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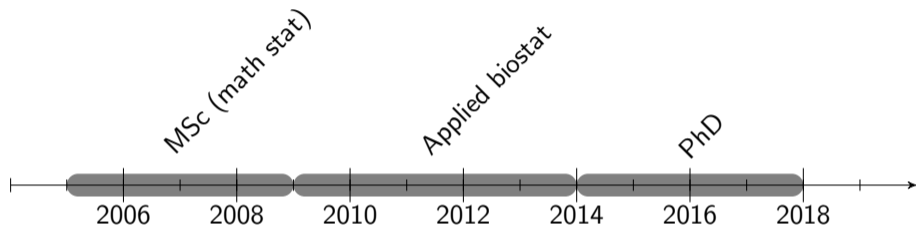
Survival by first-line treatment type and timing of progression among follicular lymphoma patients

Caroline E. Weibull

Karolinska Institutet & War on Cancer

2022 Stata Biostatistics and Epidemiology Virtual Symposium

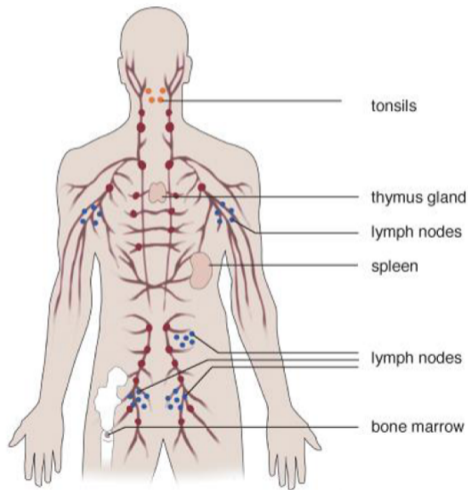
About Me



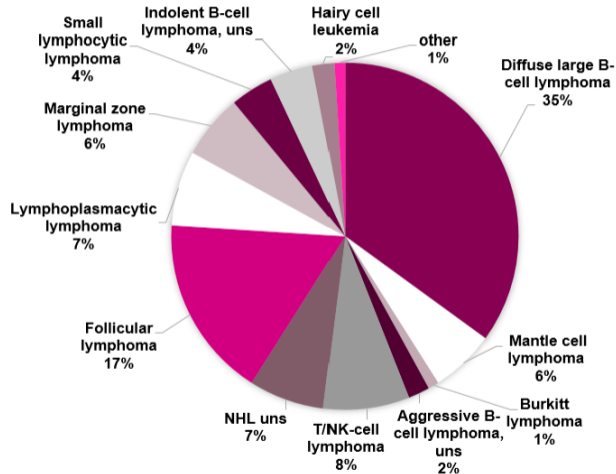
Today:

- 40% as researcher at the Clinical Epidemiology Unit, Karolinska Institutet
- 60% as lead scientist at War on Cancer (<https://waroncancer.com/>)

Lymphoma - malignancies that arise in lymphoid tissue





Lymphoma - more than 70 diseases



Follicular lymphoma

- Follicular lymphoma (FL) is a mostly indolent malignancy.
- Some patients require treatment, whereas others do not (watch and wait).
- Usually not considered curable, but more of a chronic disease.
- Clinical outcome (prognosis) is highly variable.
- POD24 (progression of disease within 24 months) has been suggested as an important prognostic marker of overall survival (OS).
- Most research on POD24 have been in clinical trial settings and with patients treated with immunochemotherapy.

Prognostic value of POD24 validation in follicular lymphoma patients initially treated with chemotherapy-free regimens in a pooled analysis of three randomized trials of the Swiss Group for Clinical Cancer Research (SAKK)



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Summary

The relapse of follicular lymphoma (FL) within 24 months (POD24) of chemoimmunotherapy has been associated with poor survival. We analyzed a pooled dataset of three randomized trials including FL patients with advanced disease, conducted by the Swiss Group for Clinical Cancer Research (SAKK). Overall, POD24 was observed in 27% of 318 patients, but rate variance among studies suggested that the rituximab schedule might affect POD24 rate. POD24 was associated with lower 10-

Prognostic value of POD24 patients initially treated with rituximab in a pooled analysis of three randomized trials in the Swiss Group for Clinical Cancer Research

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LEUKEMIA & LYMPHOMA
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ORIGINAL ARTICLE



Progression of disease within 24 months of initial therapy (POD24) detected incidentally in imaging does not necessarily indicate worse outcome

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ABSTRACT

Progression of disease within 24 months of initial therapy (POD24) has previously been identified as a predictor of reduced overall survival (OS) for patients with follicular lymphoma (FL). Here

Summary

The relapse of follicular lymphoma (FL) within 24 months (POD24) of chemotherapy has been associated with poor survival. We analyzed a pooled dataset of three randomized trials including FL patients with advanced disease, conducted by the Swiss Group for Clinical Cancer Research (SAKK). Overall, POD24 was observed in 27% of 318 patients, but rate variance among studies suggested that the rituximab schedule might affect POD24 rate. POD24 was associated with lower 10-

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Progression of disease within 24 months of initial therapy (POD24) detected incidentally in imaging does not necessarily indicate worse outcome

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<https://doi.org/10.1007/s00277-020-04025-2>

ORIGINAL ARTICLE



Progression of disease within 2 years (POD24) is a clinically relevant endpoint to identify high-risk follicular lymphoma patients in real life

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Abstract

Follicular lymphoma (FL) is an indolent non-Hodgkin's lymphoma with heterogeneous outcomes. Progression or relapse of FL within 2 years (so-called POD24) after diagnosis is associated with a poor outcome for patients treated with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone) in clinical trials. POD24 needs further validation before it can be used as a relevant endpoint to assess treatment efficacy. In the present retrospective monocentric study, we investigated the predictive value of POD24 in a cohort of 1023 FL patients treated in our institution (Nantes Medical University).

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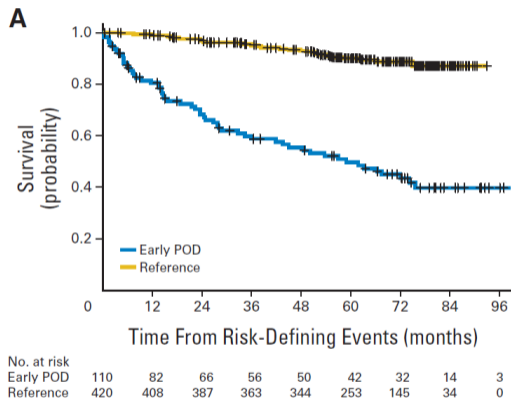
rapy (POD24) has previously been identified in patients with follicular lymphoma (FL). Here

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However, this measure has some inbuilt issues



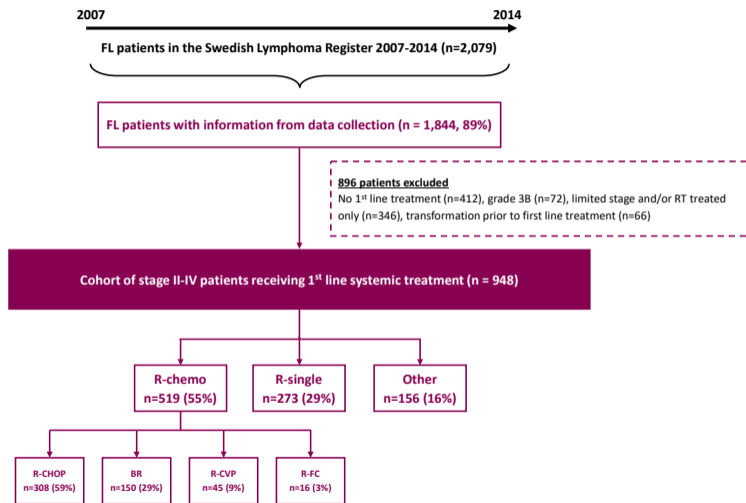
(Casulo C et. al, J Clin Oncol 2015)

- Patients are followed from the “**risk-defining event**” which makes the time scale different for progressed and progression-free patients
- Only progressions within 24 (not 25, 26, ...) months are considered
- Progression-free patients who die before 24 months are excluded from analyses

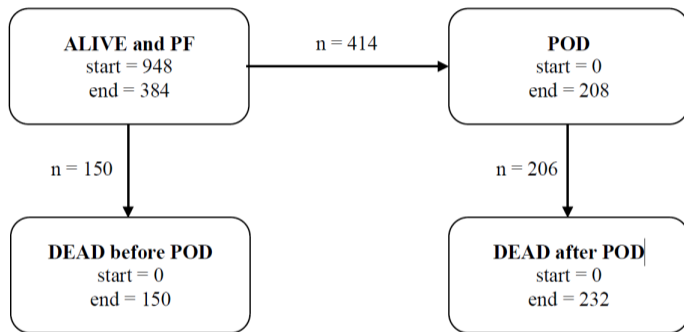
Aim

What is the impact of POD, and timing thereof, on OS among FL patients treated with immunochemotherapy versus immunotherapy only?

Population-based study



An illness-death modelling approach



PF, progression-free; POD, progression of disease

Modelling and predictions

- Modelling of transition rates:
 - Flexible parametric survival models
 - Treatment group (R-chemo, R-single, other), time-varying effects
 - Adjusting for time of entry to POD (semi-Markov)
 - Package `merlin`
- Prediction of transition probabilities:
 - 5-year OS conditional on time of POD/PF
 - Package `multistate`

Modelling transition rates with merlin

```
// Transition 1
stmerlin   tr2 tr3           /// main effects
          if _trans==1      /// fl -> dead
          , dist(rp) df(3)   /// flexible parametric model
          tvc(tr2 tr3) dftvc(2) // time-varying effects
est store m1
```

```
// Transition 2
stmerlin   tr2 tr3           /// main effects
          if _trans==2      /// fl -> POD
          , dist(rp) df(3)   /// flexible parametric model
          tvc(tr2 tr3) dftvc(2) // time-varying effects
est store m2
```

```
// Transition 3
stmerlin   tr2 tr3           /// main effects
          _t0                /// semi-Markov
          if _trans==3      /// POD -> dead
          , dist(rp) df(3)   /// flexible parametric model
          tvc(tr2 tr3) dftvc(2) // time-varying effects
est store m3
```

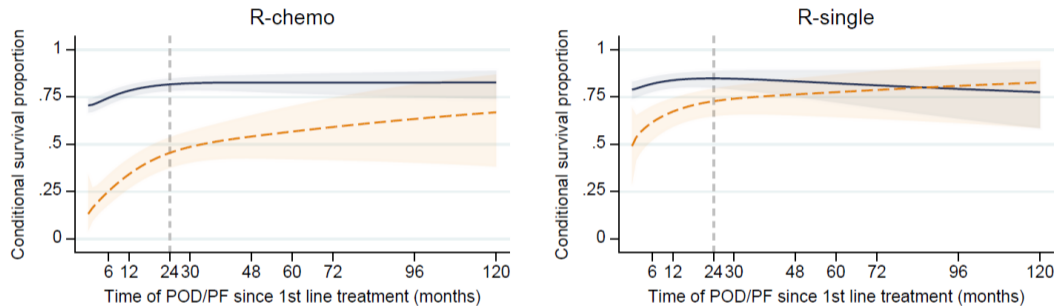
Predicting conditional 5-year OS with predictms

```
range ptime 0 10 100
gen tvar5 = 5 + ptime

// Predict the conditional 5-year overall survival
forvalues ptime = 1/100 {
    cap drop temptime
    gen temptime = tvar5[`ptime'] in 1

    predictms, transmat(tmat)           /// specify transition matrix
        models(m1 m2 m3)                /// specify models
        from(1 2)                        /// starting states
        at1(_t0 `=ptime[`ptime']' tr1 1) /// R-chemo treated patients
        at2(_t0 `=ptime[`ptime']' tr2 1) /// R-single treated patients
        at3(_t0 `=ptime[`ptime']' tr3 1) /// Patients treated with other
        timevar(temptime)                /// prediction time
        ltruncated(`=ptime[`ptime']')    /// entry time
        probability                       // transition probability
}
```

5-year OS by time of POD/PF: R-CHEMO vs R-Single



Conditional 5-year overall survival for FL patients treated with R-chemo (left) and R-single (right). The dashed line represents POD/PF-24.

Conclusions

- Progression mainly before, but also after 24 months, is associated with a worse 5-year overall survival among immunochemotherapy treated patients.
- This inferior survival remained for patients progressing at least within four years after treatment initiation .
- Among patients selected for immunotherapy only, progression of disease did not have a strong effect on the 5-year overall survival.

Thank you and some references below

Crowther, MJ and Lambert, PC. Parametric multistate survival models: flexible modelling allowing transition-specific distributions with application to estimating clinically useful measures of effect differences. *Statistics in Medicine* (2017).

Crowther MJ. merlin - a unified framework for data analysis and methods development in Stata. *Stata Journal* (2020).

Casulo C, Byrtek M, Dawson KL, Zhou X, Farber CM, Flowers CR, Hainsworth JD, Maurer MJ, Cerhan JR, Link BK, Zelenetz AD, Friedberg JW. Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. *Journal of Clinical Oncology* (2015).