Tumor size evolution in randomized clinical trials : joint modeling approach and dynamic predictions

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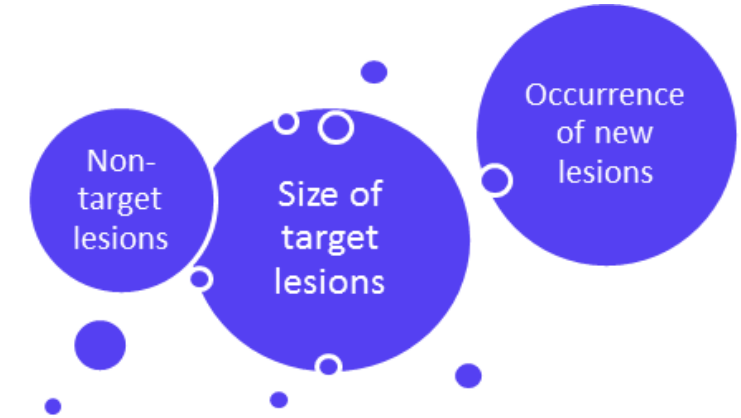
Tumor evaluations in clinical trials



- **WHO criteria** (1980s)
- **RECIST** (Response Evaluation Criteria in Solid Tumours) v1.0 (2000) and v1.1 (2009)

Tumor evaluation criteria

Comparable assessment of tumor change

- Within a trial (between patients)
- Between trials

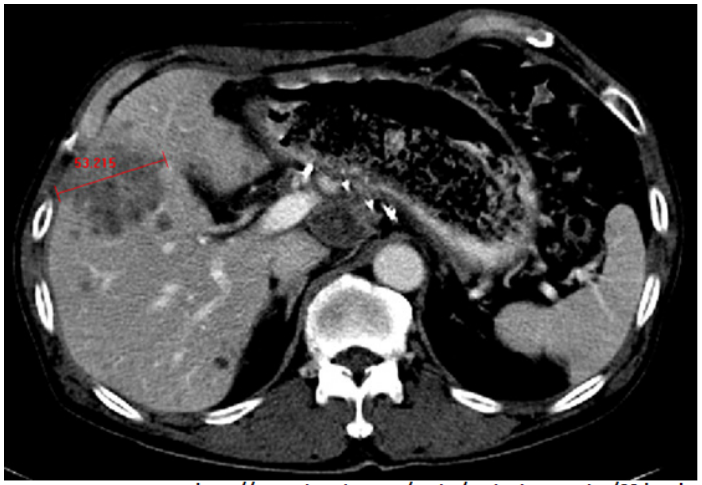
Categorical criteria - RECIST and WHO

- **WHO**
  - Bidimensional size, target lesions determined before treatment
  - Progression : >25% increase of one or more target lesions
  - Appearance of new lesions $\rightarrow$ global progression
- **RECIST** (v1.1)
  - Unidimensional size, max 2 lesions per organ and up to 5 total
  - Progression : >20% increase over smallest sum observed ($>$ 5 mm absolute increase)
  - Appearance of new lesions $\rightarrow$ global progression

4 categories (Complete Response, Partial Response, Progressive Disease, Stable Disease)

$\Rightarrow$ dichotomization : response or no response / progression or no progression

Measurement of lesions


http://www.irrecist.com/recist/recist-in-practice/02.html

- The longest diameters measured in the plane in which the images were acquired
- Measure the longest diameter of a lesion
- Measure the longest perpendicular diameter to it and the burden is their product (WHO criteria)
- Total individual tumor burden is the sum (of the longest diameters - RECIST, of the products - WHO)
- Baseline : no more than 4 weeks before treatment, Follow-up : every 6-8 weeks

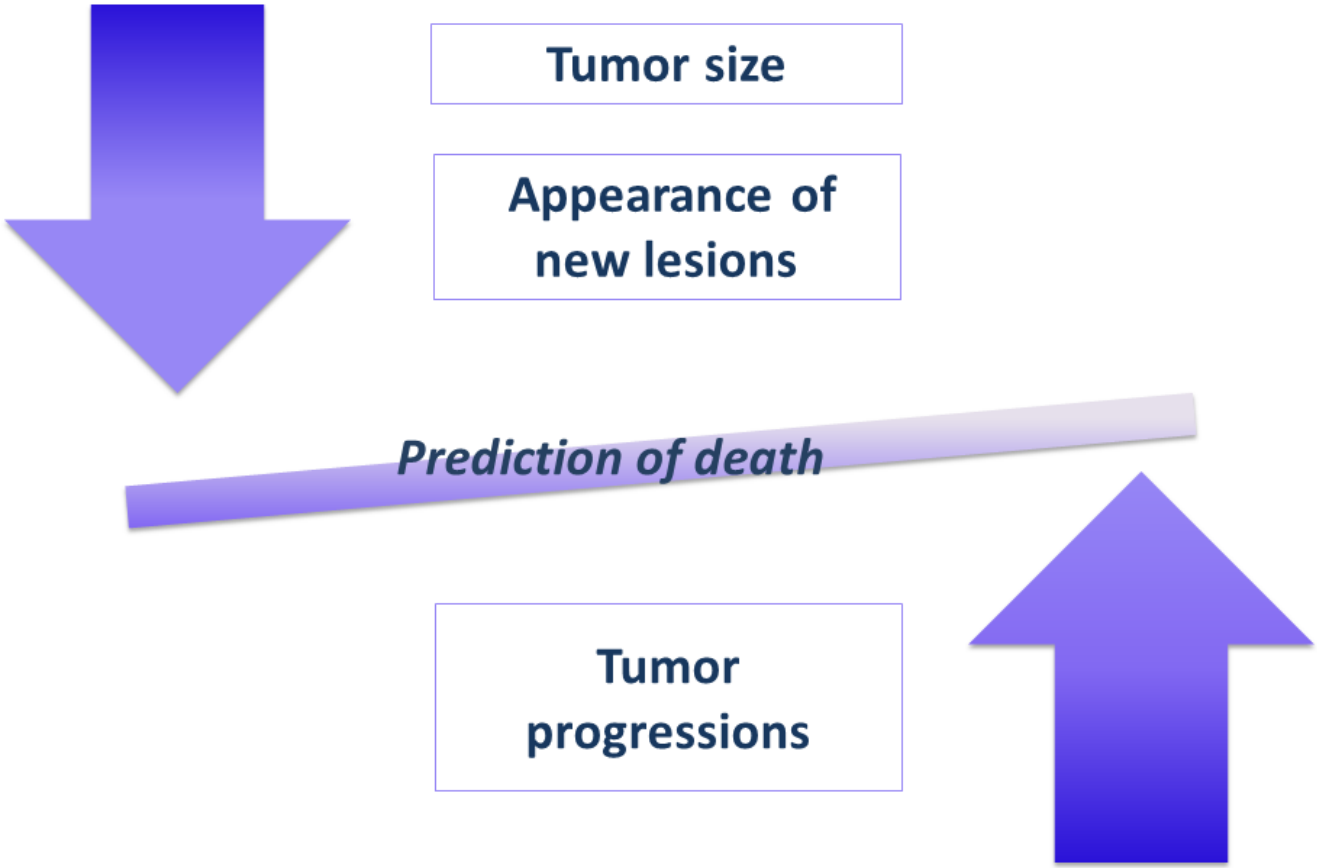
Measurability of lesions

- Measurable tumor lesions - at least one diameter with a minimum size of :
  - 10 mm by CT scan
  - 10 mm caliper measurement by clinical exam
  - 20 mm by chest X-ray

  Lymph nodes : $\geq$15 mm in *short* axis when assessed by CT scan
- Non-measurable tumor lesions
  - small lesions (longest diameter <10 mm)
  - truly non-measurable lesions, eg. leptomeningeal disease, ascites, inflammatory breast disease

Objective

Does the continuous tumor size and/or appearance of new lesions enable better prediction of the OS than times of progression ?

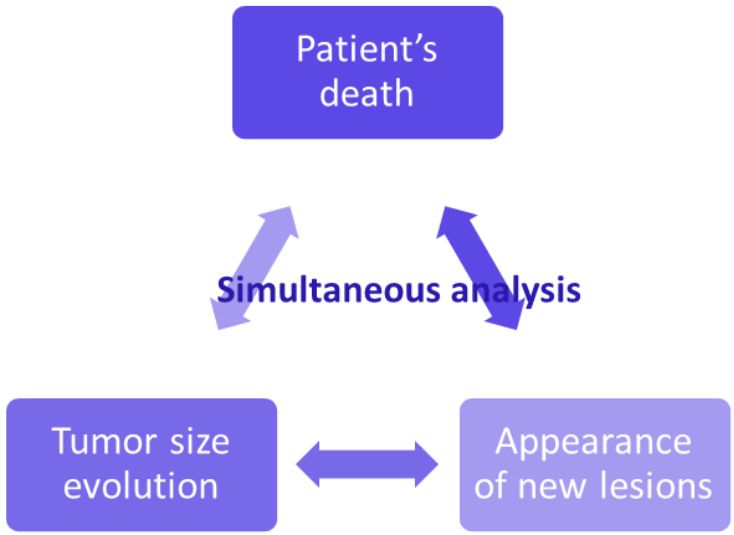


Reference : Król et al. *Biometrics*, 2016.

Observed data

For individual i ($i = 1, \ldots, N$) we observe :

- **Longitudinal biomarker** : $Y_i(t_{ik})$
- **Recurrences** : $T_{ij} = \min(T_{ij}^*, C_i, T_i^*)$ and $\delta_{ij} = \mathbb{1}_{\{T_{ij}^* = T_{ij}\}}$
- **Terminal event** : $T_i = \min(C_i, T_i^*)$ and $\delta_i = \mathbb{1}_{\{T_i^* = T_i\}}$



Joint model for longitudinal data, recurrent events and a terminal event

System of linear mixed-effects model and two hazard functions :

$$\begin{cases} Y_i(t_{ik}) = m_i(t_{ik}) + \epsilon_i(t_{ik}) = \boldsymbol{X}_{i,l}(t_{ik})^\top \beta_l + \boldsymbol{Z}_i(t_{ik})^\top \boldsymbol{b}_i + \epsilon_i(t_{ik}) & \text{(Biomarker)} \\ r_{ij}(t|v_i, \boldsymbol{b}_i) = r_0(t) \exp\left(v_i + \boldsymbol{X}_{ij,r}^\top \beta_r + g(\boldsymbol{b}_i, t)^\top \eta_r\right) & \text{(Recurrences)} \\ \lambda_i(t|v_i, \boldsymbol{b}_i) = \lambda_0(t) \exp\left(\alpha v_i + \boldsymbol{X}_{i,t}^\top \beta_t + h(\boldsymbol{b}_i, t)^\top \eta_t\right) & \text{(Death)} \end{cases}$$

- $u_i = (\boldsymbol{b}_i^T, v_i)^T \sim \mathcal{N}(\mathbf{0}, \mathbf{B})$ with $\mathbf{B} = \begin{pmatrix} \mathbf{B_1} & \mathbf{0} \\ \mathbf{0} & \sigma_v^2 \end{pmatrix}$
- measurement errors *iid*, $\epsilon_i(t_{ik}) \sim \mathcal{N}(0, \sigma_\epsilon^2)$
- $g(\boldsymbol{b}_i, t)$ and $h(\boldsymbol{b}_i, t)$ - link functions
- $r_0(t)$, $\lambda_0(t)$ - baseline hazard functions

Estimation

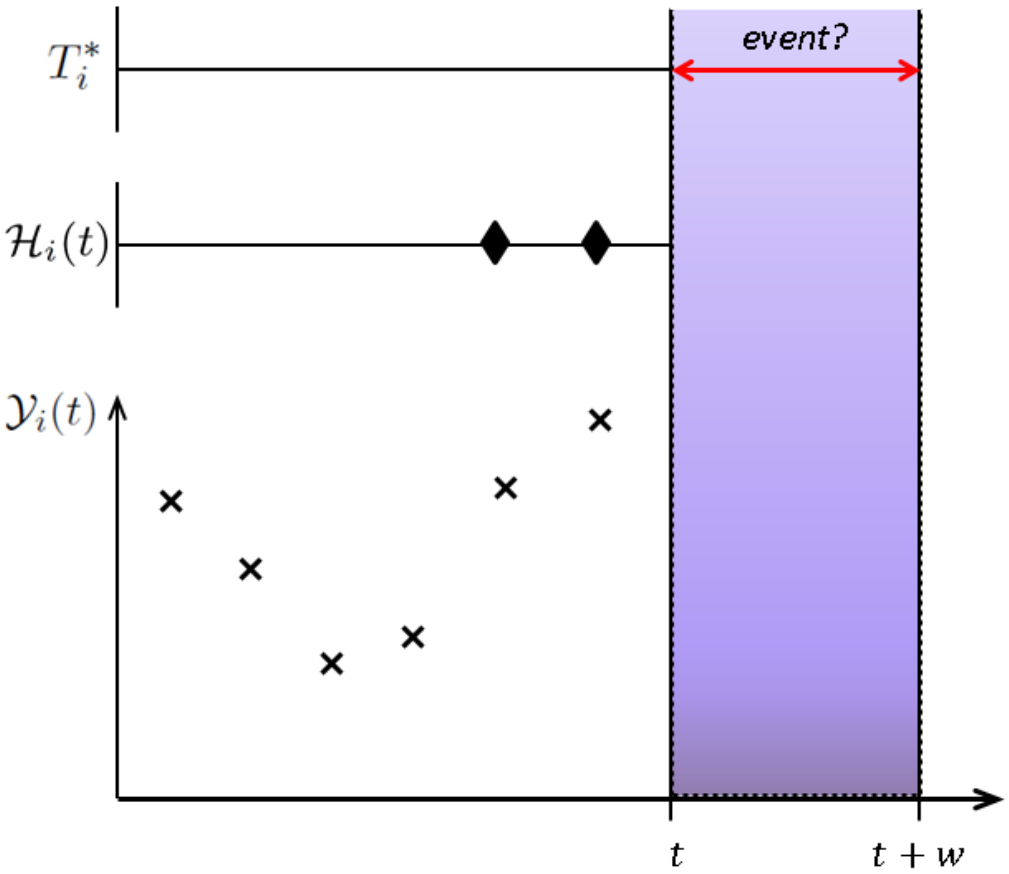
- Joint marginal likelihood

$$L_i(\boldsymbol{\theta}) = \int_{\boldsymbol{u}_i} \prod_{k=1}^{n_i} f_{Y|\boldsymbol{u}_i}(Y_i(t_{ik})|\boldsymbol{u}_i;\boldsymbol{\theta}) \prod_{j=1}^{r_i} f_{T^r|\boldsymbol{u}_i}(T_{ij},\delta_{ij}|\boldsymbol{u}_i;\boldsymbol{\theta}) \cdot f_{T^t|\boldsymbol{u}_i}(T_i,\delta_i|\boldsymbol{u}_i;\boldsymbol{\theta}) f_{\boldsymbol{u}_i}(\boldsymbol{u}_i;\boldsymbol{\theta}) \mathrm{d}\boldsymbol{u}_i$$

  - n_i - number of biomarker measurements of individual i,
    r_i - number of recurrent events of individual i
  - Parameters to estimate $\boldsymbol{\theta} = (\boldsymbol{\beta}_l^\top, \boldsymbol{\beta}_r^\top, \boldsymbol{\beta}_t^\top, \boldsymbol{\eta}_r^\top, \boldsymbol{\eta}_t^\top, \alpha, r_0(\cdot), \lambda_0(\cdot), \mathbf{B}, \sigma_\epsilon)^\top$

- Penalized maximum likelihood estimation using Marquardt algorithm
- Baseline hazard functions approximation using splines : smooth estimation
- Integrals approximated using Gauss-Hermite quadrature

Dynamic predictions



- $\mathcal{H}_i(t)$ - history of recurrences of individual i until t
  $\mathcal{Y}_i(t)$ - history of the biomarker of individual i until t
- Predicted probability of the terminal event T_i^* in a horizon $[t, t+w]$

$$\mathbb{P}(T_i^* \leq t+w | T_i^* > t, \mathcal{F}_i(t), \boldsymbol{X}_i; \boldsymbol{\theta})$$

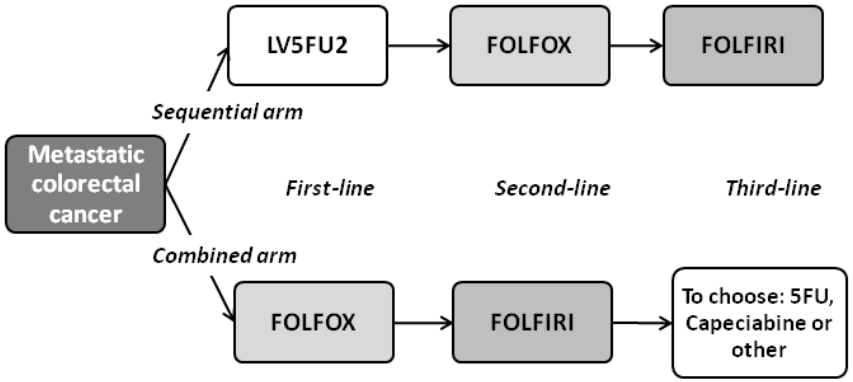
$\mathcal{F}_i(t) = \mathcal{H}_i(t)$,
$\mathcal{F}_i(t) = \mathcal{Y}_i(t)$
or $\mathcal{F}_i(t) = \{\mathcal{H}_i(t), \mathcal{Y}_i(t)\}$

Measures of predictive abilities

- EPOCE (Expected Prognostic Observed Cross-Entropy) *Commenges et al.*, 2012
  - Evaluation of conditional density of the event given the individual history
  - Internal validation : approximate cross-validated estimator CVPOL_a
- Brier score
  - The inverse probability of censoring weighted error estimator (data-based Brier score) *Gerds and Schumacher*, 2006
  - Comparison of predictions and actual observed events
  - Internal validation : *k*-fold cross-validation

Clinical trial FFCD 2000-05

- Follow-up :
  - Phase III randomized multi-center clinical trial (53 centers in France), 407 patients



  - Tumor evaluation every 8 weeks, max 4 target lesions in 2 dimensions
  - Change of line : progression (WHO criteria), unacceptable toxicity, decision of investigator

Ducreux et al., *The Lancet Oncology,* 2011

Clinical trial FFCD 2000-05

- Objectives :
  - Which of **longitudinal biomarker**, **times of appearance of new lesions** or **times of progression** provide the most accurate **prediction** of the **overall survival** ?
  - To identify the prognostic factors on the outcomes of interest
  - To evaluate the treatment effect

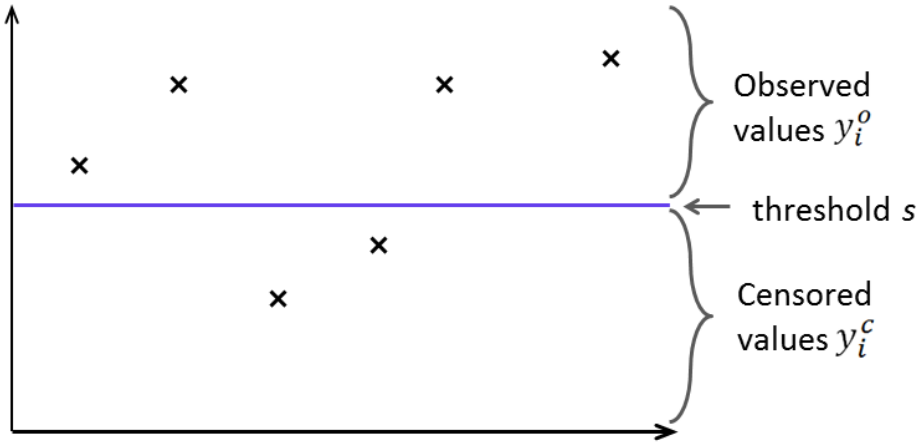
Data

- Biomarker definition : sum of the longest diameters

$$SLD_{ij} = \sum_{k=1}^{n_{ij}} d_{ijk}, \quad j = 0, 1, \ldots, n_i, \quad i = 1, \ldots, 407$$

$n_i \in \{0, 1, ..., 17\}$ - number of visits of individual i, $n_{ij} \in \{1, 2, 3, 4\}$ - number of target lesions measured during visit j, d_{ijk} - max diameter of lesion k measured during visit j of individual i

- Left-censoring



Data : FFCD 2000-05

N=402 patients analyzed. Observed :

- 6.18 tumor size measurements per patient
- 1.05 appearance of new lesions per patient
- 1.82 progression per patient
- 321 deaths
- Overall survival : 16.3 months in the combination (C) arm and 16 months in the sequential (S) arm

Results of the trivariate model

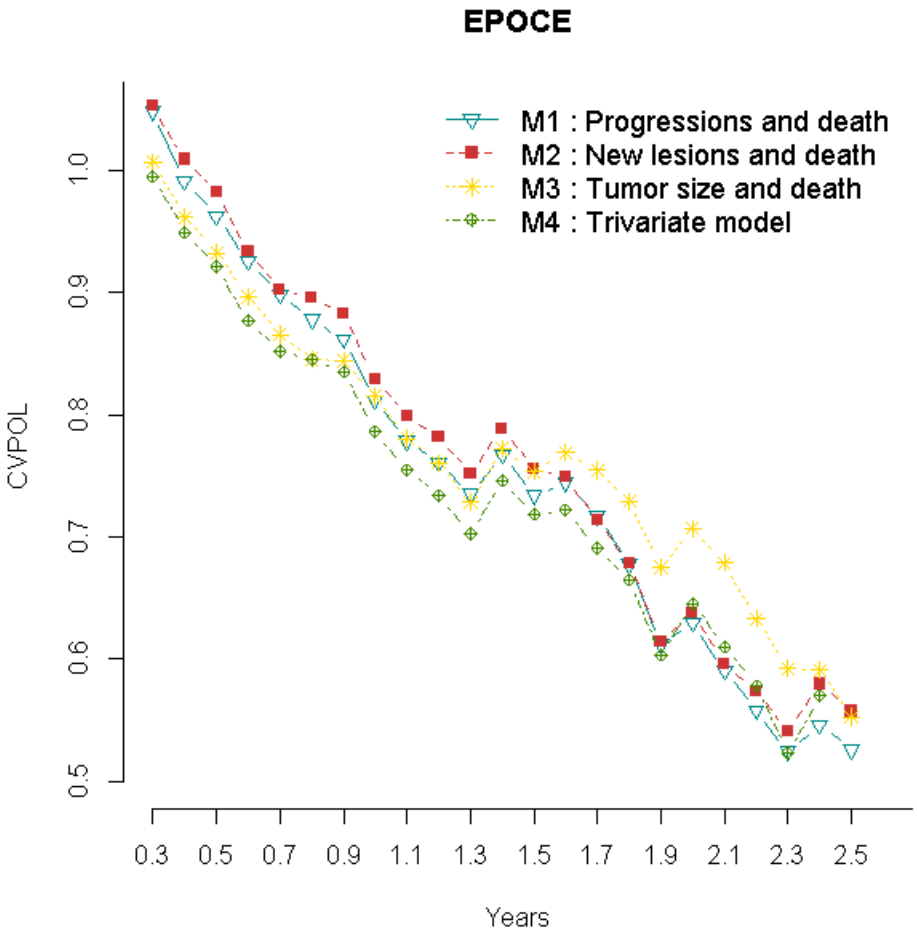
	Biomarker : SLD		New lesions	Death
Covariate	Est. (SE)	p-value	HR (95% CI)	HR (95% CI)
Intercept	2.90 (0.29)	$<$0.001	-	-
Time	$-$0.35 (0.13)	0.006	-	-
Treatement (C/S)	$-$0.20 (0.14)	0.16	0.96 (0.75-1.21)	1.02 (0.64-1.61)
Treatement (C/S)$\times$Time	$-$0.42 (0.15)	0.007	-	-
Age (60-69/$<$60 years)	0.23 (0.18)	0.20	0.75 (0.56-1.02)	1.04 (0.57-1.87)
Age ($\geq$70/$<$60 years)	0.02 (0.16)	0.91	0.82 (0.61-1.09)	1.40 (0.79-2.49)
Sex (Women/Men)	0.27 (0.14)	0.06	0.86 (0.67-1.10)	1.02 (0.63-1.65)
Baseline WHO PS (1/0)	$-$0.14 (0.15)	0.34	1.16 (0.89-1.51)	1.51 (0.85-2.68)
Baseline WHO PS (2/0)	0.45 (0.21)	0.035	2.15 (1.44-3.21)	10.22 (3.68-28.40)
. . . . .				

- Significant decreasing value of SLD with time (-0.35), and decreasing with time more pronounced for the combination arm (-0.40)
- Strong effect of WHO performance status 2 on the risk of death, new lesions and on tumor size
- No significant associations with gender and age
- Significant associations between the processes via the shared random effects (except of the link between the biomarker and recurrent events)

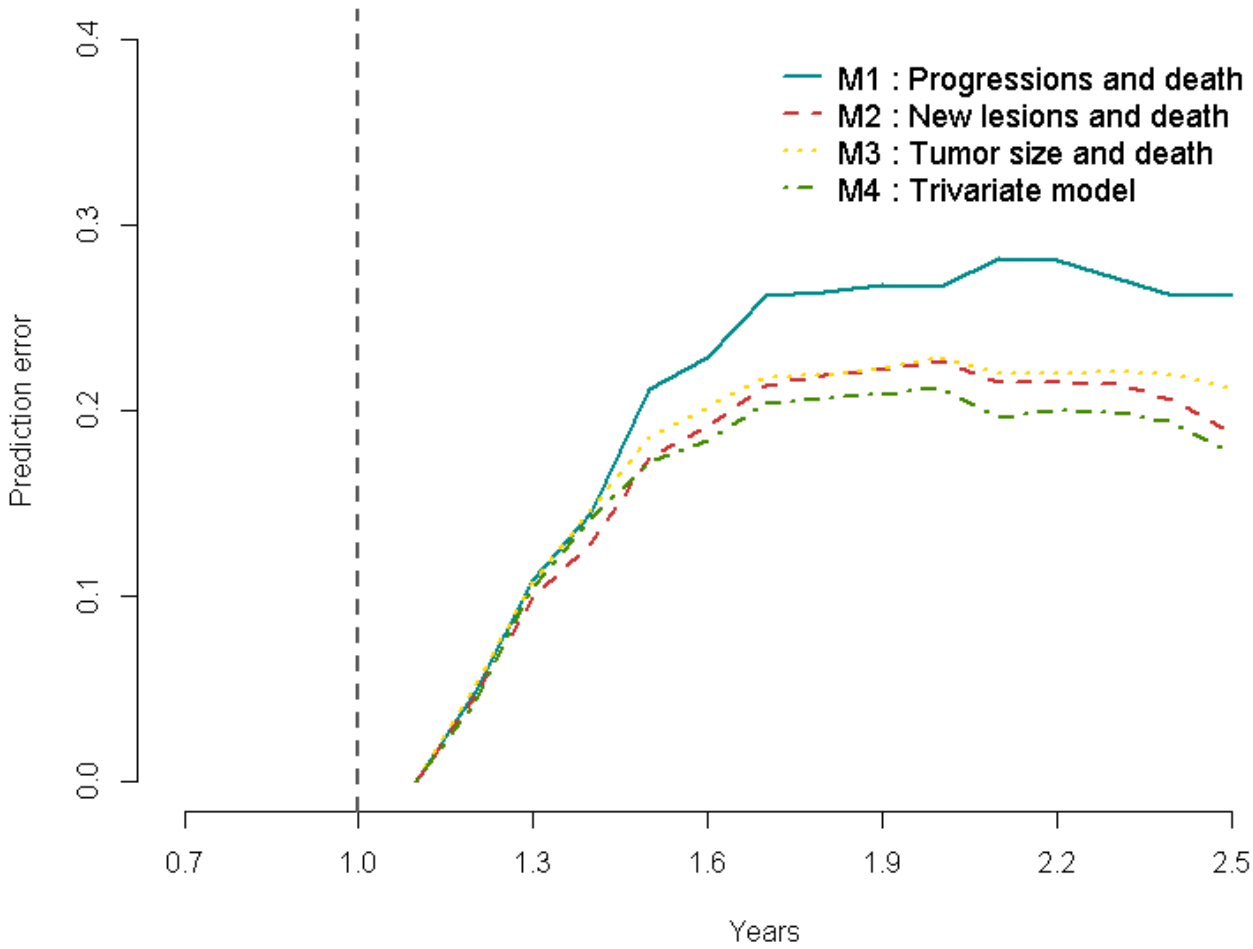
Comparison with the alternative models - predictive ability

- Comparison of the models in terms of the **predictive ability** of the overall survival
  - Joint modelling of times of progression and time of death (M1)
  - Joint modelling of times of appearance of new lesions and time of death (M2)
  - Joint modelling of tumor size (SLD) and time of death (M3)
  - Joint modelling of tumor size (SLD), times of appearance of new lesions and time of death (M4)
- Measures of predictvie ability using internal validation
  - **Brier score** (10-fold cross-validation)
  - **EPOCE** (CVPOL_a - approximated cross-validation)

Results - EPOCE



Results - Brier score

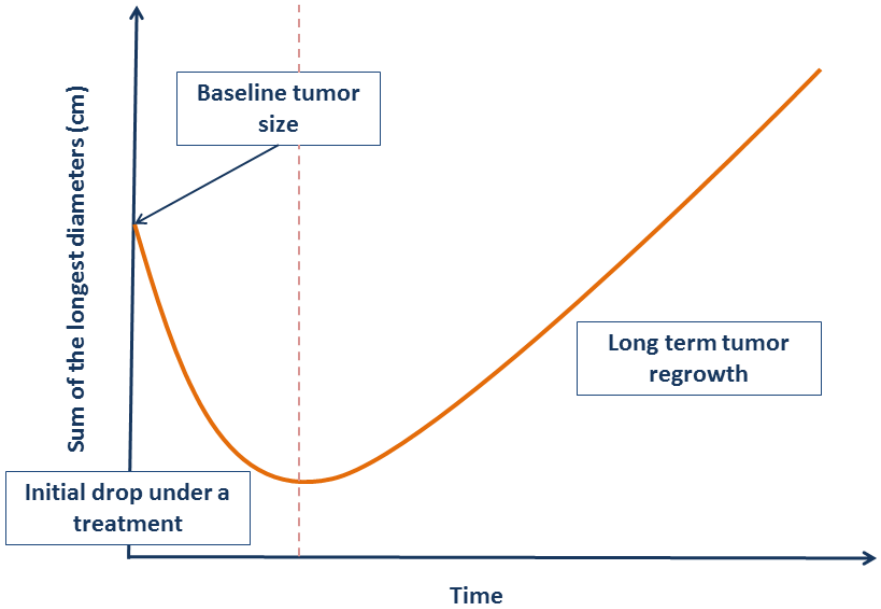


Conclusion

- Advantages of using joint models for simultaneous analysis of prognostic factors
- Comparison of joint models of different types in terms of predictive accuracy
- Proposition of a new trivariate joint model
- FFCD 2000-05 : Improvement of predictive abilities using tumor size and appearance of new lesions
- Implementation of the proposed model into the **R** package `frailtypack` *Rondeau et al.*, 2012

Perspectives

- Incorporation of information on progression of non-target disease
- Application to other clinical trials, in particular to a meta-analysis
- More flexible modeling of the biomarker
  - Parametric approach : two slopes of time
  - Approximation by B-Splines
  - Tumor dynamics modeled using ordinary differential equations *Claret et al.*, 2009



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