment group consisted of patients treated with chlorambucil (n=92/156, 59%), CHOP/B/CVP/FC without rituximab (n=27/156, 17%), or other oral chemotherapy agents/missing treatment information (n=37/156, 24%).

The median time to primary treatment initiation was 47 days (IQR, inter-quartile range: 22-133), and 205 (22%) patients started their treatment after six months or more. Median age at diagnosis was 66

(range: 24-92), 64 (27-91), and 71 (38-98) years for patients treated with R-chemo, R-single, and other treatments, respectively (Table 1). Stage distribution differed slightly across treatment groups, the proportion of stage IV for R-chemo, R-single, and other treatments were 47%, 40%, and 51%, respectively (p=0.022). Patients treated with R-single had a lower proportion of high-risk FLIPI (35%) compared to patients treated with R-chemo (57%) and other treatments (39%) (p-value<0.001). Increasing age, male sex, high-risk FLIPI, and poor performance status were associated with increased all-cause mortality (Supplementary Table 2).

The median follow-up time was 6.1 years (IQR: 3.5-8.4), during which 414 (44%) patients experienced POD (Table 2). The proportion was higher in patients treated with R-single (60%) than with R-chemo (35%) (p<0.001). Within the R-chemo group, 110 (36%) and 44 (29%) patients treated with R-CHOP and BR, respectively, experienced POD. Among all progressed patients, 270 (65%, or 28% out of the total number of patients) occurred within 24 months of first-line treatment, with similar proportions for R-CHOP (61%) and BR (59%) but higher for R-single (68%). The proportion morphologically verified transformations at POD was 15%, and did not differ significantly by treatment.

Patients experiencing POD after R-chemo had an 8-fold increased all-cause mortality rate following POD compared to progression-free patients (HR_{adj}=8.17, 95% CI: 6.09-10.94). For patients treated with R-single, the rate was 4.5-fold increased (HR_{adj}=4.54, 95% CI: 2.76-7.47) (Figure 2, top panel). Within the R-chemo treatment group, mortality was similarly increased among patients with POD after R-CHOP (HR_{adj}=8.97, 95% CI: 6.14-13.1) as among patients treated with BR (HR_{adj}=10.3, 95% CI: 5.60-18.9) (p=0.7020 from Wald test of interaction). Similar results were seen in the analysis of POD24, but with a significantly stronger effect of POD24 in BR compared to R-CHOP treated patients. Patients with POD24 after BR experienced a 17-fold increased mortality compared with progression-free patients, whereas among R-CHOP treated patients it was 6-fold increased (Figure 2, bottom panel, p=0.0154).

Figure 3 shows the 5-year conditional OS among progressed and progression-free patients by timing of POD/PF and treatment. A short time between first-line treatment and progression was associated with the lowest OS, irrespective of treatment type. For R-chemo overall, as well as R-CHOP and BR-treated patients, the negative impact of POD on OS remained for progressions occurring up to five years after first-line treatment. Among patients receiving any R-chemo who experienced POD at 12 months, the 5-year conditional OS was 34% (95% CI: 27%-43%), versus 78% (95% CI: 75%-81%) among progression-free. Among R-chemo-treated patients experiencing POD at 24 months and 60 months, the corresponding OS proportions were 46% (95% CI: 38%-54%) and 57% (95% CI: 42%-71%), compared with 78% and 82% among patients who were progression-free at 24 and 60 months, respectively. For R-single, the negative impact was limited to progression occurring during the first two years following treatment initiation. In the analysis of POD24, early progression was confirmed to be predictive of a worse OS compared to patients who were progression-free at 24 months, especially among patients treated with R-chemo (Figure 4).

DISCUSSION

Among FL patients treated with first-line immunochemotherapy, progressions following primary treatment affected OS negatively. Whereas the majority of progressions occurred within 24 months, it is important to note that the negative impact of POD on OS remained for progressions occurring up to five years after treatment initiation. For patients treated with R-single, POD had less impact on survival and was limited to progressions within two years of primary treatment. This information is highly clinically relevant, as it implies that timing of progression following standard immunochemotherapy regimens needs to be considered beyond the 24-month time point.

To the best of our knowledge, this is the first population-based study of POD and its timing in relation to first-line treatment and survival. Most previous studies have focused on POD24, and have been performed on selected patients included in clinical trials, with lower median age and more favorable baseline characteristics than in our population-based study.(13, 14, 20, 21) Still, for patients managed with R-single, we show similar OS as those reported for patients treated in clinical trials with

immunotherapy alone. For example, Lansigan et al(21) demonstrated a 5-year OS of 74% among patients treated with immunotherapy who experienced POD24 and 90% among those who did not, compared to 73% and 85% (respectively) in our study. However, our real-world data showed slightly worse survival among patients with POD within 24 months after R-chemo compared to previous studies.(13, 15) In part, this likely reflects our population-based setting. Further, the guidelines for indolent FL in Sweden recommend R-single also to higher risk patients. Thus, the patients who are selected to receive R-chemo in Sweden may represent an even more pronounced high-risk disease group, which additionally could contribute to the worse survival rates observed. For example, the use of R-CHOP in Sweden is mostly reserved for patients who need urgent therapy due to a more aggressive disease. Still, one study with comparable median age as here showed similar OS after immunochemotherapy as we do.(16)

The proportion of patients with POD in our study was 44% over a median follow-up of 6.1 years, whereas the proportion of POD24 was 28% overall and 21% among patients managed with R-chemo, which is in line with previous reports.(13, 17) The higher proportion of POD is likely a result of not restricting to progressions within two years, but could additionally be driven by progressions in patients managed with R-single, which has also been reported in clinical trials of FL patients receiving immunotherapy only.(14, 21, 22) Still, the proportion of R-single treated patients who progress in our study is high also compared to some of these studies, which may reflect our population-based setting with more high risk patients being selected for R-single. In contrast to other studies that have shown a lower proportion of POD24 after treatment with BR, we demonstrate a similar proportion of POD (and POD24) in both R-CHOP and BR treated patients.

Regardless of first-line treatment strategy, POD was associated with poor prognosis on both the relative and absolute survival scale. While patients treated with R-single had higher proportion of POD, its impact on survival was less dramatic compared to immunochemotherapy treated patients who experienced POD. This is in line with previous findings on POD24 in patients treated with immunotherapy only(14, 15, 22) and may be explained both by more favorable disease, but also a

demonstration of high efficacy of second-line treatment after initial management with immunotherapy only. Interestingly, the adverse impact of POD among patients managed with R-single was restricted to progression within two years of treatment initiation, which was not the case for immunochemotherapy treated patients. The difference according to treatment was also shown in the GALLIUM-study, where fewer patients experienced POD24 among those who received obinutuzumab rather than R, but with similar outcomes among those who did progress.(20)

The association between POD24 and transformation has varied between studies, with almost 76% of patients who experienced POD24 after BR treatment having transformed disease in one study,(16) compared with most other studies where approximately 20% of POD24 patients represented transformed disease.(20, 22) In our study, only 62 patients (15%) out of all progressed patients had a morphologically verified transformation, and this did not significantly differ between patients treated with R-CHOP, BR, or R-single. When including also clinically suspected transformation the total percentage was 17%, which is still lower than in previous reports. Thus, the inferior outcome among patients who experience POD after immunochemotherapy in our study is not explained by an increased risk of transformation, as was the case of POD24 in BR-treated patients in British Columbia.(16)

The main strength of this study is the population-based setting with unselected patients in combination with a detailed medical chart review, providing comprehensive data and few missing values. Another strength lies in our choice of statistical approach to analyze the prognostic value of timing of POD. Previous publications have reported POD24, which due to its time-fixed definition inherits a number of issues and limitations. Firstly, the choice of time point can be considered more or less arbitrary, and dichotomizing an exposure implicitly results in loss of information. Moreover, patients progressing even shortly after the 24-month mark will only contribute as progression-free, and patients without progression that die before 24 months will not enter the analysis, resulting in a loss of data. Lastly, the time scale has a different meaning for progression-free and progressed patients in previous studies focusing on POD24, as all patients who are progression-free at 24 months start their follow-up then, whereas progressed patients may start follow-up shortly after diagnosis. We believe that the prognostic

impact of POD is best studied when progression at different time points are accounted for, all patients are included, and the time scale has the same meaning for all. However, to aid interpretation we chose to complement our novel approach with an analysis of POD24, and note that at the 24 month mark the estimators aim to estimate a similar entity (the difference being that POD24 covers all progressions by 24 months, and our POD estimate at 24 months covers progressions at 24 months).

As is inevitable in observational studies, our study comes with an inherent bias due to selection to treatment. Although we have adjusted for several baseline characteristics affecting treatment selection the possibility of residual confounding remains. Further, our definition of progression (mainly relapse/progression/transformation as indication for second-line treatment) might lead to misclassification of patients progressing outside of this definition or that the exact date of progression is not accurately captured. However, we believe that capturing patients with POD who require second-line treatment has the highest clinical interest and relevance.

In this population-based study we show that among patients who progress, the majority do so within 24 months across all different treatments, but with a higher proportion among R-single treated patients. In the landmark study by Casulo et al, the 24 month mark was chosen with the aim to capture most events, although they also demonstrated that progression at other time points were of significance.(13) Thus, our estimates on the impact of progression over time provide an even more complete picture of FL patient trajectories and highlights that patients who progress shortly after the POD24–mark may also benefit from novel or modified second-line treatment approaches. The recently reported use of response-adapted therapy in FL(30) as well as the rapid development of novel agents such as CAR-T cell therapy and bispecific antibodies in FL,(31, 32) augment the need for improved individual risk assessment and treatment choice. The reported findings on how the impact of progression on OS varies by timing of POD and by treatment constitutes important factors for this assessment. In future research, it is crucial to identify prognostic and predictive markers, not only for patients with POD24 but also for patients progressing after this time point. In previous studies, several different markers have been associated with the risk of POD24, such as elevated LDH, male sex, poor PS, high FLIPI score and

stage III-IV disease.(13, 20, 21, 23) Also, it is hypothesized that patients who experience POD24 may have a different disease biology such as primary genetic changes in the tumor cells or variability in the host immune response/tumor microenvironment or other tumor- or host-related factors.(33)

CONCLUSIONS

Progression of disease up to five years after first-line systemic treatment has strong prognostic value for patients treated with immunochemotherapy, but less so for patients treated with R-single. POD should be regarded as a continuous time-varying factor to avoid patient selection and choice of arbitrary time points, to improve its prognostic value and aid choice of second-line treatment. Future studies should also aim to determine factors that predict progression at different time points and evaluate whether progression can be inhibited through alternative initial management.

Author Contributions

CEW, TW, and KES conceptualized and designed the study. CEW, SE, and KES did the data collection. CEW and MJC performed all statistical analyses. CEW, TW, and KES drafted the article. All authors took an active part in interpretation of the results and revisions of the article. All authors have approved the final version to be published.

Competing Interests

This study/project was funded through grants from the public-private research partnership for real-world data analysis between Karolinska Institutet and Janssen Pharmaceutica NV (Ref: 5-63/2015).

Data Availability Statement

The data underlying this study are available at the National Board of Health and Welfare, Sweden, and Statistics Sweden for investigators with the appropriate approvals, but restrictions apply. However, data can be made available from the authors upon reasonable request for meta-analyses, and with the appropriate approvals of the Swedish Ethical Review Authority (https://etikprovningsmyndigheten.se).

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295

Figure legends and footnotes *(in italic font)*:

FIGURE 1 Flowchart of included patients and reasons for exclusions and distribution of first-line treatment among patients diagnosed with indolent follicular lymphoma (FL) in Sweden 2007-2014.

Abbreviations: n; number, R; rituximab, chemo; chemotherapy, CHOP; cyclophosphamide, doxorubicin, vincristine, and prednisone, CVP; cyclophosphamide, vincristine, and prednisone, FC; fludarabine and cyclophosphamide, B; Bendamustine.

** Among whom 27 patients (42%) received CHOP/B/CVP/FC without R and remaining 37 patients (58%) received oral chemotherapy such as trophosphamide or lenalidomide, or had missing information on type of systemic treatment.*

FIGURE 2 Forest plot showing unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) comparing all-cause mortality among patients with progression of disease (POD) and patients still progression-free, by first-line treatment. In the top panel, POD could occur at any time point during follow-up whereas in the bottom panel POD occurred within 24 months (POD24).

Unadj. - Estimates from Cox proportional hazards models adjusted for time since 1st line treatment.

Adj. – Estimates from Cox proportional hazards models additionally adjusted for age at diagnosis (categorised), sex, calendar year of diagnosis (categorised), and FLIPI.

FIGURE 3 Conditional 5-year survival among follicular lymphoma (FL) patients who experienced progression of disease (POD) or were still progression-free (PF), as a function of time point of POD/PF since first line treatment initiation (in months), by first line treatment type (top panel: R-chemo and R-single, bottom panel: R-CHOP and BR). The vertical dashed line indicates POD24/PF24. The table shows point estimates of the 5-year conditional overall survival (OS) with 95% confidence intervals (CIs) for POD/PF at 6, 12, 24, and 60 months.

FIGURE 4 Overall survival (OS) estimated with the Kaplan-Meier method among patients with follicular lymphoma (FL) treated with R-chemo or R-single as first-line therapy, by POD24

(progression of disease within 24 months of 1st line treatment initiation). Follow-up started at date of progression for POD24-patients and at 24 months after treatment for progression-free patients ("reference"). Eighty patients not experiencing POD within 24 months were excluded due to death (n=74) or administrative censoring (n=6). Top panel: R-chemo and R-single, bottom panel: R-CHOP and BR.

Figures

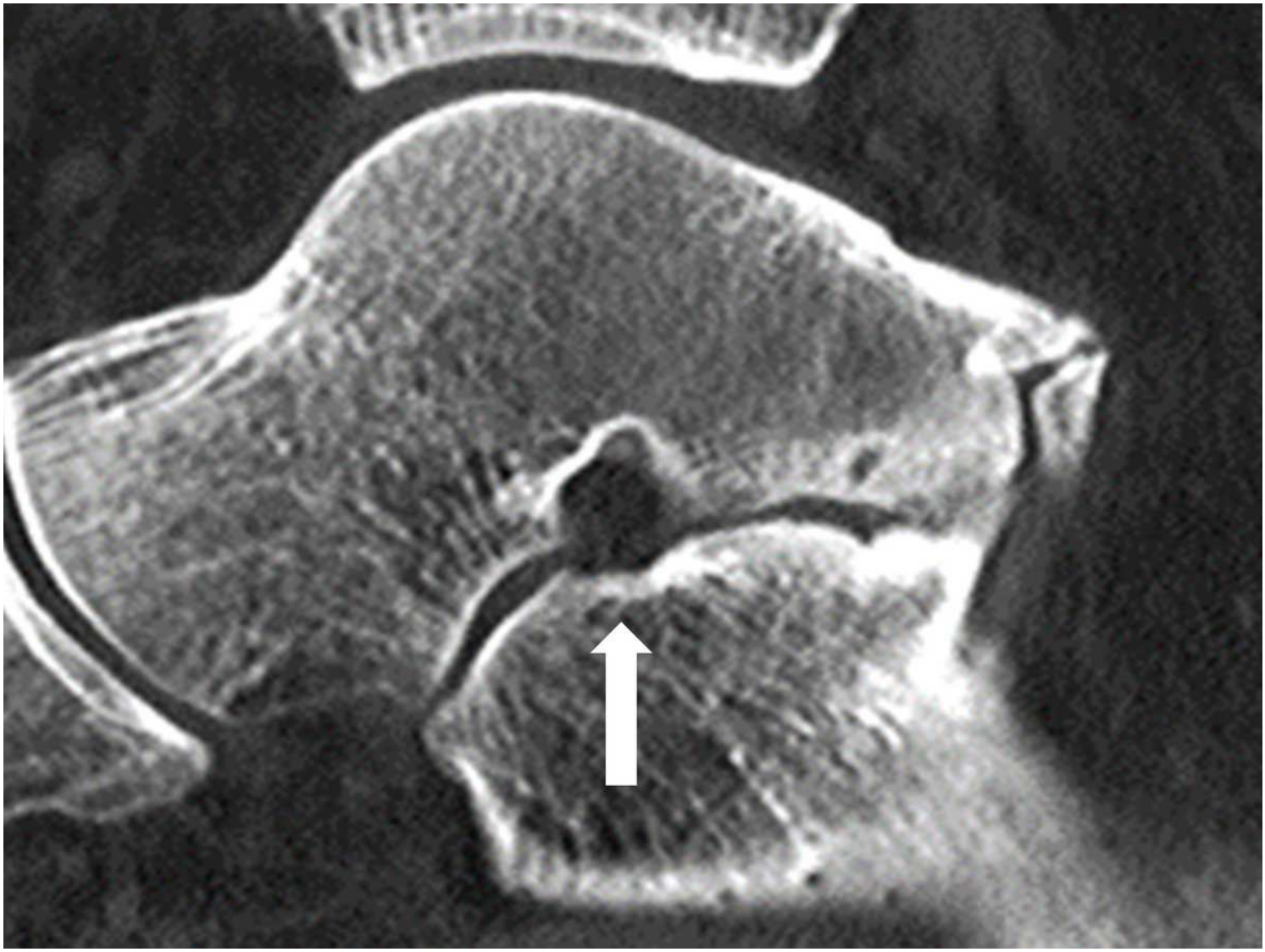

Figure 1

Flowchart of included patients and reasons for exclusions and distribution of first-line treatment among patients diagnosed with indolent follicular lymphoma (FL) in Sweden 2007-2014.

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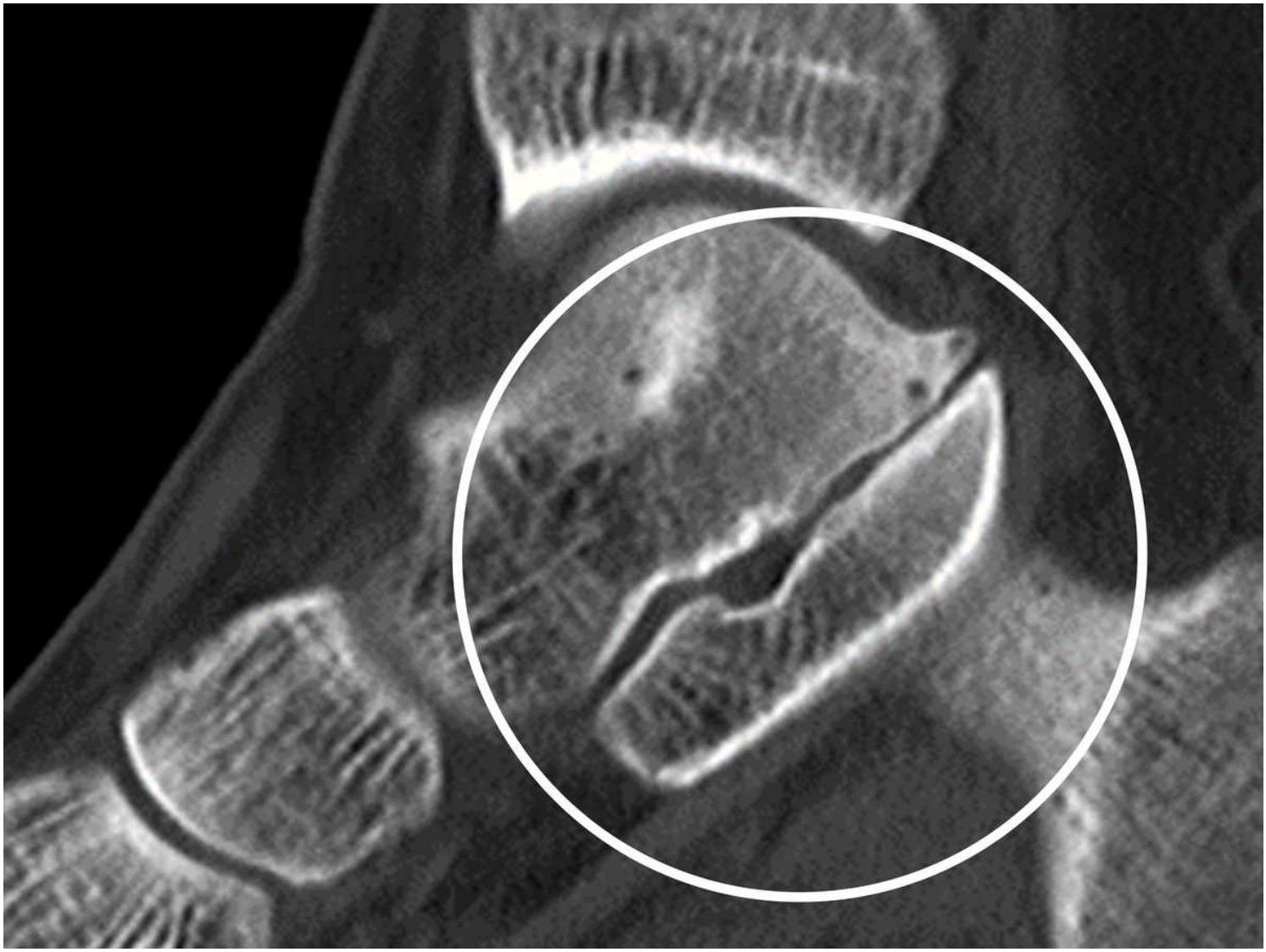

Figure 2

Forest plot showing unadjusted and adjusted hazard ratios (HRs) with 95% confidence 306 intervals (CIs) comparing all-cause mortality among patients with progression of disease (POD) and patients still progression-free, by first-line treatment. In the top panel, POD could occur at any time point during follow-up whereas in the bottom panel POD occurred within 24 months (POD24).

Unadj. - Estimates from Cox proportional hazards models adjusted for time since 1st line treatment. Adj. – Estimates from Cox proportional hazards models additionally adjusted for age at diagnosis (categorised), sex, calendar year of diagnosis (categorised), and FLIPI.

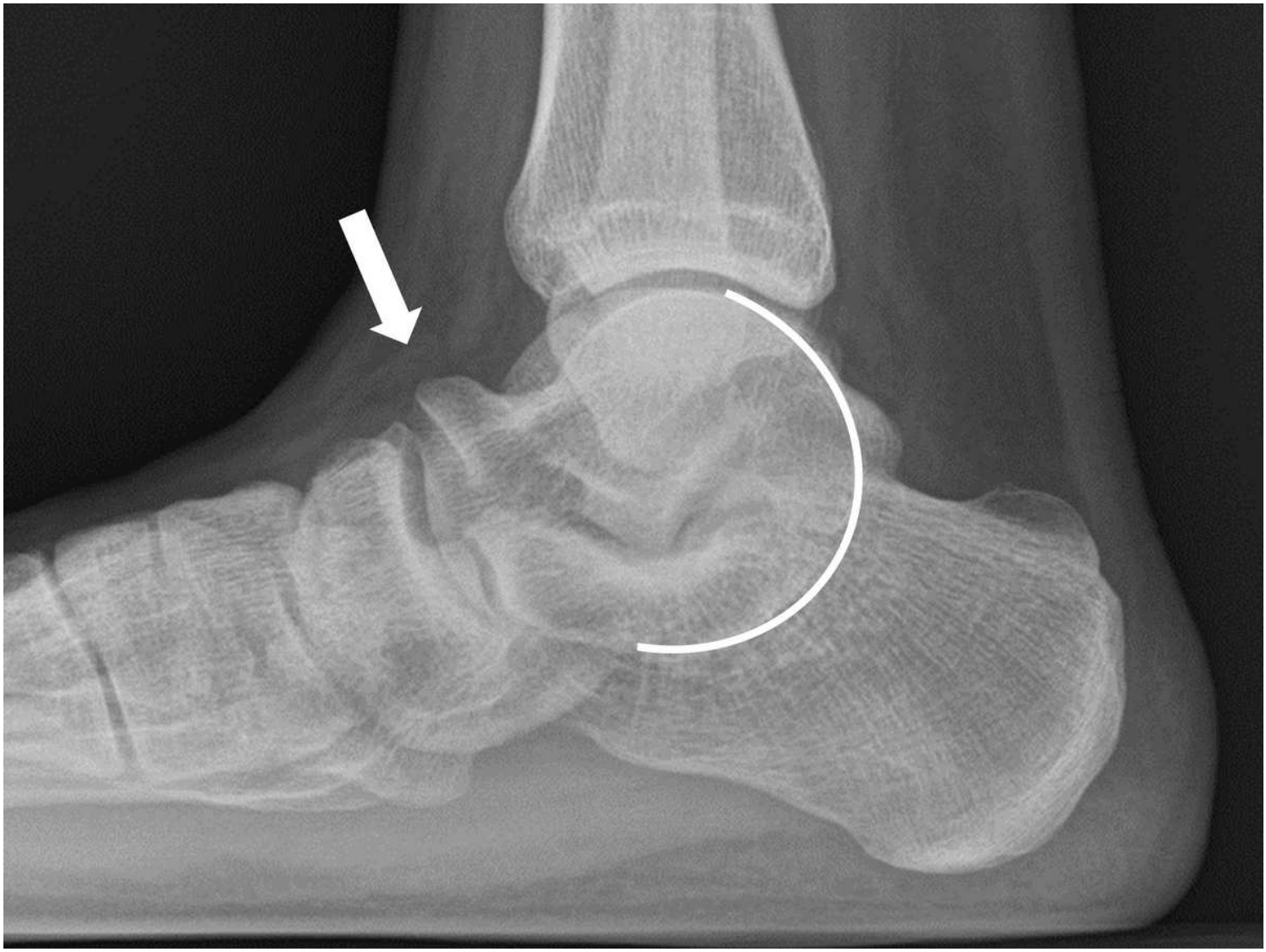

Figure 3

Conditional 5-year survival among follicular lymphoma (FL) patients who experienced progression of disease (POD) or were still progression-free (PF), as a function of time point of POD/PF since first line treatment initiation (in months), by first line treatment type (top panel: R-chemo and R single, bottom panel: R-CHOP and BR). The vertical dashed line indicates POD24/PF24. The table shows point estimates of the 5-year conditional overall survival (OS) with 95% confidence intervals (CIs) for POD/PF at 6, 12, 24, and 60 months.

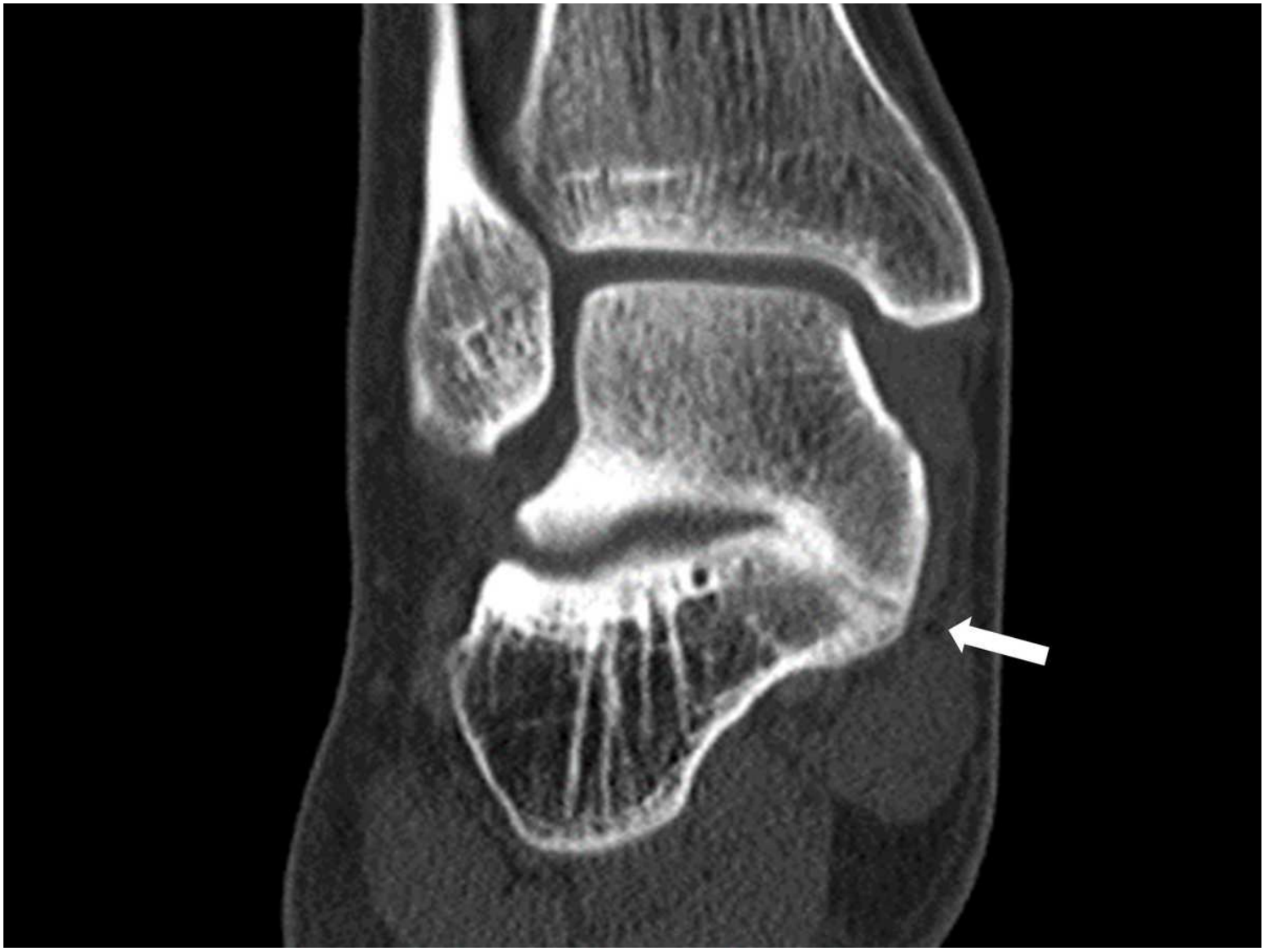

Figure 4

Overall survival (OS) estimated with the Kaplan-Meier method among patients with follicular lymphoma (FL) treated with R-chemo or R-single as first-line therapy, by POD24 (progression of disease within 24 months of 1st line treatment initiation). Follow-up started at date of progression for POD24-patients and at 24 months after treatment for progression-free patients 325 (“reference”). Eighty patients not experiencing POD within 24 months were excluded due to death (n=74) or administrative censoring (n=6). Top panel: R-chemo and R-single, bottom panel: R-CHOP and BR

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Weibulletalsupplement.pdf
- table1.pdf
- table2.pdf