Analysing Survival Endpoints in Randomized Clinical Trials using Generalized Pairwise Comparisons

Dr Julien PERON
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Department of Biostatistics HCL – LBBE UCBL
Department of Medical oncology HCL – LBBE UCBL

Outline

- The standard procedure of generalized pairwise comparisons
- An extension for right-censored data
- A patient-oriented measure of treatment benefit
- Benefit-risk balance
  - NCIC PA.3 trial => erlotinib in pancreatic cancer

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- The standard procedure of generalized pairwise comparisons
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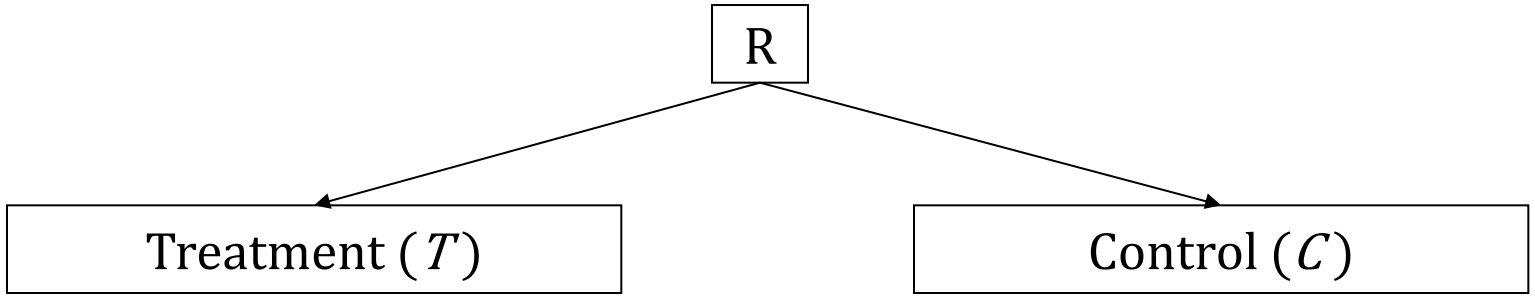
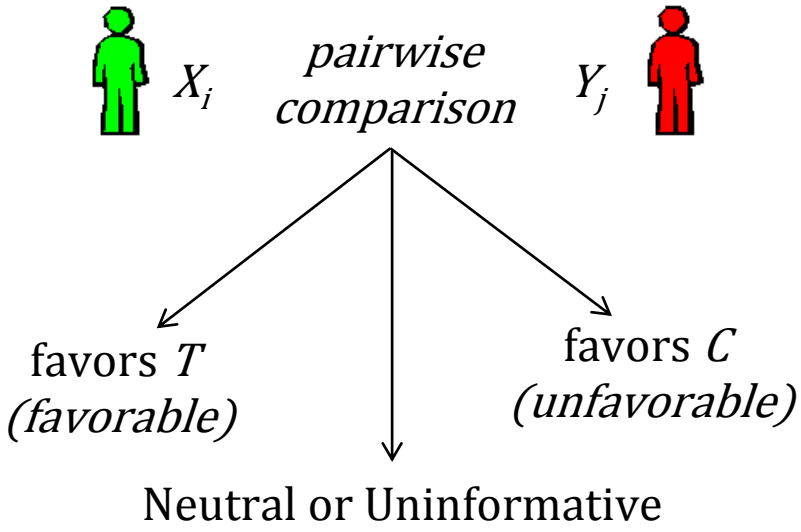
Methods – Pairwise comparisons



Let x_i be the outcome of i^{th} subject in T $(i = 1. \ldots . n)$

Let y_j be the outcome of j^{th} subject in C $(j = 1. \ldots . m)$



Buyse M. stat in med 2010

Methods – Definition of thresholds

Coutinuous outcome

Pair	Rating
$x_i - y_j > \tau$	Favorable
$x_i - y_j < (-\tau)$	Unfavorable
$\mid x_i - y_j \mid \leq \tau$	Neutral
x_i or y_j missing	Uninformative

Buyse. stat in med 2010

Methods – Definition of priority

First priority outcome	Second priority outcome	Pair rating
Favorable	NA	Favorable
Unfavorable	NA	Unfavorable
Neutral/Uninf	Favorable	Favorable
Neutral/Uninf	Unfavorable	Unfavorable
Neutral/Uninf	Neutral/Uninf	Neutral/Uninf

Buyse. stat in med 2010

Methods – Definition of priority

First priority outcome	Second priority outcome	Pair rating
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Unfavorable	NA	Unfavorable
Neutral/Uninf	Favorable	Favorable
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Neutral/Uninf	Neutral/Uninf	Neutral/Uninf

Buyse. stat in med 2010

Methods – Definition of priority

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Neutral/Uninf	Favorable	Favorable
Neutral/Uninf	Unfavorable	Unfavorable
Neutral/Uninf	Neutral/Uninf	Neutral/Uninf

Buyse. stat in med 2010

Methods – Standard procedure for pairwise scoring

$$U_{ij} = \begin{cases} +1 \text{ when the pair } \left(X_i, Y_j\right) \text{ is favorable} \\ -1 \text{ when the pair } \left(X_i, Y_j\right) \text{ is unfavorable} \\ 0 \text{ otherwise} \end{cases}$$

$$\Delta = U = \frac{1}{m \cdot n} \sum_{i=1}^{n} \sum_{j=1}^{m} U_{ij}$$

Δ in named «net chance of a better outcome»

Buyse. stat in med 2010

Some notations

- x_i^0 and y_j^0 : time-to-event
- x_i and y_j : time-to-observation
- Event indicator :

$$\delta_i = \left.\begin{cases} 1 \; if \; x_i = \; x_i^0 \\ 0 \; if \; x_i < \; x_i^0 \end{cases}\right\} \text{in group T}$$

$$\varepsilon_j = \left.\begin{cases} 1 \; if \; y_j = \; y_j^0 \\ 0 \; if \; \; y_j < \; y_j^0 \end{cases}\right\} \text{in group C}$$

- Survival function:

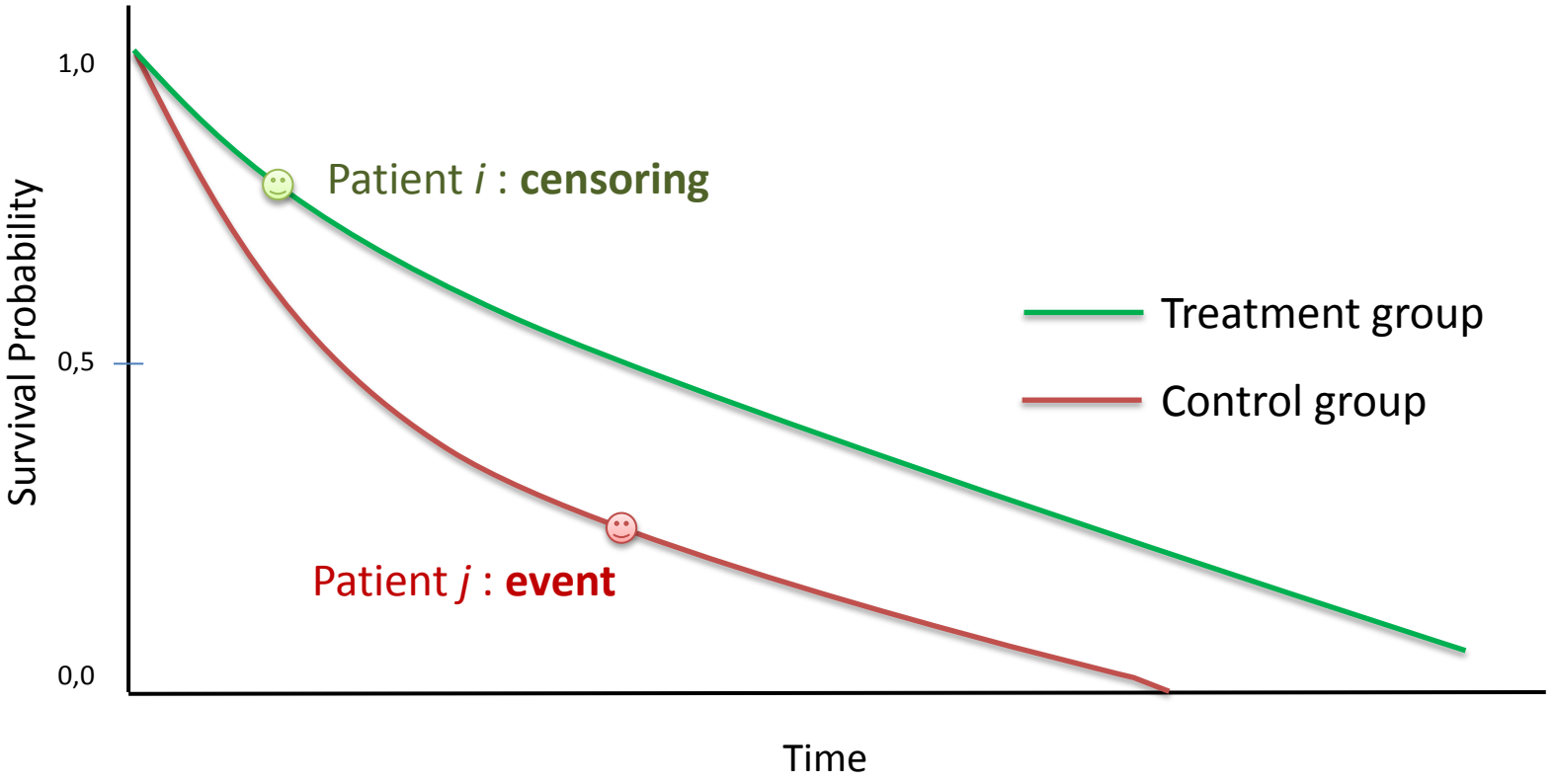
$$S_{Ttt}(t) = \mathbb{P}\left[x_i^0 \geq t\right] \text{ and } S_{Ctrl}(t) = \mathbb{P}\left[y_j^0 \geq t\right]$$

The standard procedure to include time-to-event' outcome

$(\delta_i, \varepsilon_j)$	$x_i - y_j \geq \tau$	$x_i - y_j \leq -\tau$	$\lvert x_i - y_j \rvert < \tau$
$(1,1)$	Favorable	Unfavorable	Neutral
$(0,1)$	Favorable	Uninformative	Uninformative
$(1,0)$	Uninformative	Unfavorable	Uninformative
$(0,0)$	Uninformative	Uninformative	Uninformative

Buyse M. *Stat in med*, 2010

The standard procedure to include time-to-event outcome



Gehan. *Biometrika,* 1965

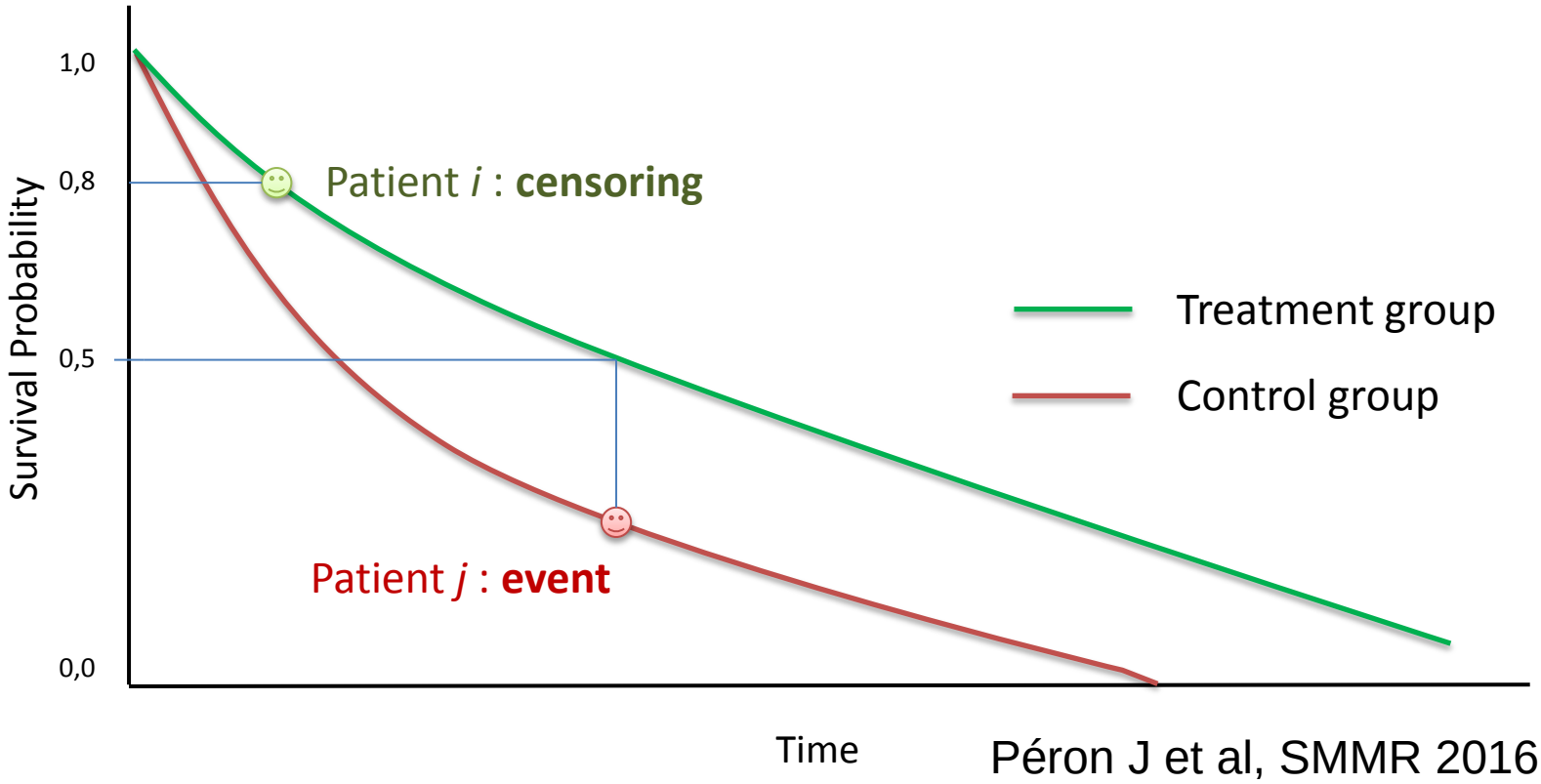
Outline

- The standard procedure of generalized pairwise comparisons
- An extension for right-censored data
- A patient-oriented measure of treatment benefit
- Benefit-risk balance
  - NCIC PA.3 trial => erlotinib in pancreatic cancer

The extended procedure taking into account 'non-informative' pairs

Based on the Kaplan-Meier estimate of the survival function

$$\mathbb{P}\left[\left(x_i^0 > y_j^0\right) \middle| \left(x_i^0 > x_i\right)\right] = \frac{\hat{S}_{Ttt}(y_j)}{\hat{S}_{Ttt}(x_i)} = \frac{0{,}5}{0{,}8}$$

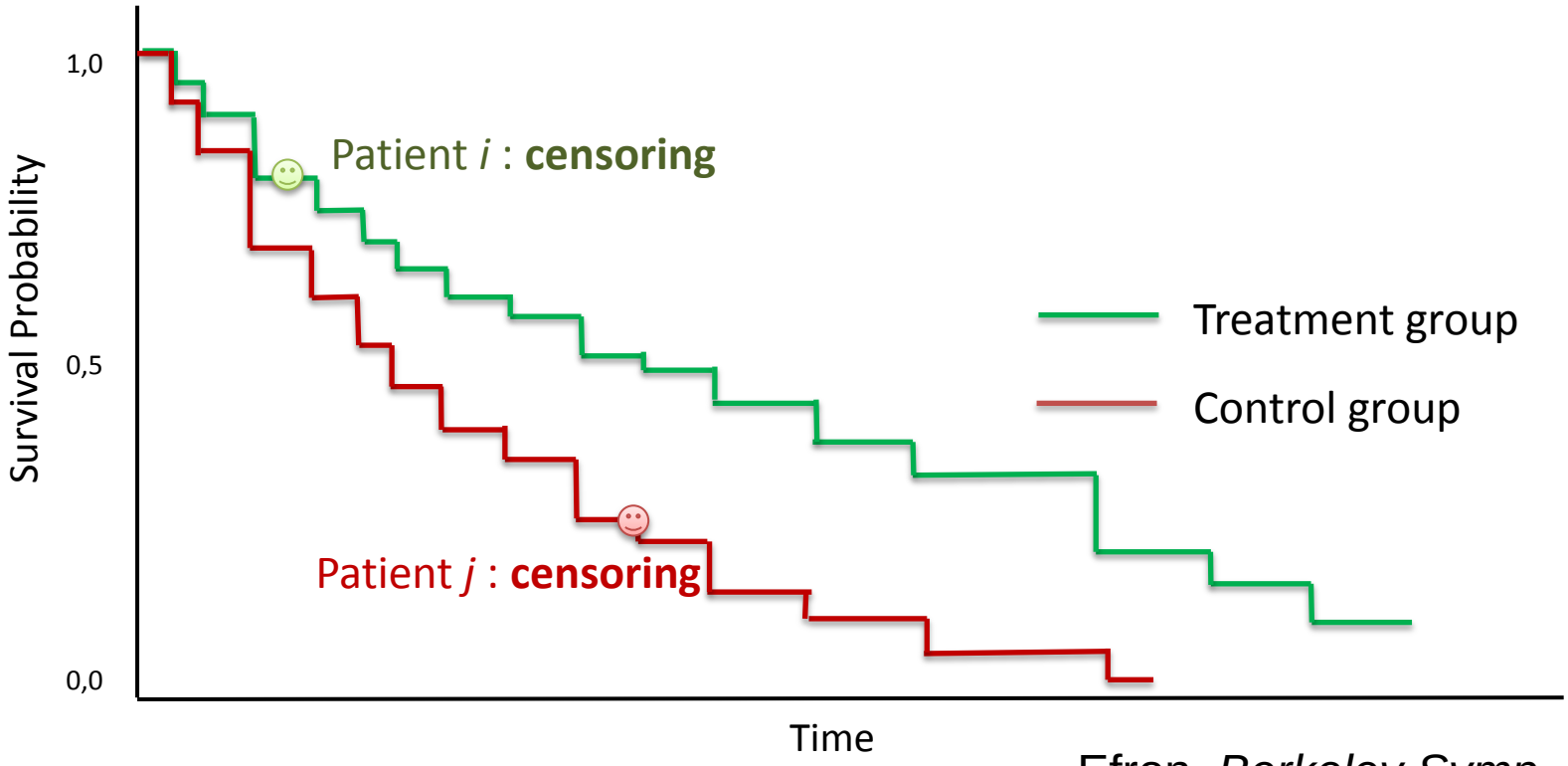


Péron J et al, SMMR 2016

The extended procedure taking into account 'non-informative' pairs

When the estimation of the survival function is discontinue :

$$\mathbb{p}\left[\left(x_i^0 > y_j^0\right) \middle| \left(x_i^0 > x_i\right), \left(y_j^0 > y_j\right)\right] = -\sum_{t>y_j}^{\infty} \frac{\hat{S}_{Ttt}(t)}{\hat{S}_{Ttt}(x_i)\hat{S}_{Ctrl}(y_j)} \cdot \left(\hat{S}_{Ctrl}(t^+) - \hat{S}_{Ctrl}(t^-)\right)$$



Efron, *Berkeley Symp,* 1967

The extended procedure taking into account 'non-informative' pairs

For pairs that can not be decidely classified because of censoring, we compute:

$$\mathbb{P}\left(x_i^0 > y_j^0 + \tau\right), \text{ et } \mathbb{P}\left(y_j^0 > x_i^0 + \tau\right), \text{ et } \mathbb{P}\left(|x_i^0 - y_j^0| < \tau\right)$$

The pairwise score is:

$$s_{ij} = \mathbb{P}\left(x_i^0 > y_j^0 + \tau\right) - \mathbb{P}\left(y_j^0 > x_i^0 + \tau\right)$$

The net chance of a better outcome is then:

$$\hat{\Delta} = \frac{1}{m \cdot n} \sum_{i=1}^{n} \sum_{j=1}^{m} s_{ij}$$

The pairwise weight the analysis of an outcome of lower priority is:

$$\omega_{ij} = \mathbb{P}\left(|x_i^0 - y_j^0| < \tau\right)$$

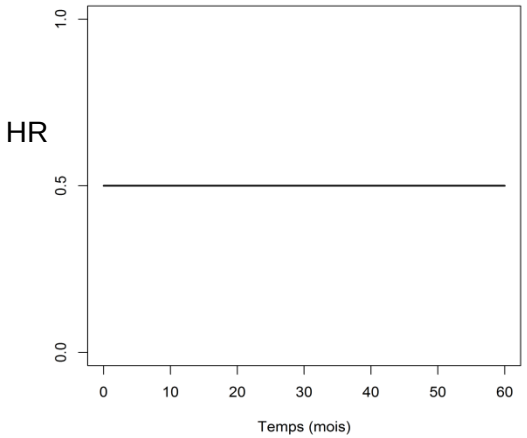
Simulation study - Design

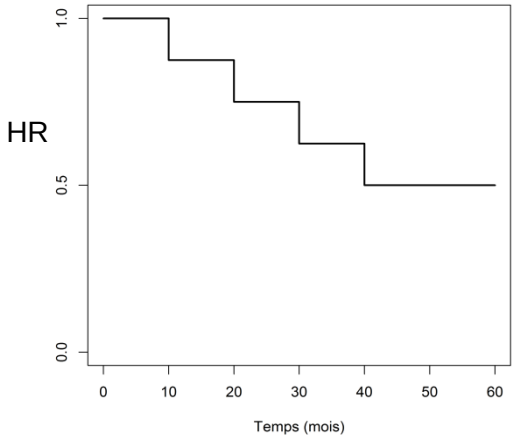
- **Objective:** To compare the standard and the extended procedures of generalized pairwise comparison
- Simulation of M = 1000 datasets of with N = 200 patients
  - One time-to-event outcome
  - Threshold τ = 0 months

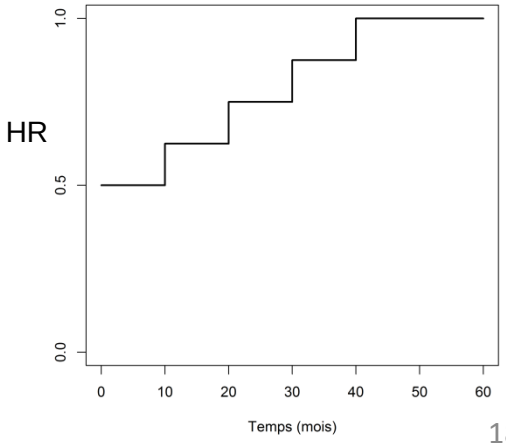
Simulation study - Design

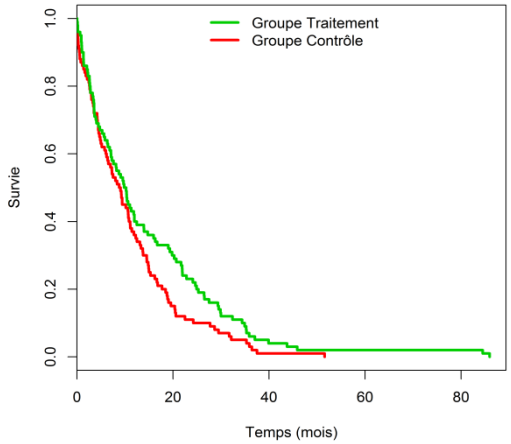
- Survival time: exponential distributions

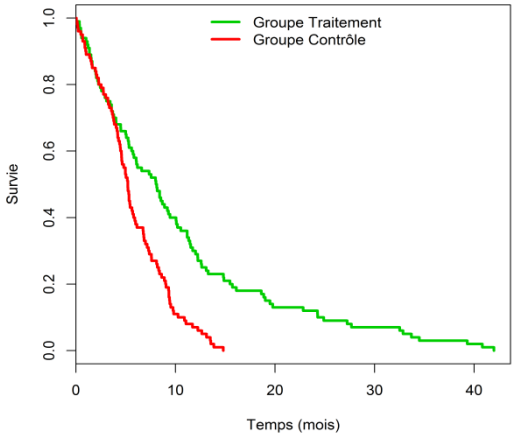
Scenario 1 : Proportional hazards	Scenario 2 : Late treatment effect	Scenario 3 : early treatment effect

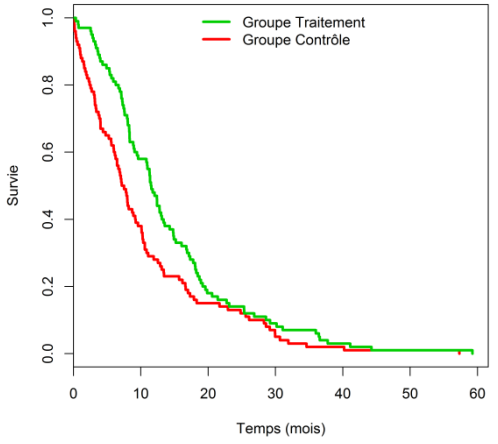












Simulation study - Design

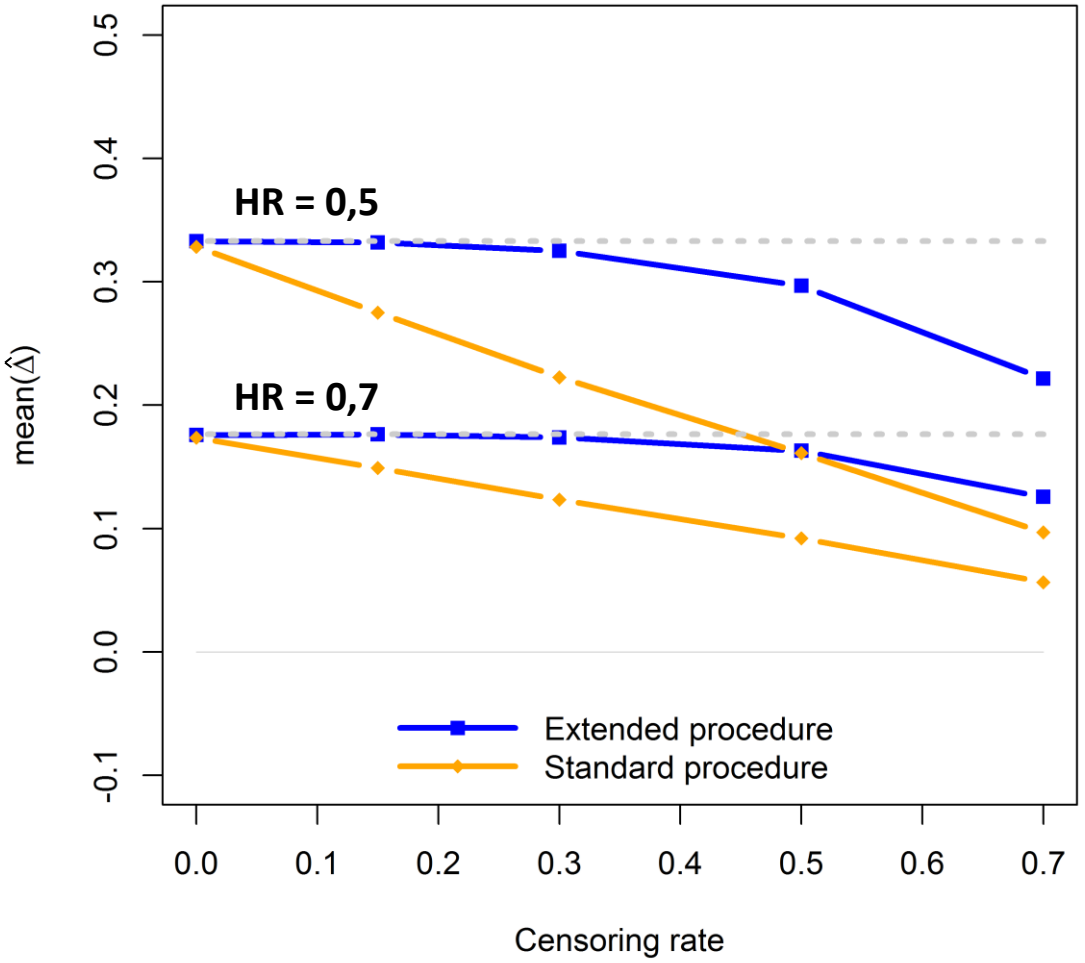
- Several treatment effect sizes
  - Hazard ratio $\{0{,}5;\ 0{,}7;\ 1\}$
- Administrative censoring proportion
  - Uniform distribution
  - Between 0% and 70%

Simulation study - Design

- For each simulated dataset
  - Estimation of the net chance of a better outcome (standard and extended procedure)
  - Test of the null hypothesis (Permutation test, Log-Rank test)

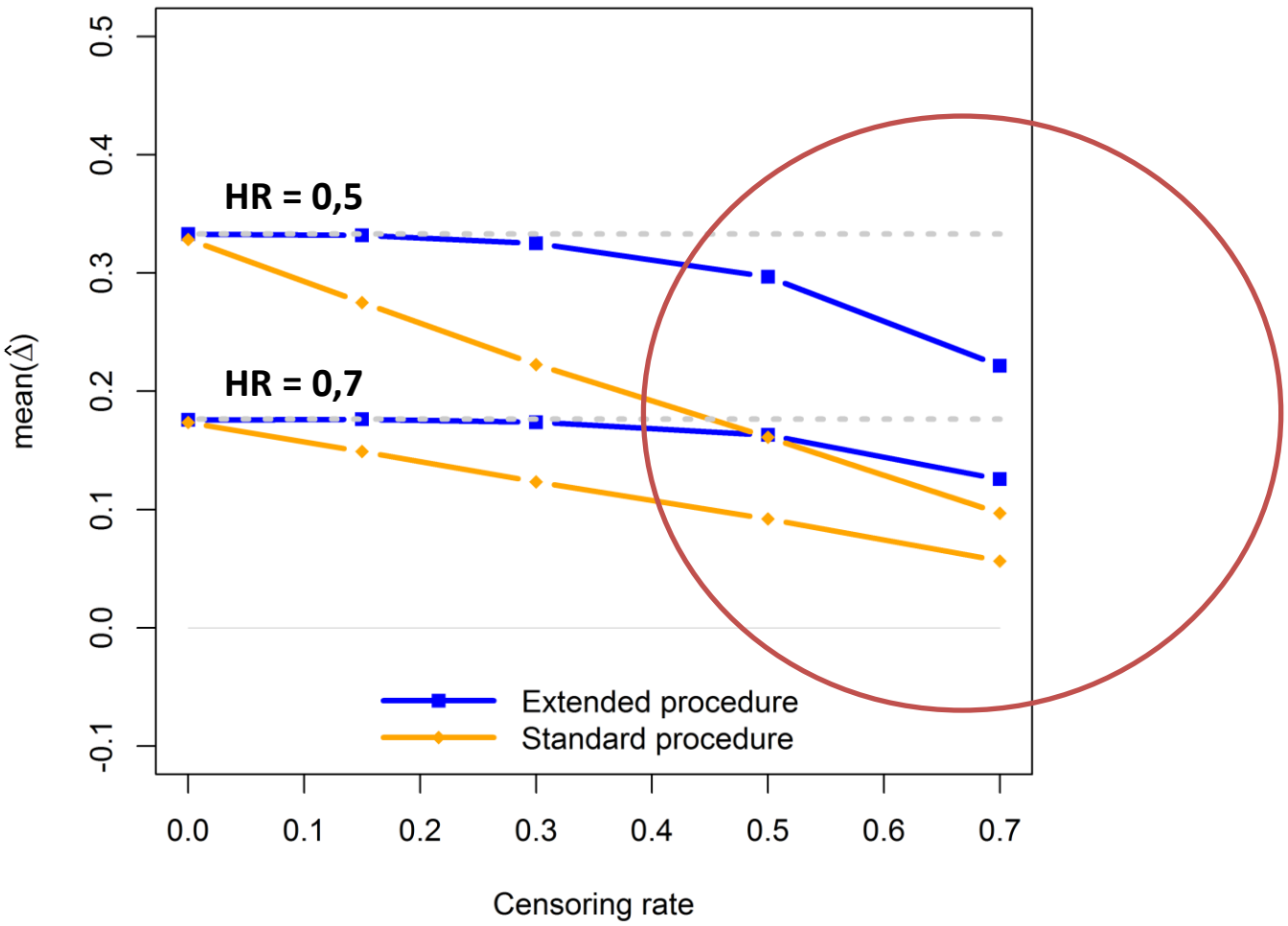
- Endpoints
  - Bias
  - Power
  - Type 1 error

Scenario 1 – Proportionnal hazards



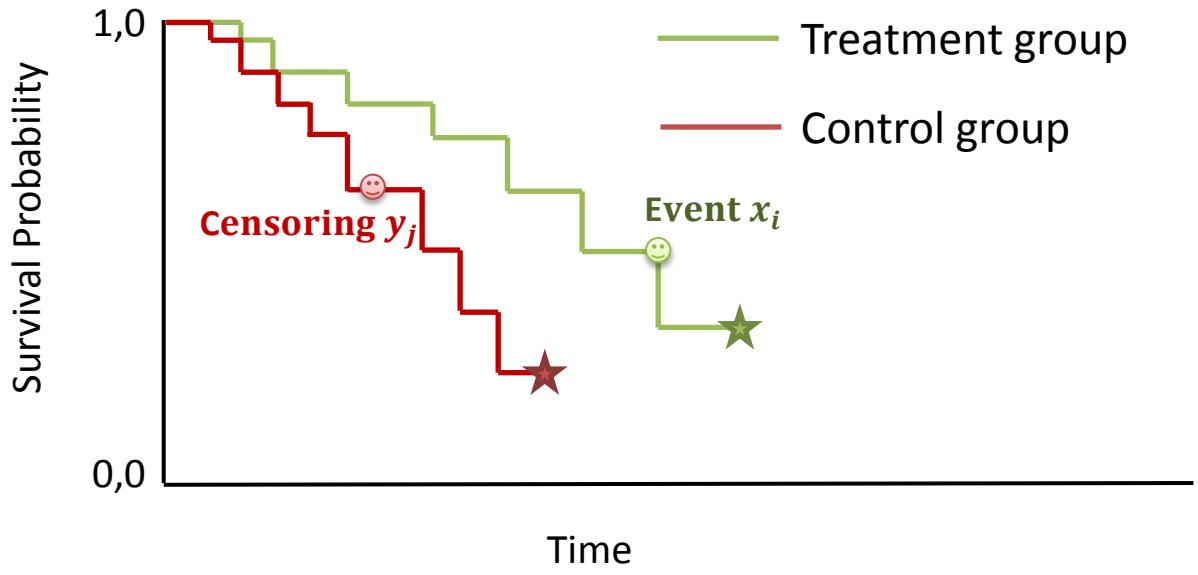
Péron, et al. *SMMR 2016*

Scenario 1 – Proportionnal hazards



Péron, et al. *SMMR 2016*

An explanation for this bias?



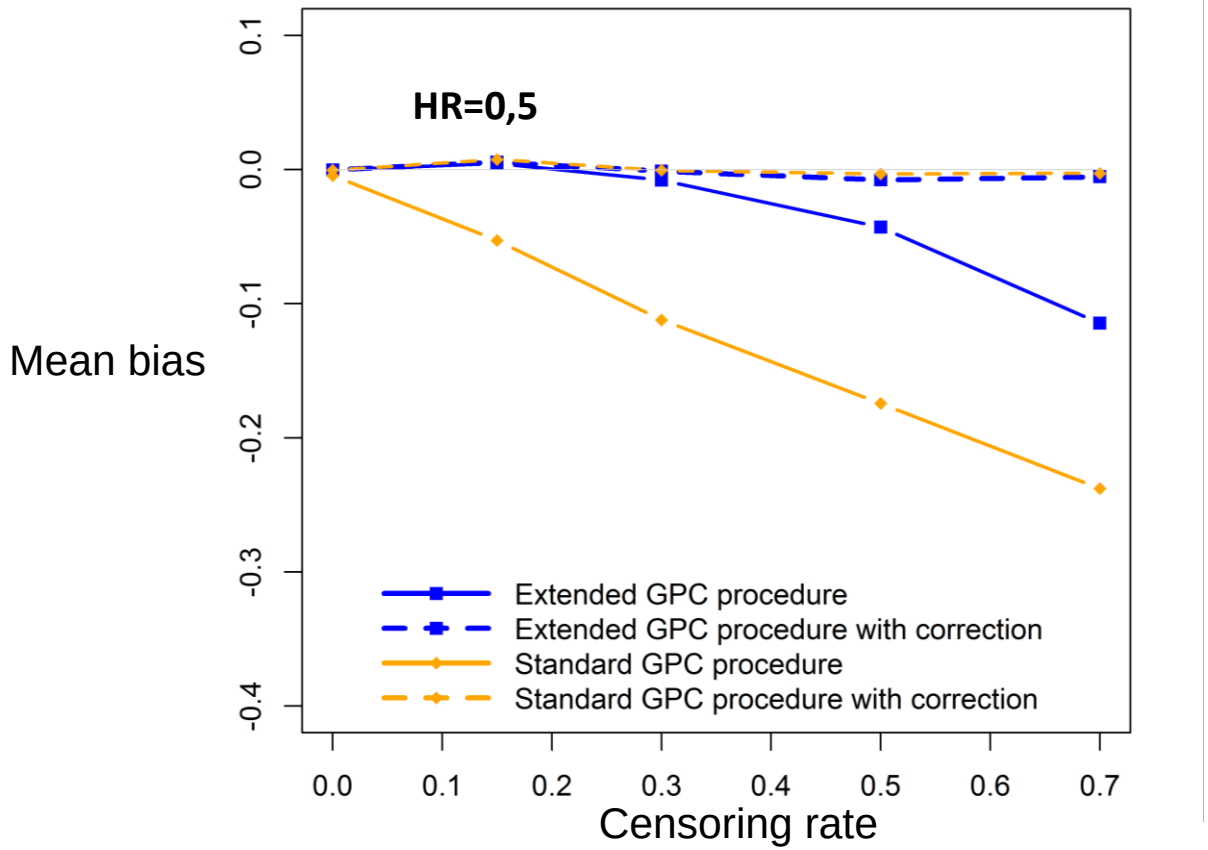
Standard procedure: **Uninformative** $\rightarrow p_{ij} = 0$

Extended procedure: $\begin{cases} \mathbb{P}\left[x_i^0 > y_j^0 + \tau\right] = 1 - \frac{\hat{S}_C(x_i - \tau)}{\hat{S}_C(y_j)} \\ \mathbb{P}\left[y_j^0 > x_i^0 + \tau\right] = \frac{\hat{S}_C(x_i + \tau)}{\hat{S}_C(y_j)} \end{cases}$ **Uninformative also** $\rightarrow p_{ij} = 0$

A correction for this bias

f_m : Proportion of informative pairs for the trial $m (m = 1, \dots, M)$

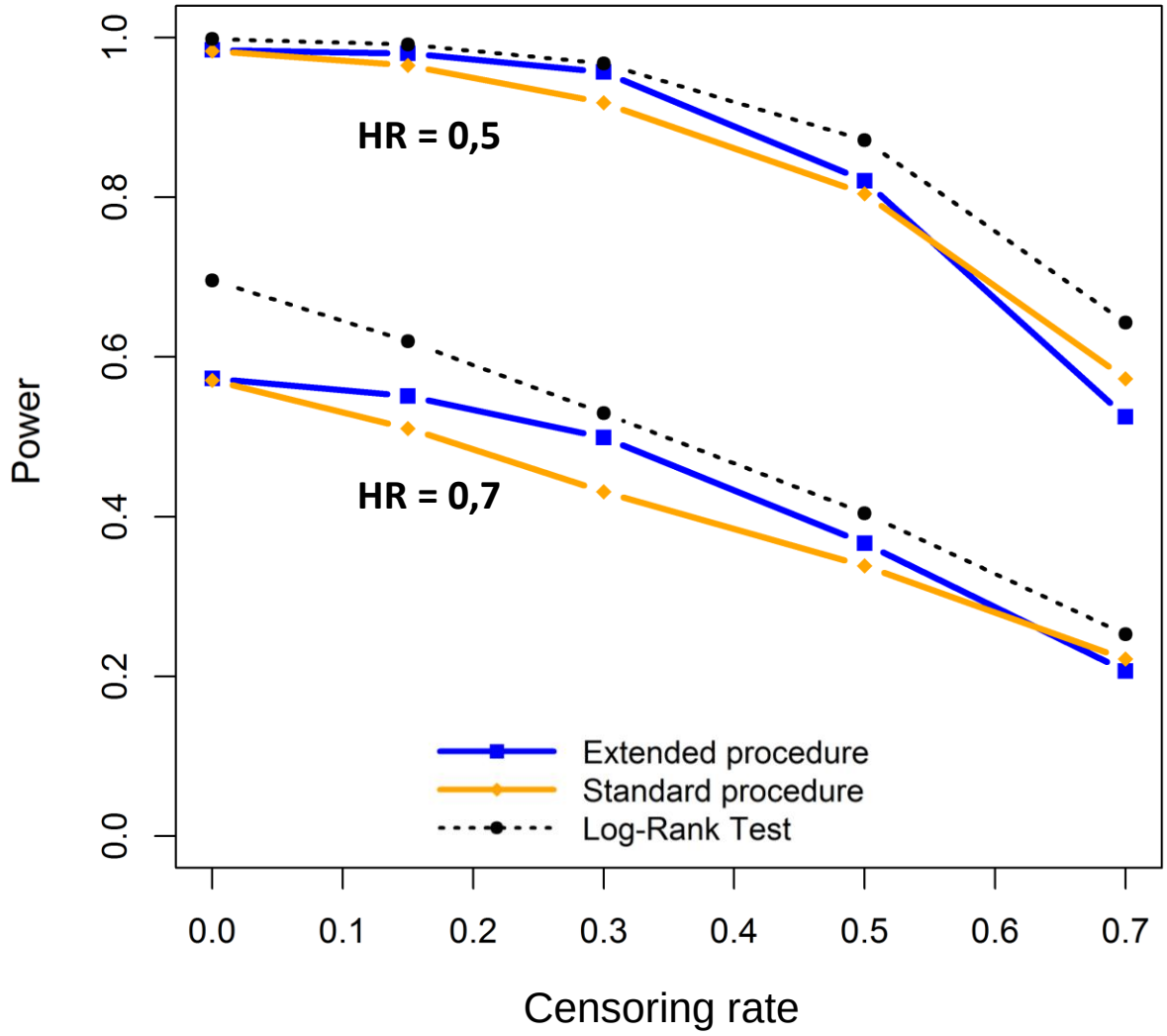
$\widehat{\Delta} corr_m = \frac{\widehat{\Delta}_m}{f_m}$: corrected net chance of a better outcome



$$Bias = \mathbb{E}\left(\widehat{\Delta} - \Delta\right)$$

Péron, et al. *SMMR 2016*

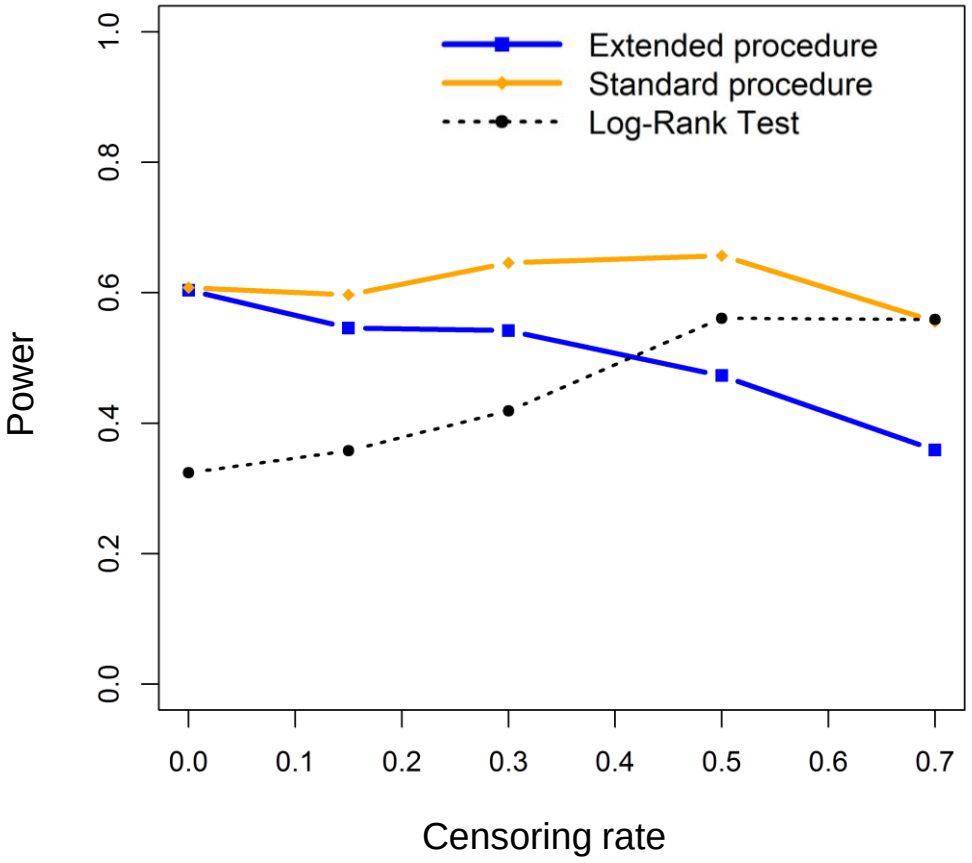
Scenario 1 – Proportional hazards



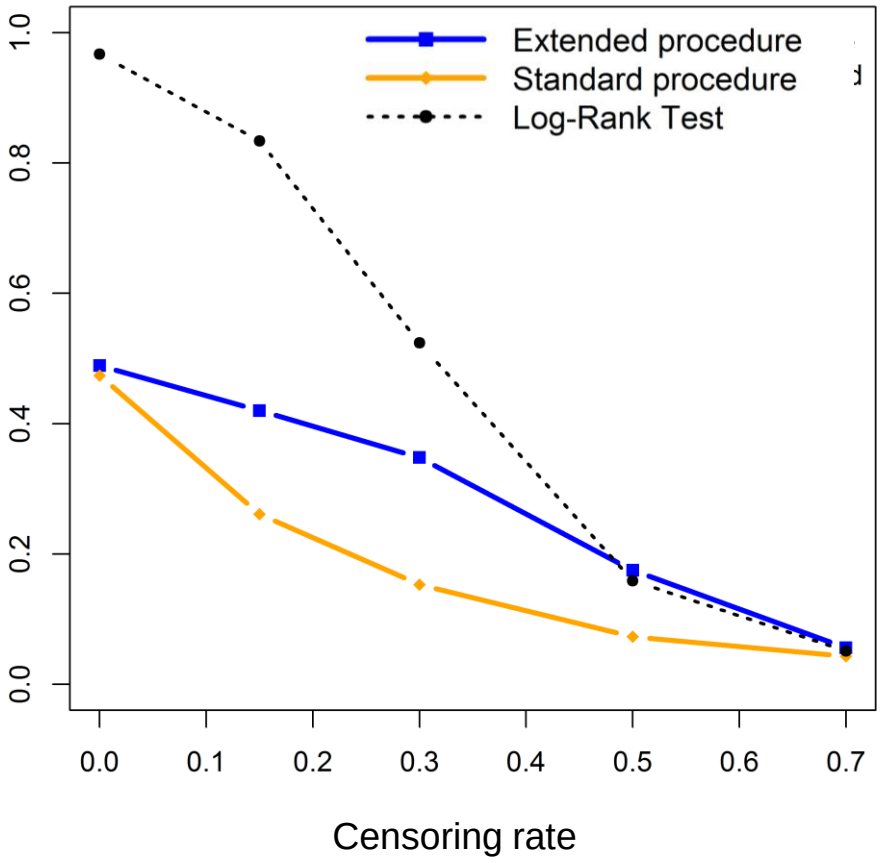
Péron, et al. *SMMR 2016*

Scenario 2 et 3 – Non Proportional hazards

Early treatment effect



Late treatment effect



Type 1 error rate ≈ 5%

Péron, et al. *SMMR 2016*

Conclusions of the simulation study

- Bias in the estimation of Δ
  - Less important
  - Correction available when only one endpoint

- Power of the permutation test extended procedure > standard procedure
  - Exponential distribution
  - Proportional hazards and administrative censoring < 67% (B Efron, Stanford Univ, 1967)
  - Late treatment effect

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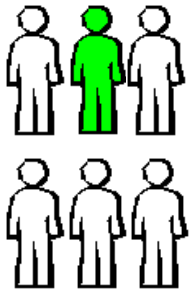
The net chance of a better outcome

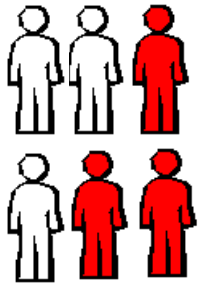
Probability for a random patient in the Treatment group to have a 'better outcome' than a random patient in the Control group …

Treatement group



$$\Delta = \mathbb{P}(\boldsymbol{X} > \boldsymbol{Y}) - \mathbb{P}(Y > X)$$

Control group

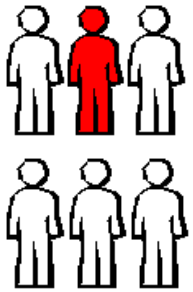


Buyse M. *Stat in med*, 2010

The net chance of a better outcome

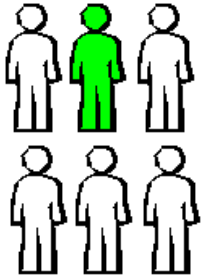
…minus the opposite probability.

Treatement group



$$\Delta = \mathbb{P}(X > Y) - \mathbb{P}(\boldsymbol{Y} > \boldsymbol{X})$$

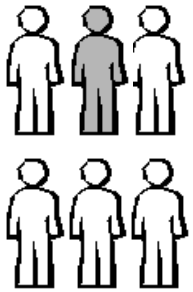
Control group



Buyse M. *Stat in med*, 2010

The net chance of a better outcome

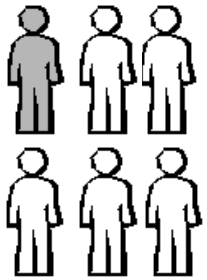
Treatement group



$$\mathbb{P}(\boldsymbol{Y} = \boldsymbol{X})$$

$$\Delta = \mathbb{P}(X > Y) - \mathbb{P}(Y > X)$$

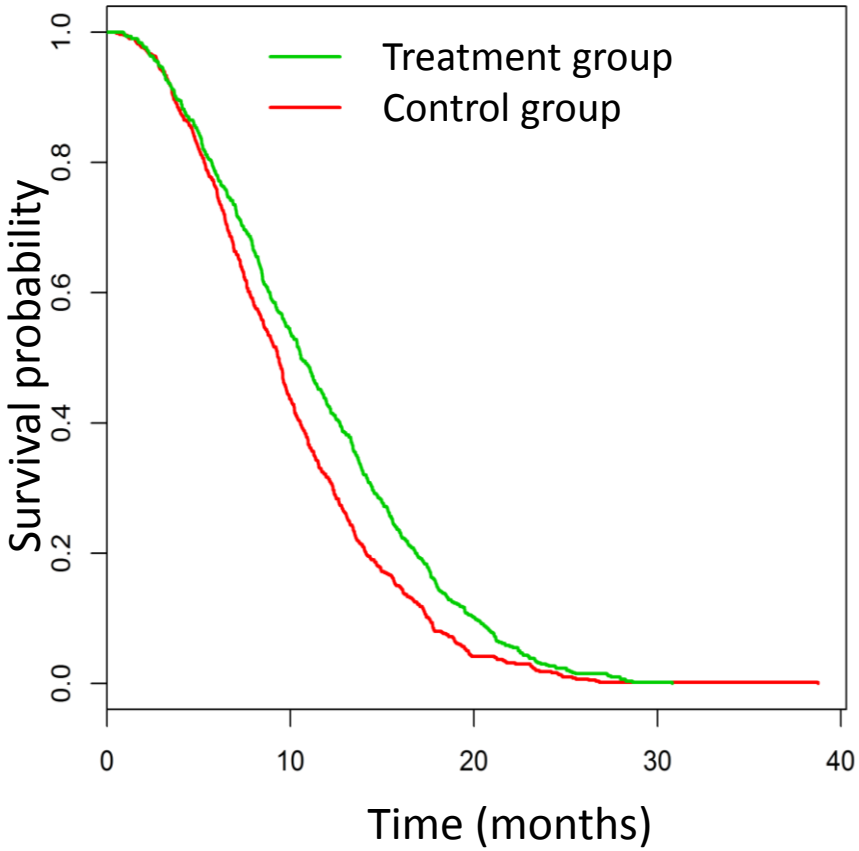
Control group

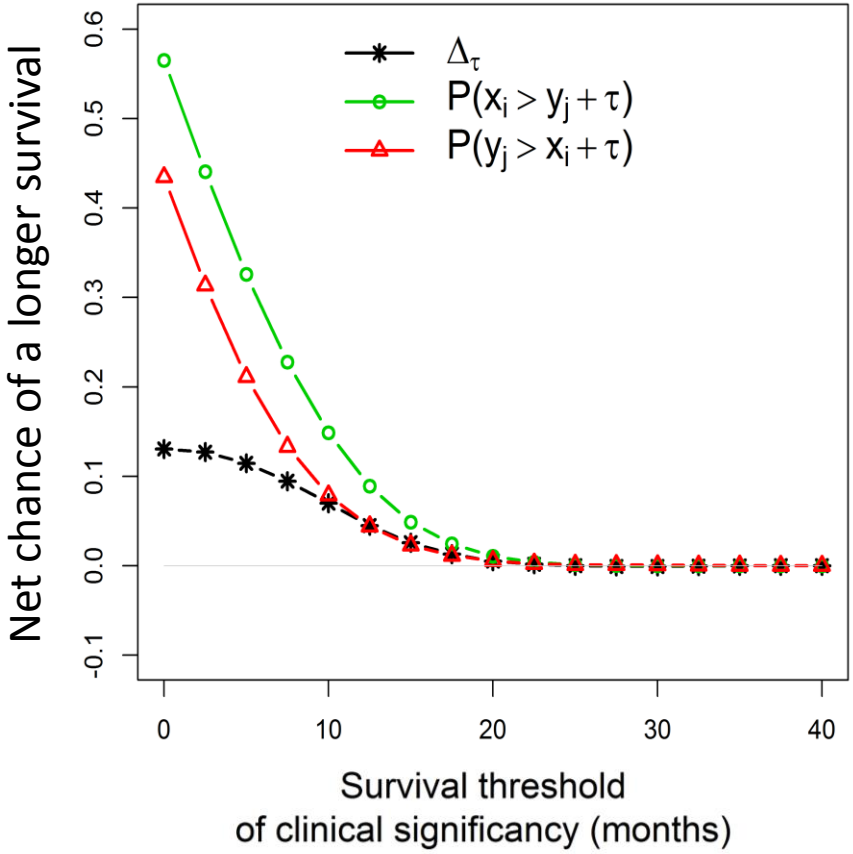


Buyse M. *Stat in med*, 2010

The net chance of a longer survival

Proportional hazards

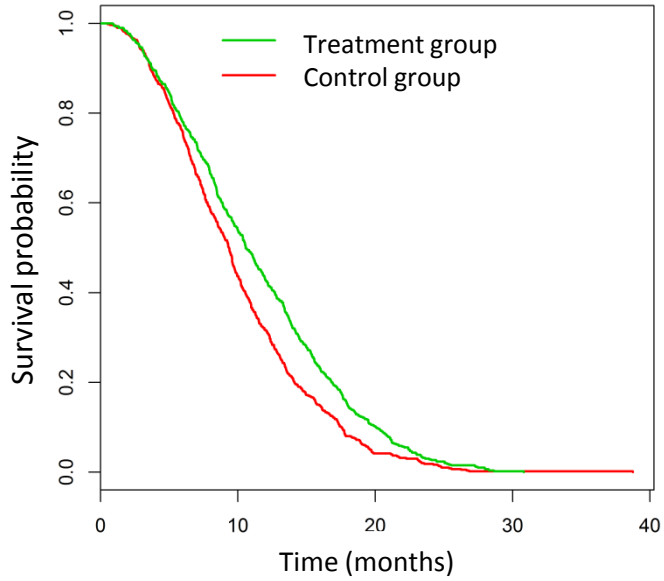


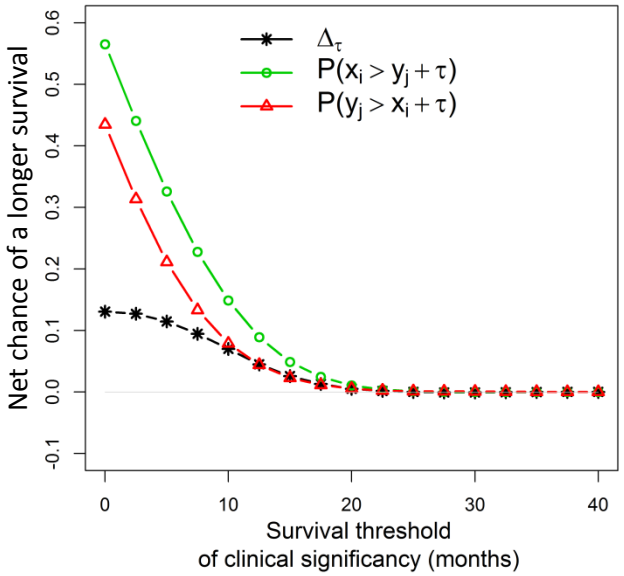


Péron et al, *JAMA oncology, 2016*

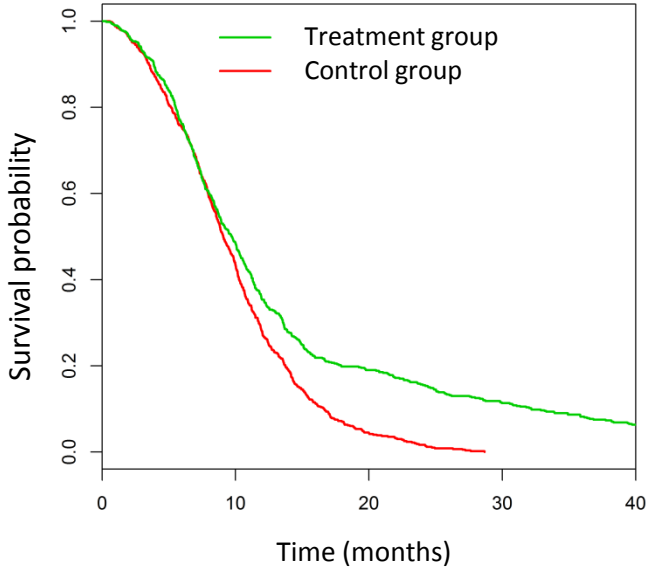
The net chance of a longer survival

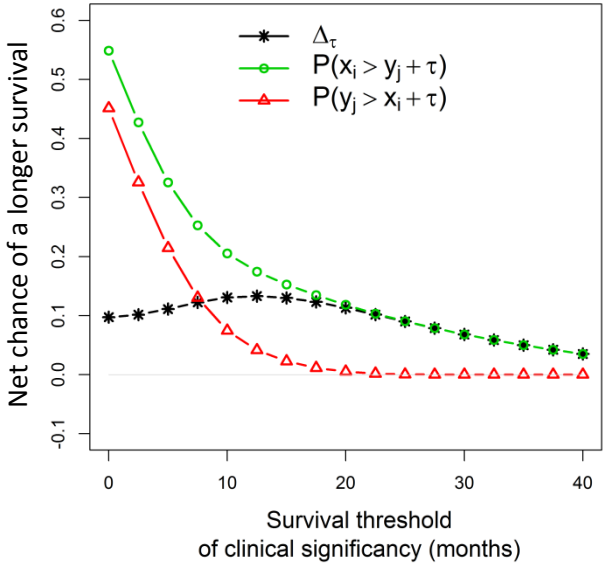
Proportional Hazards





Delayed treatment effect

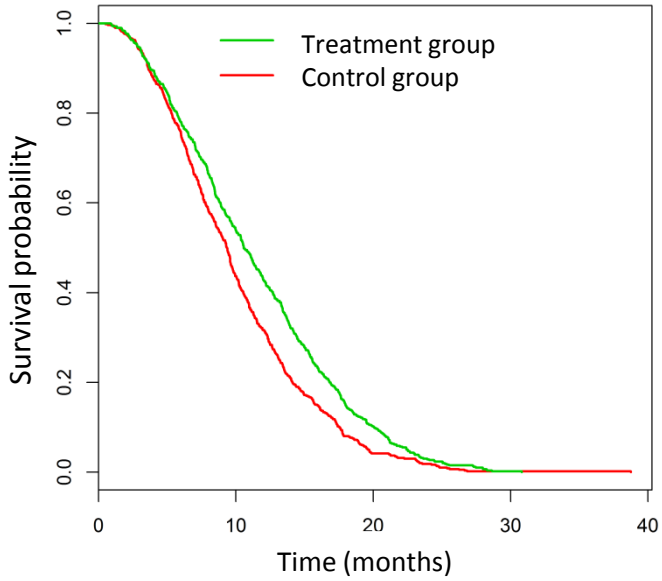


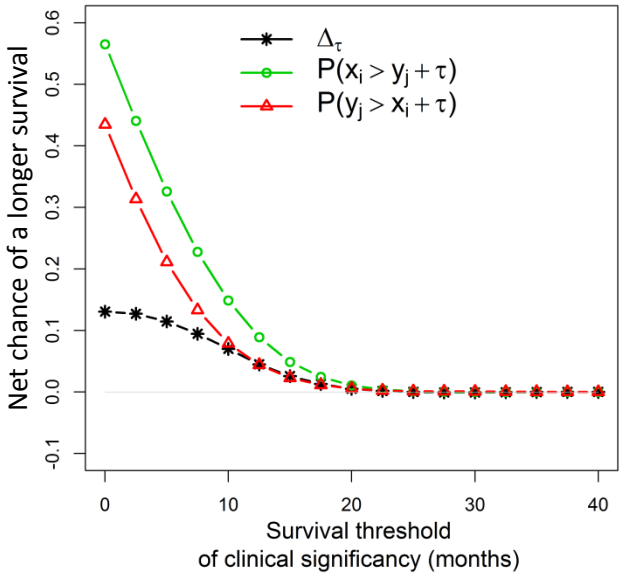


Péron et al, *JAMA oncology, 2016*

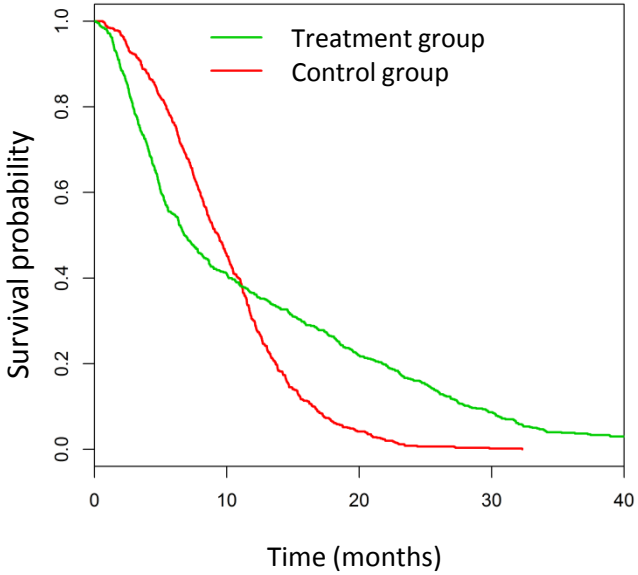
The net chance of a longer survival

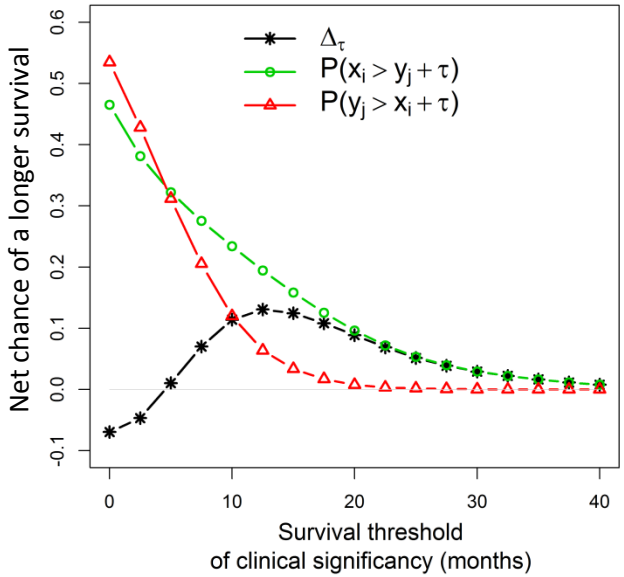
Proportional Hazards





Opposite hazards





Péron et al, *JAMA oncology, 2016*

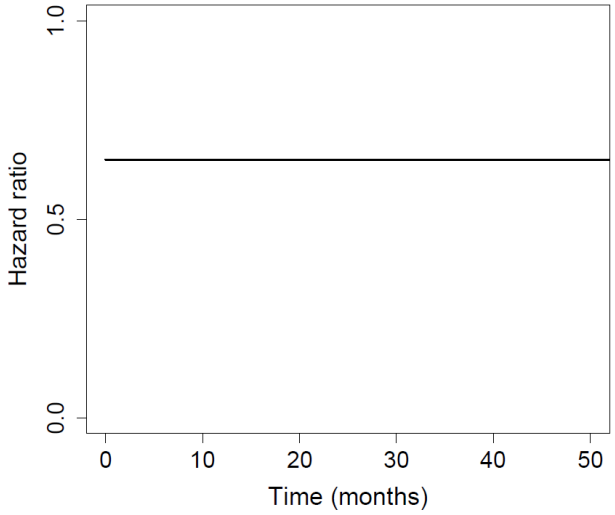
Simulation study - Design

- **Objective:** To assess the power of tests based on generalized pairwise comparisons for delayed treatment effect

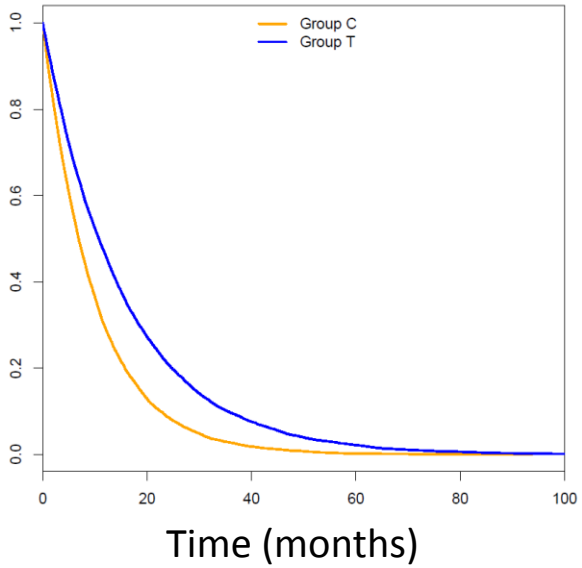
- Simulation of M = 1000 datasets of with N = 200 patients
  - One time-to-event outcome

Simulation study - Design

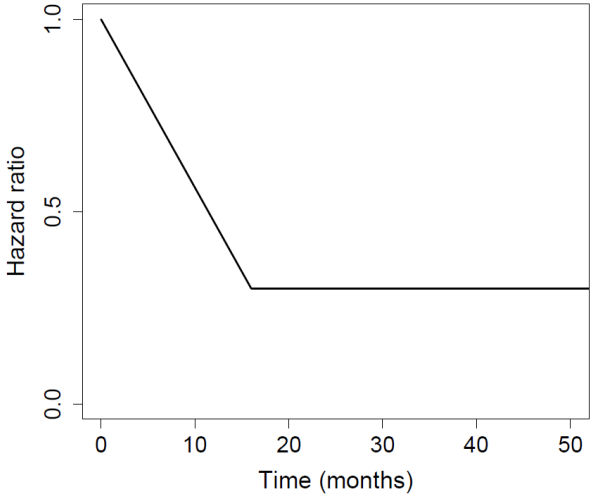
Scenario 1 : Proportional hazards



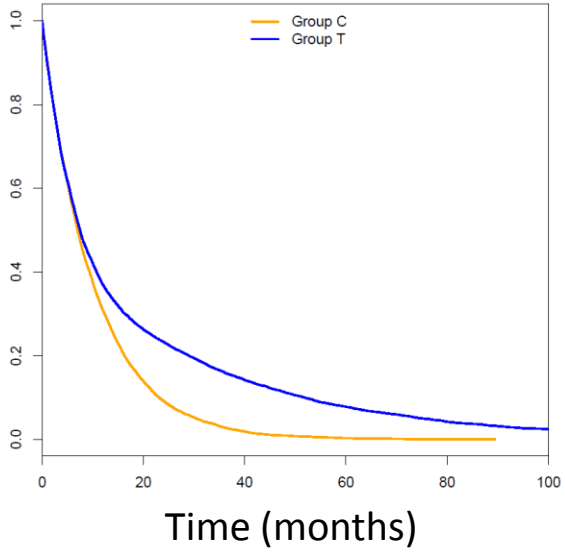
Survival



Scenario 2 : Late treatment effect



Survival

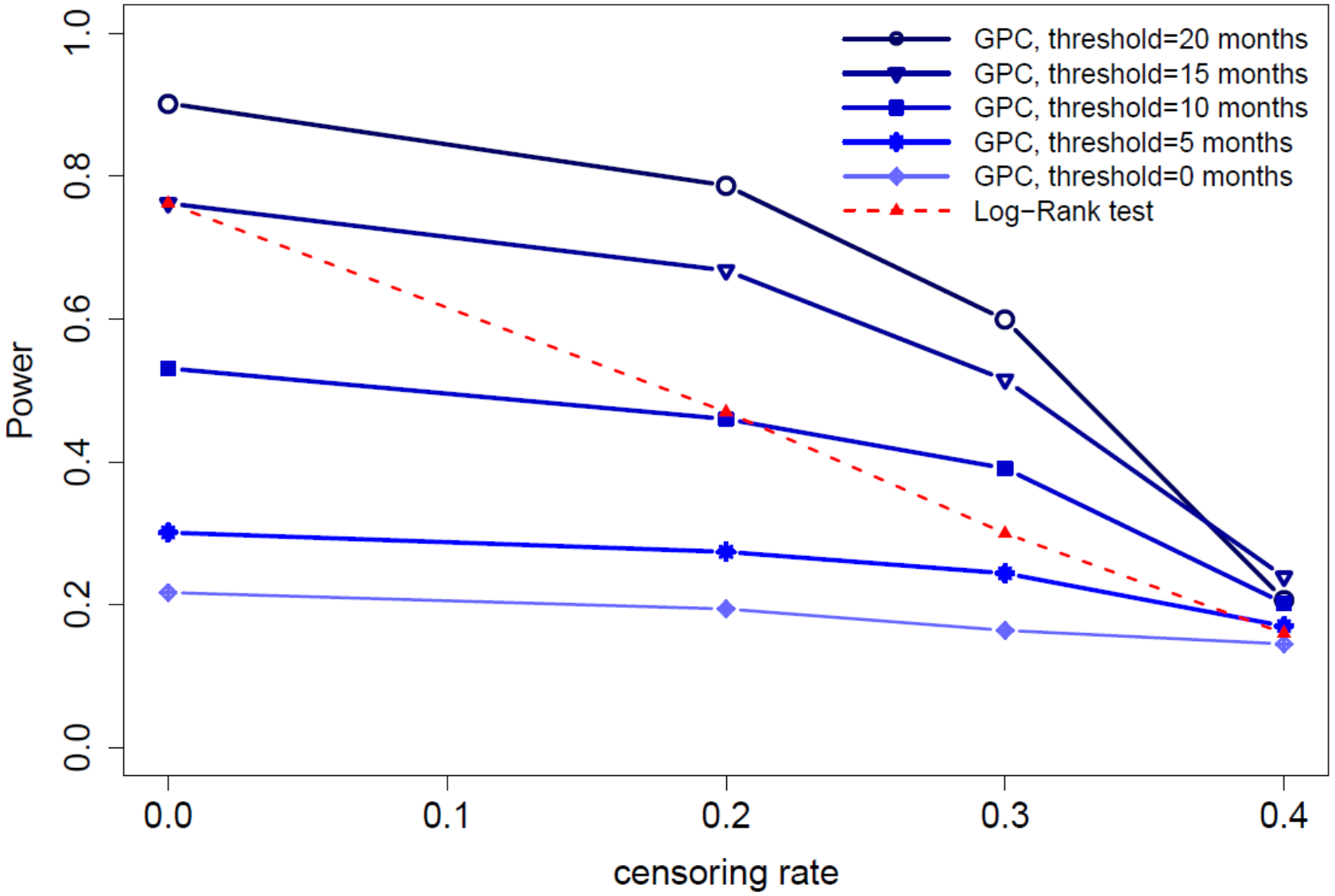


Simulation study - Design

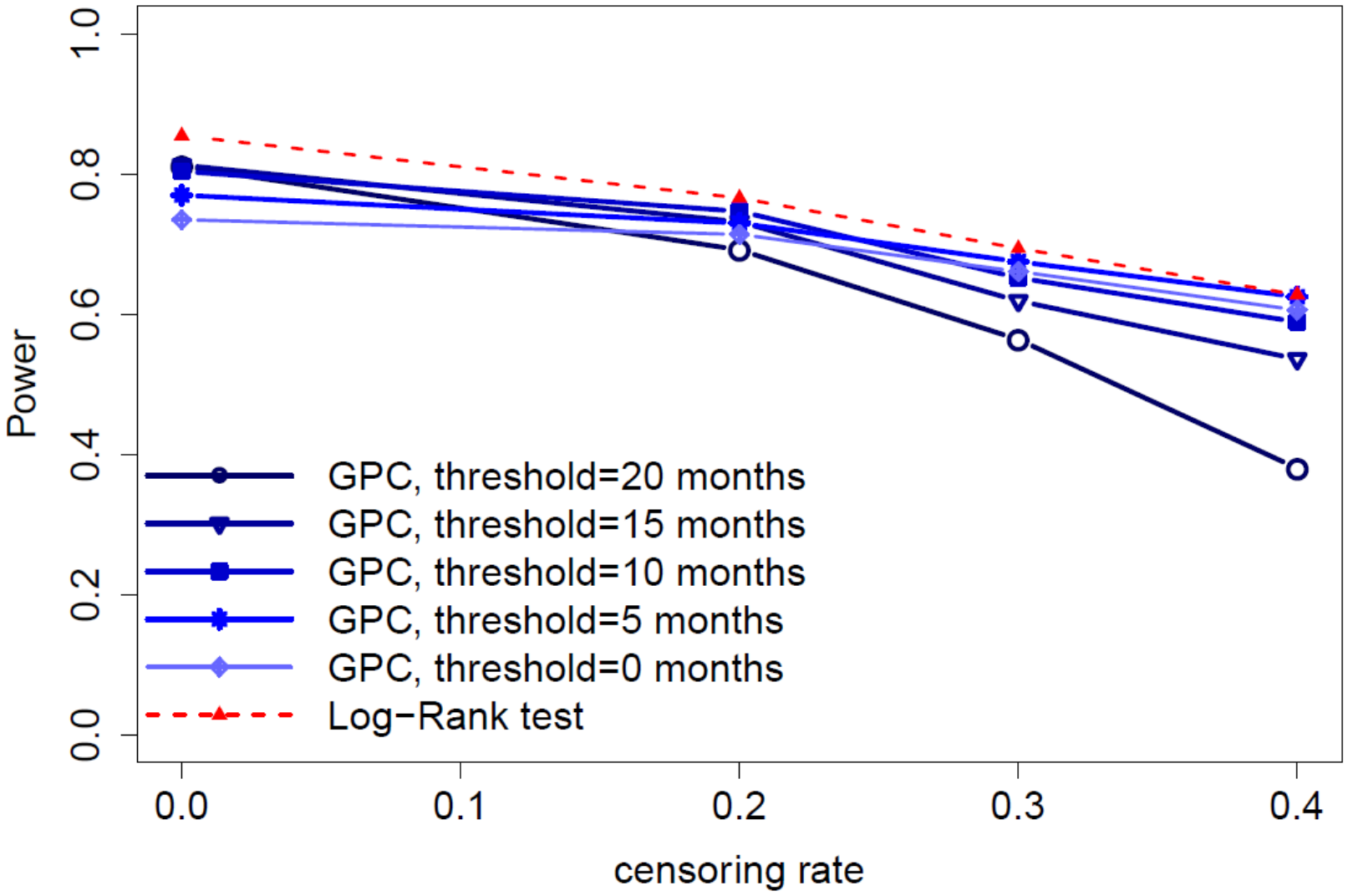
- Administrative censoring proportion
  - Uniform distribution
  - Between 0% and 40%

- For each simulated dataset
  - Estimation of the net chance of a better outcome (extended procedure) with threshold τ $[0 \text{ to } 20 \text{ months}]$
  - Test of the null hypothesis (Permutation test, Log-Rank test)

Delayed treatment effect - POWER



Proportional Hazards - POWER



Conclusions

When a long-term survival benefit is expected

(anticancer immune therapy)

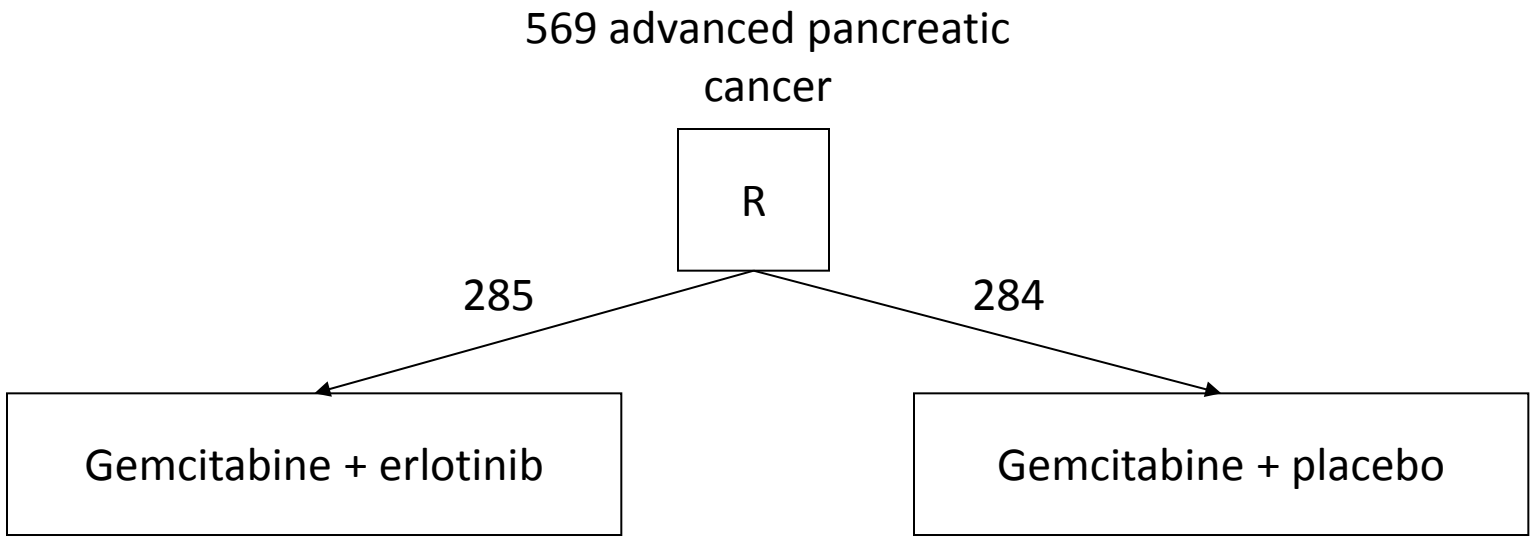
The net chance of a longer survival is:

- Arguably more relevant than traditional methods
- More powerful than traditional method

Outline

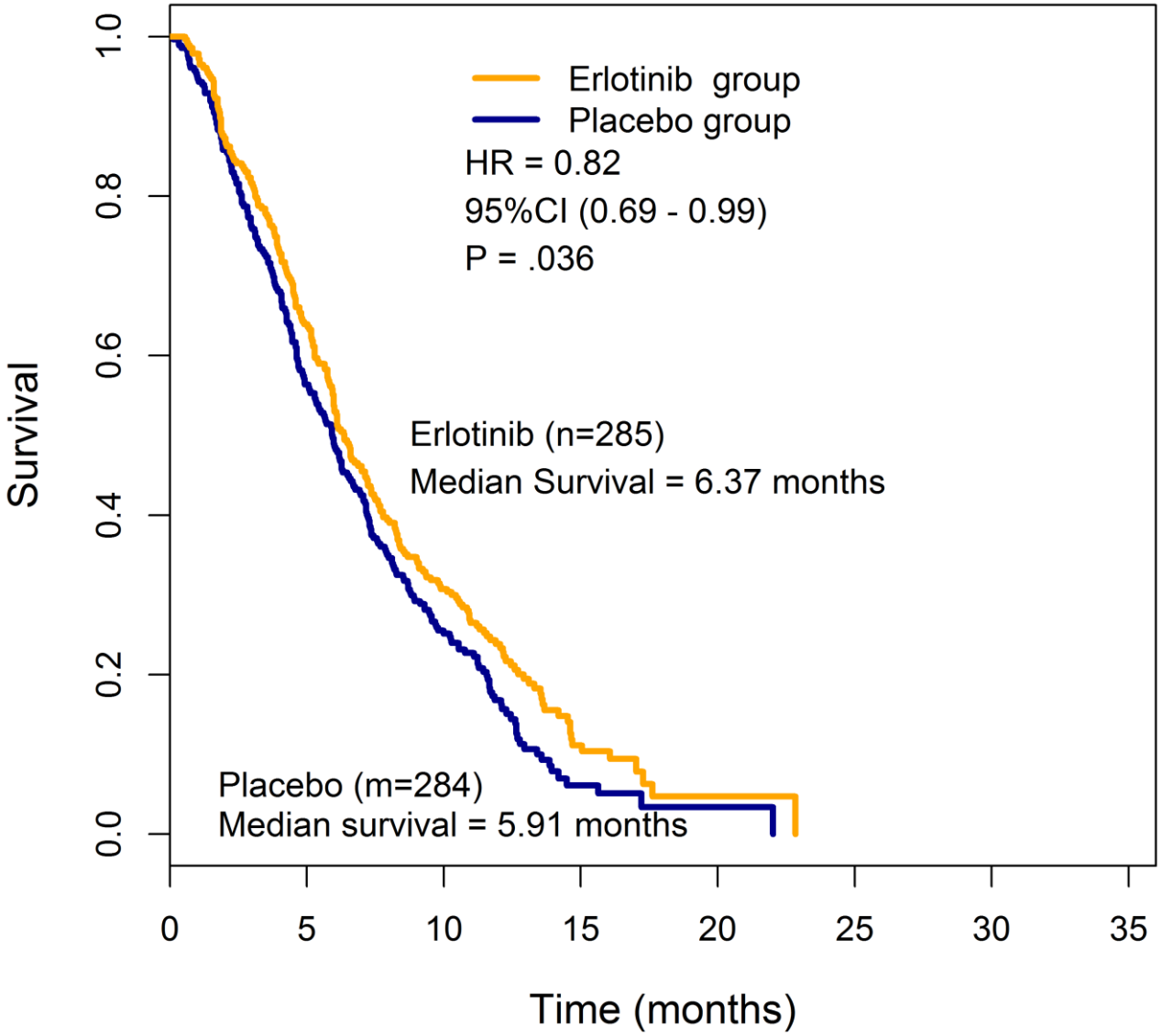
- The standard procedure of generalized pairwise comparisons
- An extension for right-censored data
- A patient-oriented measure of treatment benefit
- Benefit-risk balance
  - NCIC PA.3 trial => erlotinib in pancreatic cancer

The benefit-risk balance in the PA.3 trial



Moore et al. JCO 2007

The benefit-risk balance in the PA.3 trial



The benefit-risk balance in the PA.3 trial

Worst grade related AE	Erlotinib group (n=282)	Placebo group (n=280)
Grade 1	48 (17%)	69 (24.6%)
Grade 2	118 (41.8%)	89 (31.8%)
Grade 3	72 (25.5%)	47 (16.8%)
Grade 4	11 (3.9%)	6 (2.1%)
Grade 5	4 (1.4%)	3 (1.1%)

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29,4% **18,9%**

Benefit-risk balance

Extended procedure

Priority	Erlotinib > Placebo	Placebo > Erlotinib	Δ[erlotinib]
1 : OS (Threshold = 2 months)	40.3 %	34.5 %	5.8 %
2 : Worst related AE grade	6.8 %	12.4 %	-5.6 %
Global	47.1 %	46.9 %	**0.2 % (P=.96)**

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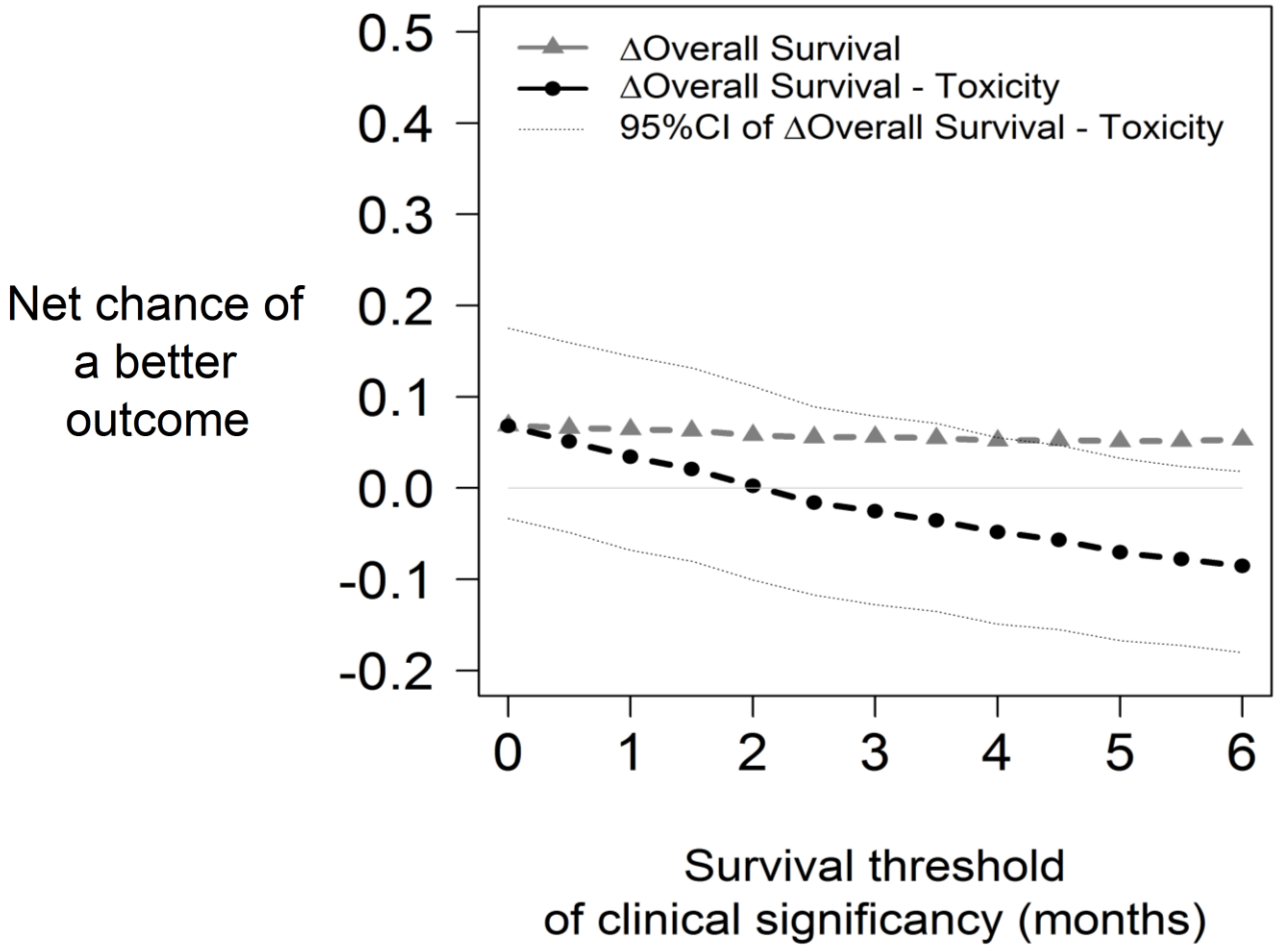
Benefit-risk balance



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Software implementation

A package  corresponding to the standard procedure and to the extended procedure

- Available on CRAN (“BuyseTest”)
- Available on github (“https://github.com/bozenne/BuyseTest”)

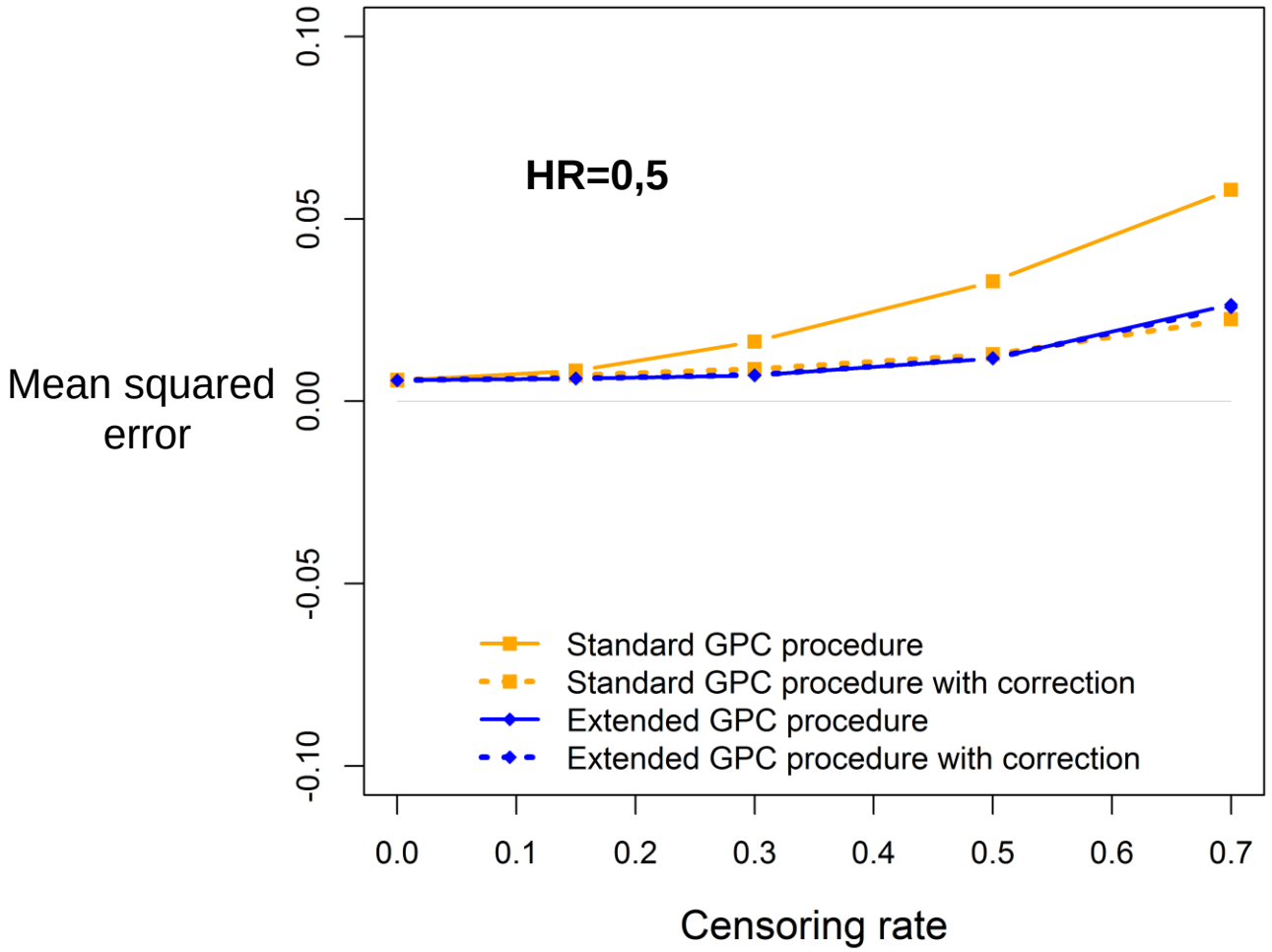
Conclusions

The net chance of a better outcome

- Is **flexible**
- Is **meaningful**
- Allows **multicriteria analysis**
- Can focus on **long-term survival differences**
- Is OK when hazards are **not proportionals**
- Is **available**

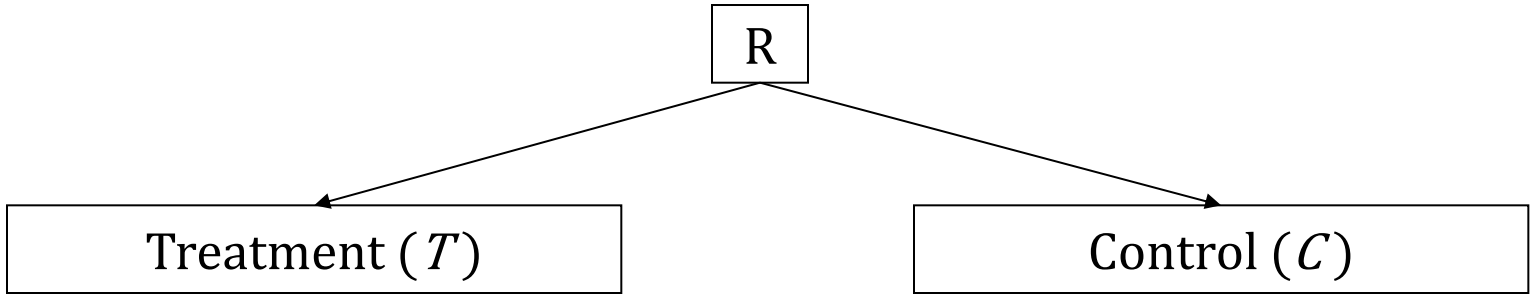
Thank you

Scénario 1 – Mean squared error



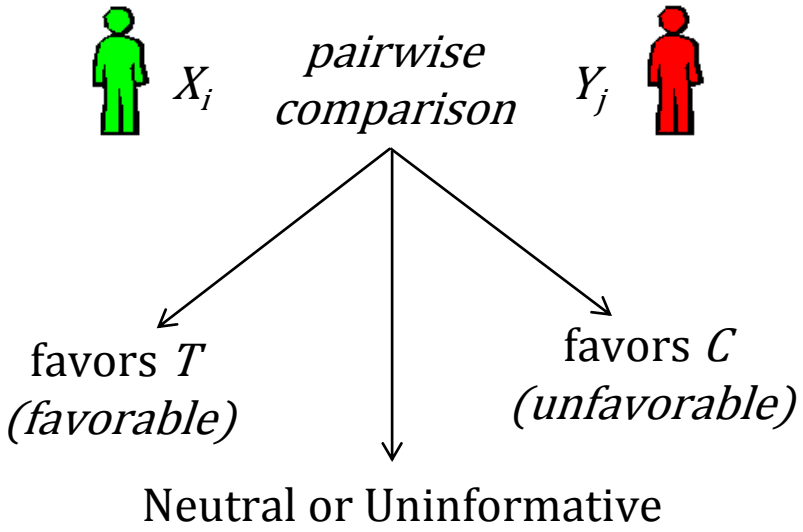
$$Mean\ squared\ error = \mathbb{E}\left(\left(\hat{\Delta} - \Delta\right)^2\right)$$

Methods – Pairwise comparisons



Let x_i be the outcome of i^{th} subject in T $(i = 1. \ldots . n)$

Let y_j be the outcome of j^{th} subject in C $(j = 1. \ldots . m)$



Buyse M. stat in med 2010

Methods – Definition of thresholds

Coutinuous outcome

Pair	Rating
$x_i - y_j > \tau$	Favorable
$x_i - y_j < (-\tau)$	Unfavorable
$\mid x_i - y_j \mid \leq \tau$	Neutral
x_i or y_j missing	Uninformative

Buyse. stat in med 2010

Methods – Definition of thresholds

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x_i or y_j missing	Uninformative

Buyse. stat in med 2010

Methods – Definition of priority

First priority outcome	Second priority outcome	Pair rating
Favorable	NA	Favorable
Unfavorable	NA	Unfavorable
Uninformative	Favorable	Favorable
Uninformative	Unfavorable	Unfavorable
Uninformative	Uninformative	Uninformative

Buyse. stat in med 2010

Methods – Definition of priority

First priority outcome	Second priority outcome	Pair rating
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Uninformative	Uninformative	Uninformative

Buyse. stat in med 2010

Methodes – Standard procedure for pairwise scoring

$$U_{ij} = \begin{cases} +1 \text{ when the pair } \left(X_i, Y_j\right) \text{ is favorable} \\ -1 \text{ when the pair } \left(X_i, Y_j\right) \text{ is unfavorable} \\ 0 \text{ otherwise} \end{cases}$$

$$\Delta = U = \frac{1}{m \cdot n} \sum_{i=1}^{n} \sum_{j=1}^{m} U_{ij}$$

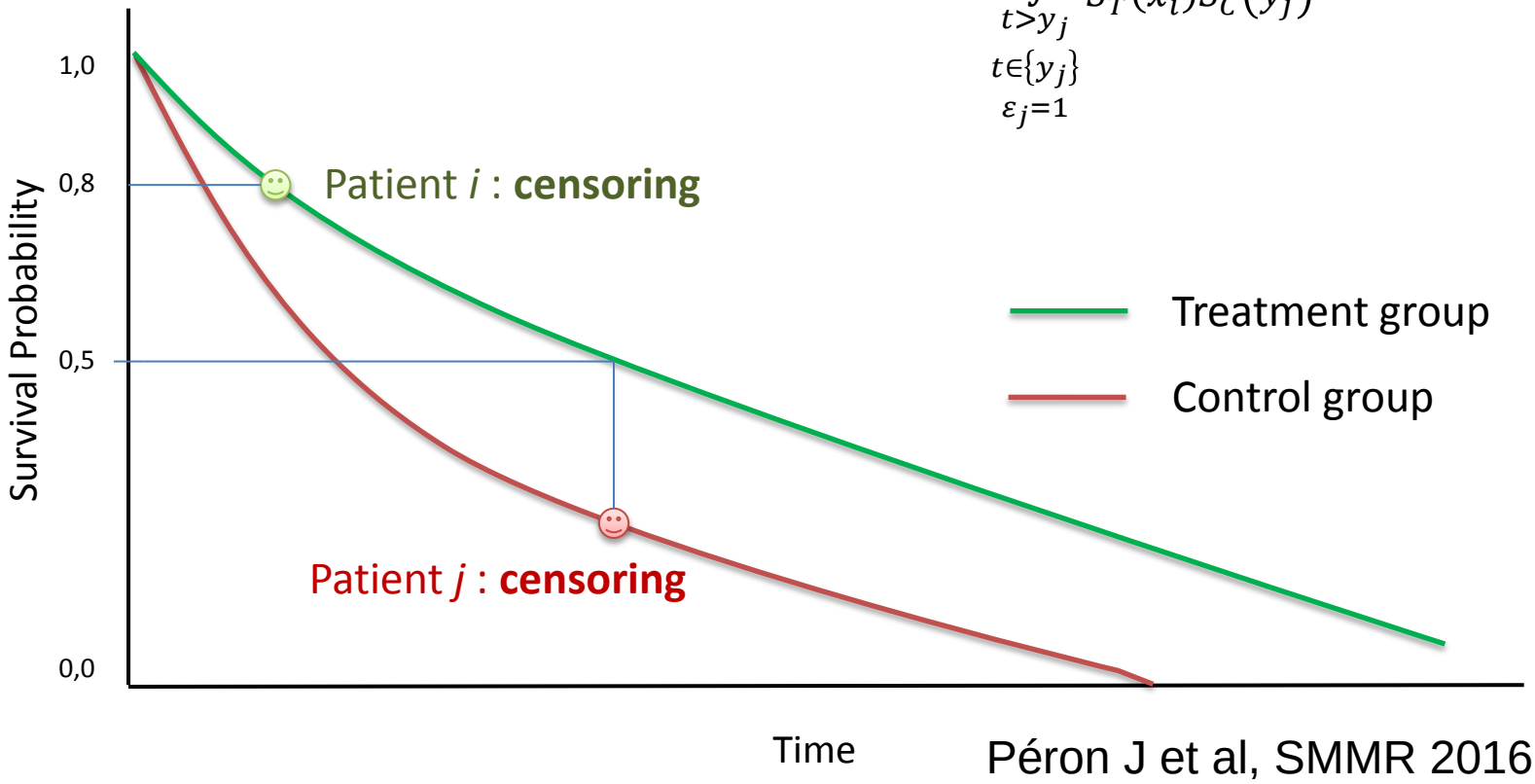
Δ in named «chance of a better outcome»

Buyse. stat in med 2010

The extended procedure taking into account 'non-informative' pairs

Based on the Kaplan-Meier estimate of the survival function

$$\mathbb{p}\left[\left(x_i^0 > y_j^0\right) \middle| \left(x_i^0 > x_i\right)\right] = -\int_{\substack{t>y_j \\ t\in\{y_j\} \\ \varepsilon_j=1}}^{\infty} \frac{\hat{S}_T(t)}{\hat{S}_T(x_i)\hat{S}_C(y_j)} d\hat{S}_C(t)$$

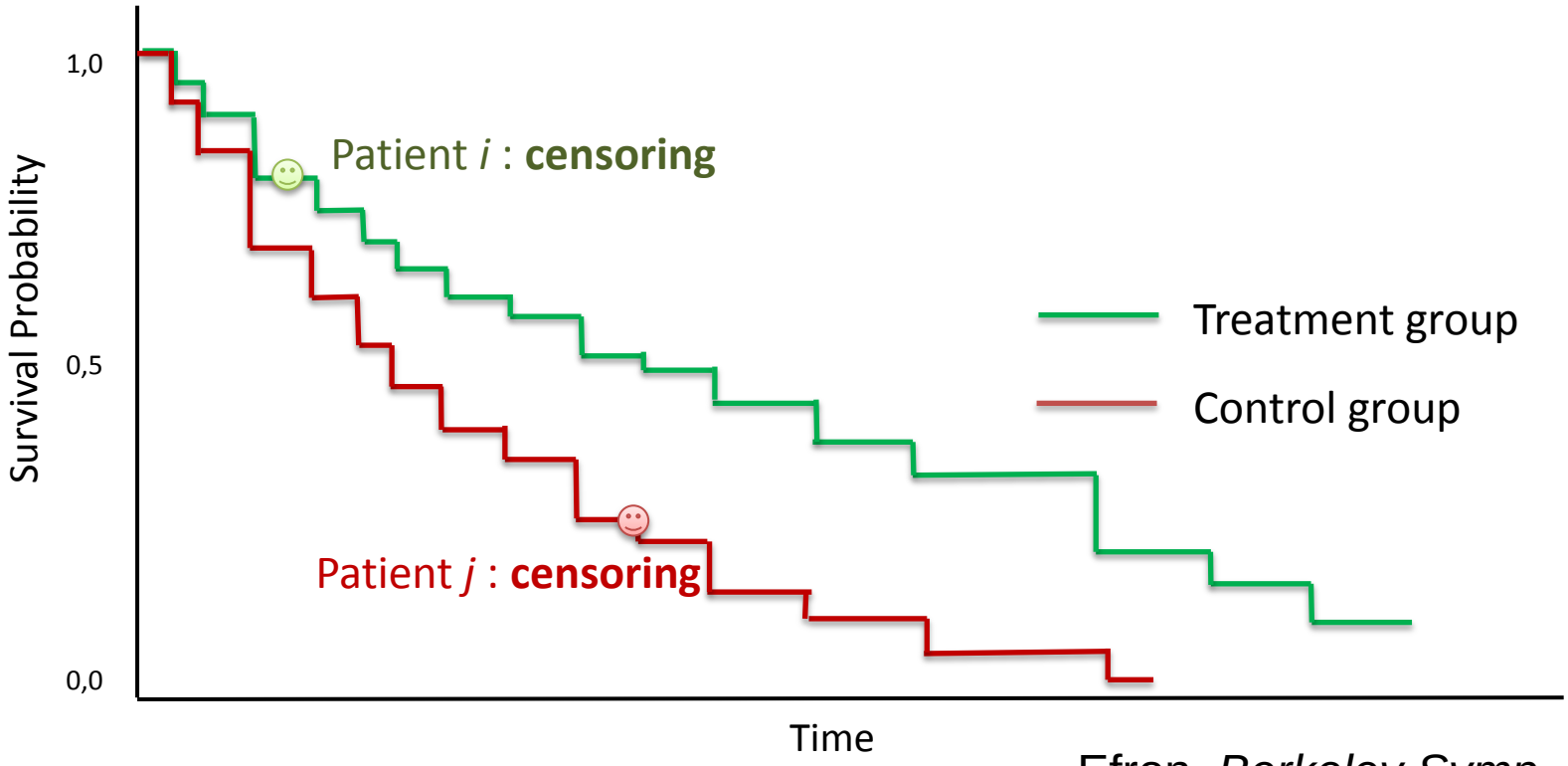


Péron J et al, SMMR 2016

The extended procedure taking into account 'non-informative' pairs

When the estimation of the survival function is discontinue :

$$\mathbb{p}\left[\left(x_i^0 > y_j^0\right) \middle| \left(x_i^0 > x_i\right), \left(y_j^0 > y_j\right)\right] = -\sum_{t>y_j}^{\infty} \frac{\hat{S}_{Ttt}(t)}{\hat{S}_{Ttt}(x_i)\hat{S}_{Ctrl}(y_j)} \cdot \left(\hat{S}_{Ctrl}(t^+) - \hat{S}_{Ctrl}(t^-)\right)$$



Efron, *Berkeley Symp,* 1967

Extension prenant en compte les temps jusqu'à censure

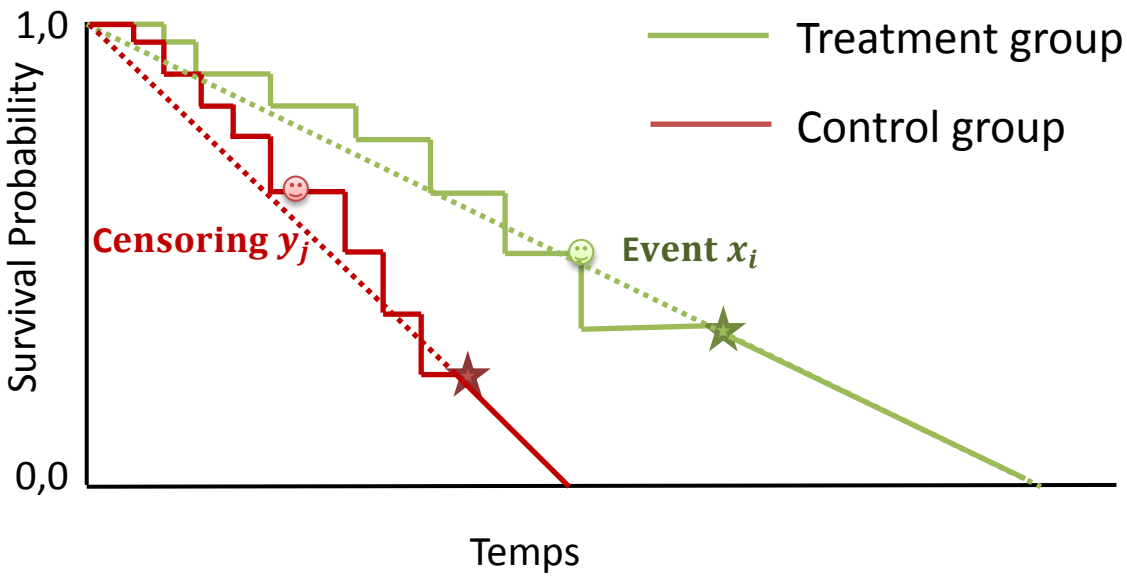
$(\delta_i, \varepsilon_j)$	$x_i - y_j > \tau$	$x_i - y_j < -\tau$	$\lvert x_i - y_j \rvert < \tau$
$(1,1)$	1	-1	0
$(0,1)$	1	$\frac{\hat{S}_T(y_j+\tau)+\hat{S}_T(y_j-\tau)}{\hat{S}_T(x_i)} - 1$	$\frac{\hat{S}_T(y_j+\tau)}{\hat{S}_T(x_i)}$
$(1,0)$	$1 - \frac{\hat{S}_C(x_i+\tau)+\hat{S}_C(x_i-\tau)}{\hat{S}_C(y_j)}$	-1	$-\frac{\hat{S}_C(x_i+\tau)}{\hat{S}_C(y_j)}$
$(0,0)$	$1 - \frac{\hat{S}_C(x_i-\tau)+\hat{S}_C(x_i+\tau)}{\hat{S}_C(y_j)}$ $- \int_{\substack{t>x_i-\tau \\ t\in\{y_j\} \\ \varepsilon_j=1}}^{\infty} \frac{\hat{S}_T(t+\tau)}{\hat{S}_T(x_i)\hat{S}_C(y_j)} d\hat{S}_C(t)$ $- \int_{\substack{t>x_i+\tau \\ t\in\{y_j\} \\ \varepsilon_j=1}}^{\infty} \frac{\hat{S}_T(t-\tau)}{\hat{S}_T(x_i)\hat{S}_C(y_j)} d\hat{S}_C(t)$	$- \int_{\substack{t>y_j \\ t\in\{y_j\} \\ \varepsilon_j=1}}^{\infty} \frac{\hat{S}_T(t+\tau)+\hat{S}_T(t-\tau)}{\hat{S}_T(x_i)\hat{S}_C(y_j)} d\hat{S}_C(t)$ -1	$- \int_{\substack{t>y_j \\ t\in\{y_j\} \\ \varepsilon_j=1}}^{\infty} \frac{\hat{S}_T(t+\tau)}{\hat{S}_T(x_i)\hat{S}_C(y_j)} d\hat{S}_C(t)$ $- \int_{\substack{t>x_i+\tau \\ t\in\{y_j\} \\ \varepsilon_j=1}}^{\infty} \frac{\hat{S}_T(t-\tau)}{\hat{S}_T(x_i)\hat{S}_C(y_j)} d\hat{S}_C(t)$ $- \frac{\hat{S}_C(x_i+\tau)}{\hat{S}_C(y_j)}$

Valeurs du score attribué à chaque paire en fonction d'un seuil τ représentant la différence minimale cliniquement significative

Sensitivity analysis

Priority	Threshold	proportion of pairs (%)		Δerlotinib
		Erlotinib > Placebo	Placebo > Erlotinib	
1 : OS	6 months	16.8	13.1	3.6
2 : PFS	6 months	3.0	1.8	1.2
3 : Worst related AE grade	3 grades	2.3	5.8	-3.5
4 : OS	3 months	11.2	10.8	0.4
5 : PFS	3 months	3.4	2.7	0.7
6 : Worst related AE grade	2 grades	2.3	6.0	-3.7
7 : OS	0 months	9.5	9.1	0.4
8 : PFS	0 months	0.5	0.6	-0.1
9 : Worst related AE grade	1 grade	0.2	0.5	-0.3
Overall		49.2	50.4	**-1.2 (P=.82)**

Hypothesis of the correction



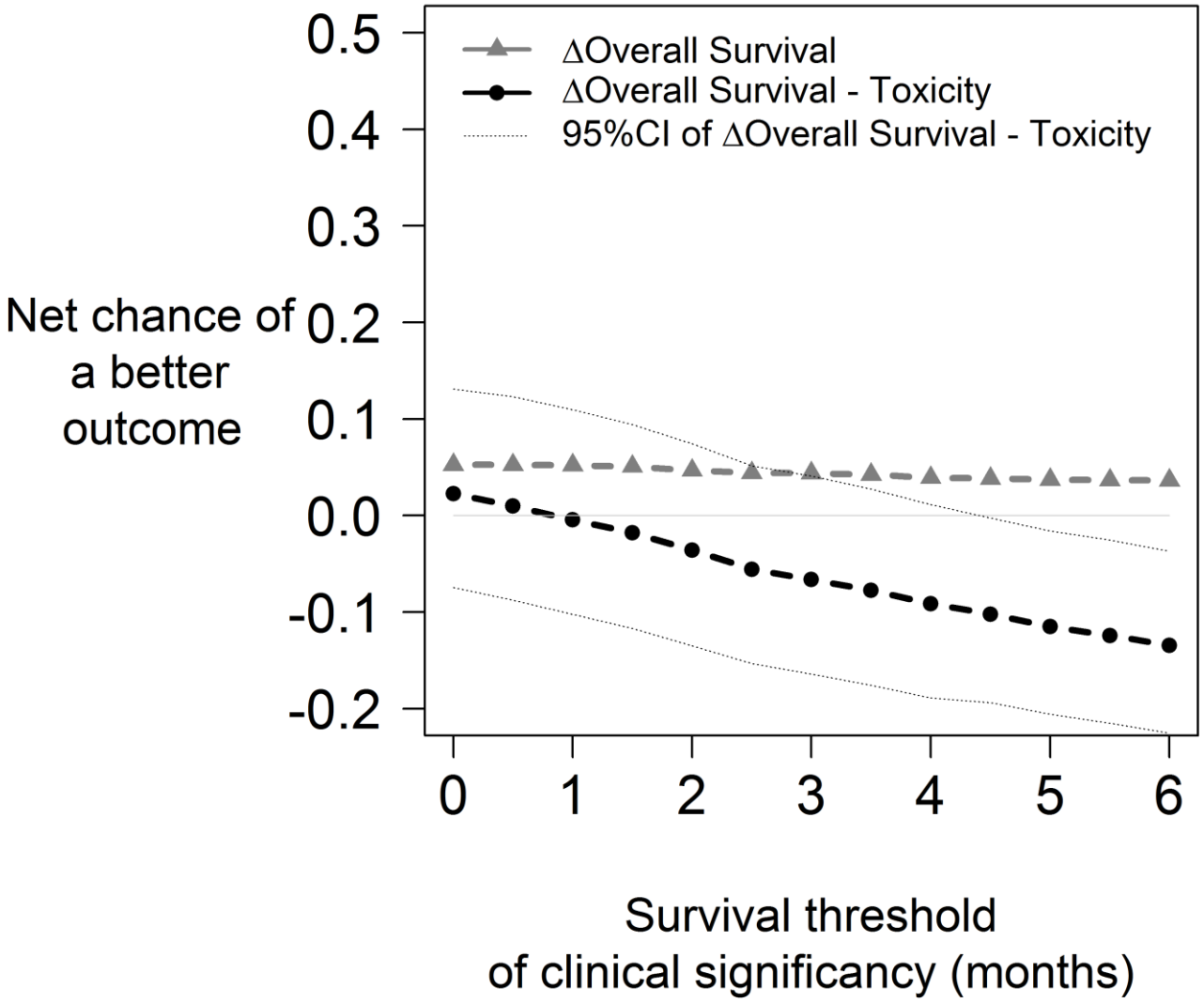
With the standard procedure

	proportion of pairs (%)		
	Erlotinib > Placebo	Placebo > Erlotinib	Δerlotinib
1 : OS (Threshold = 2 months)	37.0	32.3	4.7
2 : Worst related AE grade	7.5	15.7	-8.3
Overall	44.5	48.1	**-3.6 (P=.51)**

Main analysis of the benefit-risk balance of the erlotinib and gemcitabine combination

Péron J. Roy P. Ding K. Parulekar WR. Roche L and Buyse M. BJC 2015

Sensitivity analysis



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Benefit-risk balance

Standard procedure

Priority	Erlotinib > Placebo	Placebo > Erlotinib	Δ[erlotinib]
1 : OS (Threshold = 2 months)	37.0 %	32.3 %	4.7 %
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Global	44.5 %	48.1 %	**-3.6% (P=.51)**

Extended procedure

Priority	Erlotinib > Placebo	Placebo > Erlotinib	Δ[erlotinib]
1 : OS (Threshold = 2 months)	40.3 %	34.5 %	5.8 %
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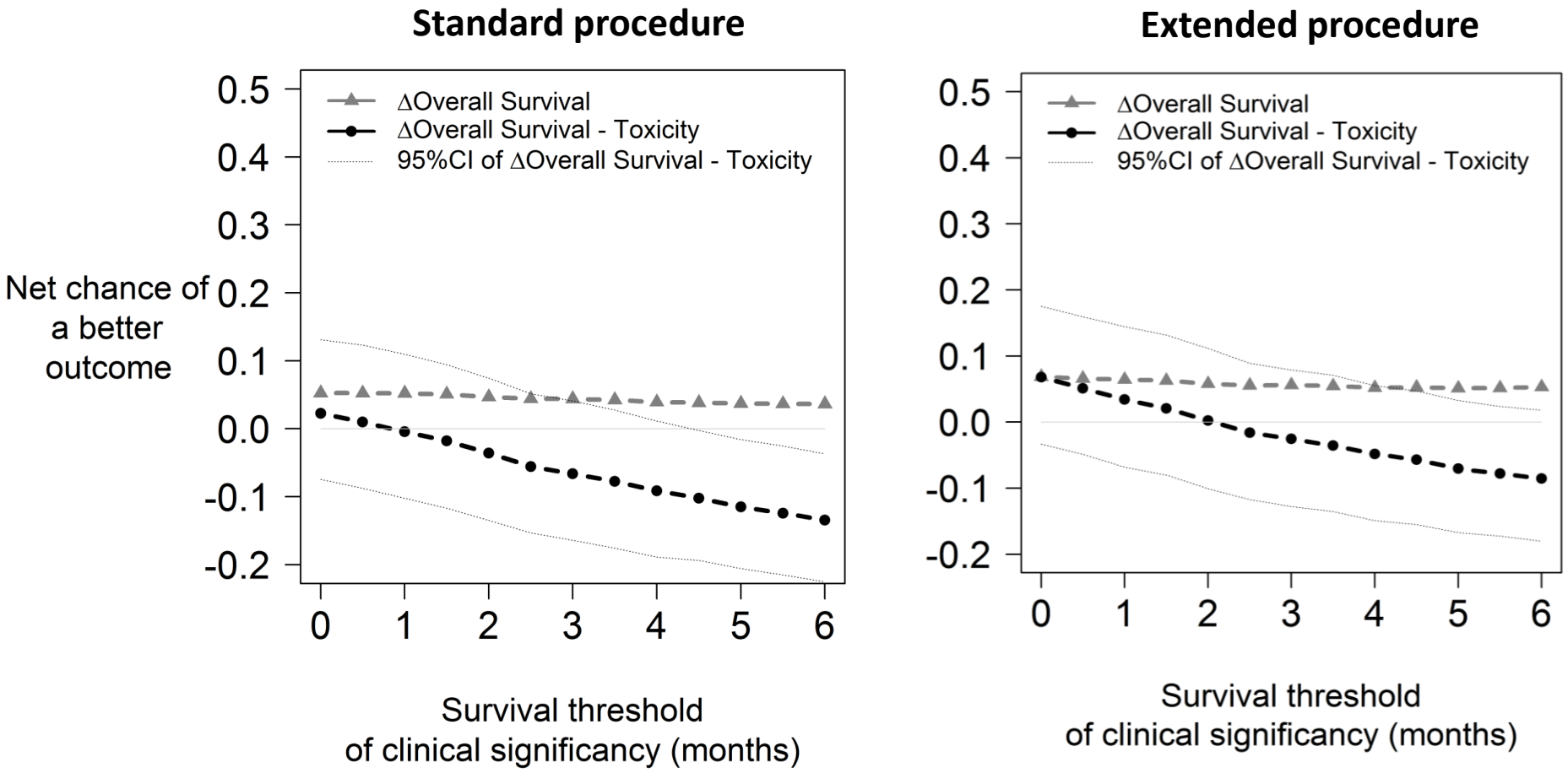
Benefit-risk balance



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Benefit-risk balance

PRODIGE 4 trial

Priority	FOLFIRINOX > Gemcitabine	Gemcitabine > FOLFIRINOX	Δ[FOLFIRINOX]
1 : OS (Threshold = 2 months)	43.0%	21.7%	21.3%
2 : Worst related AE grade	8.2%	15.4%	-7.2%
Global	51.2%	37.1%	**14.0% (P=0.029)**

Benefit-risk balance

PRODIGE 4 trial

Priority	FOLFIRINOX > Gemcitabine	Gemcitabine > FOLFIRINOX	Δ[FOLFIRINOX]
1 : OS (Threshold = 2 months)	43.0%	21.7%	21.3%
2 : Worst related AE grade	8.2%	15.4%	-7.2%
Global	51.2%	37.1%	**14.0% (P=0.029)**

NCIC PA-3 trial

Priority	Erlotinib > Placebo	Placebo > Erlotinib	Δ[erlotinib]
1 : OS (Threshold = 2 months)	37.0 %	32.3 %	4.7 %
2 : Worst related AE grade	7.5 %	15.7 %	-8.3 %
Global	44.5 %	48.1 %	**-3.6% (P=.51)**

NCIC PA-3 trial