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Long-term effect of adjuvant tamoxifen: adherence-based analysis

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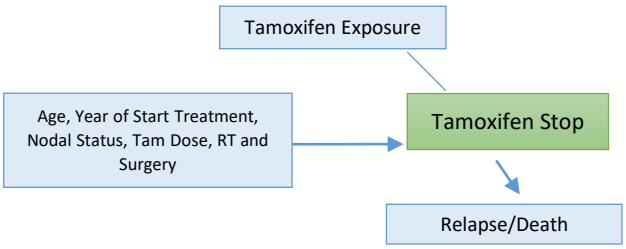
INTRODUCTION

Although randomized clinical trials (RCTs) often suffer from non-adherence or noncompliance of trial participants to the intervention(s) protocol to which they are randomized, the analyses are usually performed according to intention-to-treat (ITT) principle. This leads to biased estimates of treatment effects if crossover is not appropriately controlled for. Several crossover adjustment methods are available, but previous research has shown that the optimal adjustment method depends upon the characteristics of the trial [1].This study applies switching adjustment methods to an RCT comparing short-term (ST) adjuvant tamoxifen treatment with lifelong adjuvant tamoxifen treatment (LT), and investigates which adjustment method best fits this case study. There were 1882 women in ST arm (3 year treatment group: tamoxifen was immediately stopped after randomization) and 1911 in LT arm (patients continued tamoxifen assumption for further 10 years). 27 % of LT group patients, switched onto the experimental treatment.

Switching process from the Tamoxifen exposure to stop treatment



OBJECTIVES

This study aims at estimating the switching-adjusted treatment effect of tamoxifen for OS and iDFS using several causal inference methods, performing simulation study to assess the operational characteristics of each method

ADJUSTMENT METHODS AND THEIR KEY REQUIREMENTS

Inverse Probability Censoring Weighting (IPCW) and Rank Preserving Structural Failure Time Model (RPSFTM):
these methods aim to emulate the original randomization of the treatment by creating a pseudo-population

IPCW
The IPCW involves censoring switchers at the time of treatment switch, and weighting remaining patients according to their similarity to switchers, using information on baseline and time-dependent covariates.
A weighted Cox regression model is utilized to estimate the adjusted hazard ratio. A weighted Kaplan-Meier curve can also be obtained

IPCW
The method creates a "pseudo population" adjusted for the distortions that arise from the prognostic differences between switchers and non-switchers.

RPSFTM
The method estimates the survival end-points relative to a specific treatment, constructing a pseudo-population that hypothesizes what would have happened to the survival of the switchers, if they would not have switched to the alternative treatment

RPSFTM
The standard single parameter RPSFT model splits the observed event time Ti, into time spent "on treatment" (T_{Oni}) and time spent "off treatment" (T_{OFFi}). Counterfactual event times, Ui, are calculated, and are related to observed event times with the following causal model:

$$Ui = T_{OFFi} + e^{\varphi} T_{oni}$$

$e^{-\varphi}$ represents the acceleration factor associated with the intervention-the amount by which an individual's expected survival time is increased by treatment

Key IPWC requirements:
- No unmeasured confounders: need data collected at baseline and over time on all variables that are prognostic of switching or survival
- E.g. patient choice as to whether to switch
- Correctly specified models for switching and survival

Software

Analysis are performed using *ipcwswitch* R-package. Several sensitivity analyses were performed to evaluate robustness of IPCW
-RPSFTM:. We adapted *rpsftm* R-package to TAM01 (it was created for situation in which patients in the control group switch to experimental arm, while in TAM01, in ST arm (control) there are no crossover to LT arm).

Key RPSFTM requirements:
- Non-active (e.g. placebo) comparator
- Common treatment effect: the treatment effect of the experimental treatment is the same for switchers and experimental group patients, regardless of the disease stage at which it is received

Results

ITT analysis estimated a 6% reduction in the hazard of death and a 10% reduction of hazard of relapse with tamoxifen treatment (hazard ratio (HR) respectively, 0.94 (0.84-1.07) and 0.90 (0.81-0.99)). All causal inference methods adjusted for switching showed that a significant survival benefit would have been observed had there been no selective switching (see **Table**). Results from counterfactual and RPSFTM methods differ on iDFS endpoint, which underlines the need for careful assessment of underlying assumptions in each method

Outcome: Overall Survival			Outcome: Invasive Disease Free Survival		
NAIVE METHODS			**NAIVE METHODS**		
Method	**HR (95% CI)**	**p-value**	**Method**	**HR (95% CI)**	**p-value**
ITT ANALYSIS (unadjusted)	0.94 (0.84-1.07)	0.352	ITT ANALYSIS (unadjusted)	0.90 (0.81-0.99)	0.045
PP ANALYSIS	1.14 (1.00-1.30)	0.005	PP ANALYSIS	0.99 (0.89-1.18)	0.95
Censoring switchers	0.96 (0.84-1.09)	0.506	Censoring switchers	0.94 (0.84-1.05)	0.283
Switching as time-dependent covariate	0.95 (0.84-1.08)	0.459	Switching as time-dependent	1.08 (0.97-1.21)	0.159
COMPLEX-METHODS			**COMPLEX METHODS**		
Method	**HR (95% CI)**	**p-value**	**Method**	**HR (95% CI)**	**p-value**
IPCW	0.73 (0.63-0.84)	<0.001	IPCW	0.45 (0.38-0.51)	<0.001
MSM	0.73 (0.62-0.84)	<0.001	MSM	0.48 (0.42-0.56)	<0.001
RPSFTM (with re-censoring)	0.75 (0.57-0.99)	//	RPSFT (with re-censoring)	0.70 (0.53-0.92)	//
RPSFT (without re-censoring)	0.80 (0.65-0.99)	//	RPSFT (without re-censoring)	0.83 (0.72-0.96)	//

Conclusion

- **Adjusting for treatment compliance reveals a significant higher protective effect of Tamoxifen on both OS and IDFS compared as standard ITT analysis**
- Effect size is variable and related to assumption underlying causal model
- It is important to analyze trial characteristics and model output carefully when identifying which applications of the adjustment methods are most plausible.
- RPSFTM relies on the common treatment effect assumption, which may be implausible.
- The unmeasured confounders assumption is important for IPCW
- Re-censoring of the data can be applied for the RPSFTM to reduce bias by breaking the dependence between censoring time and treatment

[1]Latimer NR, et al. Adjusting survival time estimates to account for treatment switching in randomised controlled trials – an economic evaluation context: Methods, limitations and recommendations. Med Decis Making, January 21, 2014