A weighted log-rank test and associated effect estimator for cancer trials with delayed treatment effect

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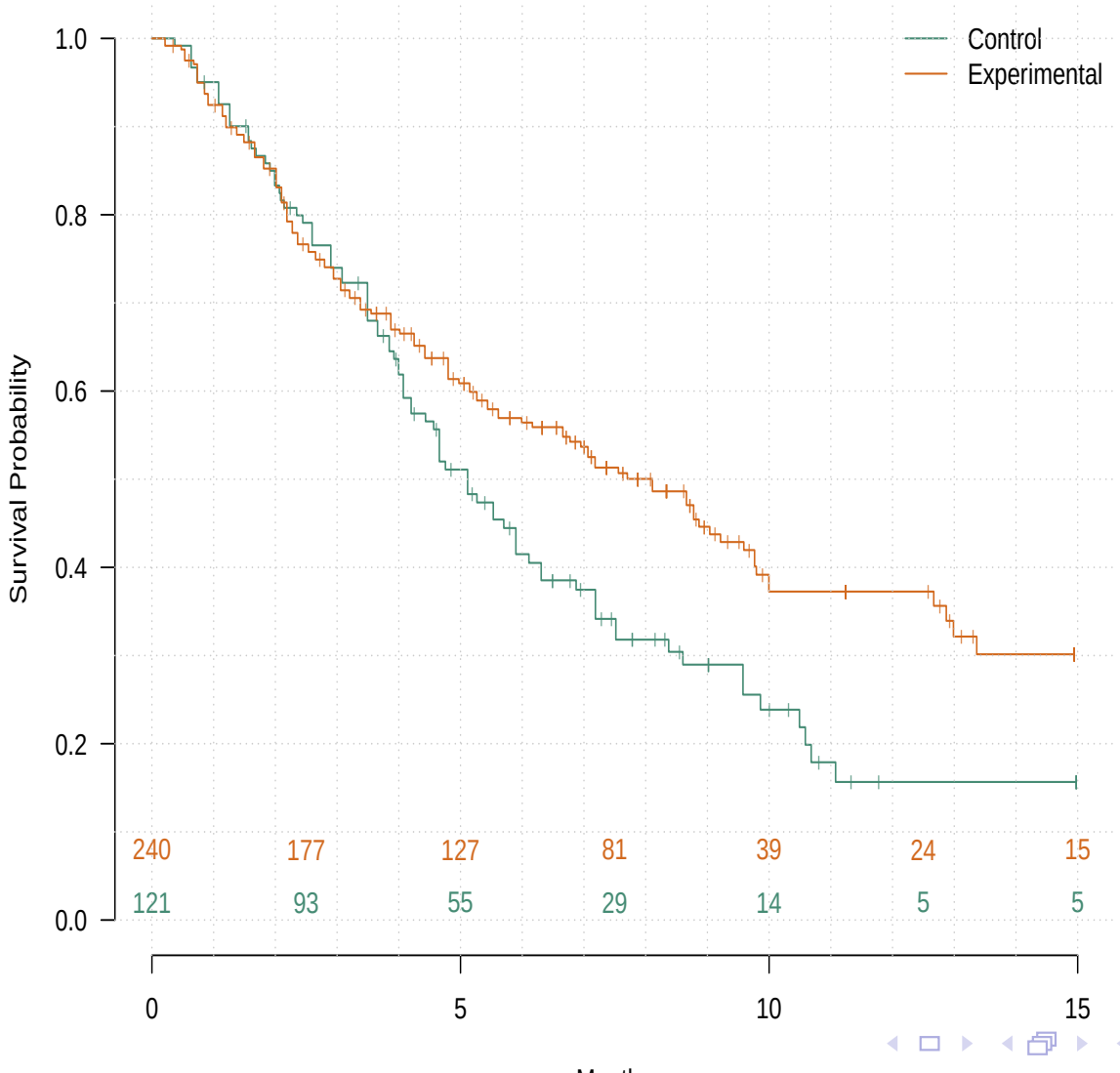
Nivolumab on head and neck cancer, Overall Survival, Re-constructed data from Ferris et al. (2016)



Setup and notation

- Randomize n subjects into two treatment groups ($X_j = 0$: control arm and $X_j = 1$: experimental arm, $j = 1, ..., n$).
- D is the set of subjects who experienced the event.
- t_j is the event time or censoring time for the j^{th} subject and we assume the event times are distinct.
- Let $n_i(t)$ be the number of subjects at risk for the event before time t for treatment group i.
- $p(t) = n_1(t)/\{n_0(t) + n_1(t)\}$

Motivated by Schoenfeld (1981) *Biometrika*

- The test statistic

$$S = \frac{\sum_{j \in D} w_j \left(X_j - p(t_j)\right)}{\left[\sum_{j \in D} w_j^2 p(t_j)(1 - p(t_j))\right]^{1/2}} \tag{1}$$

- The standard log-rank test when $w_j = 1$.
- The Fleming-Harrington test (Fleming & Harrington, 1991) when

$$w(t) = \widehat{S}(t)^{\rho}(1 - \widehat{S}(t))^{\gamma},$$

where $\rho \geq 0$, $\gamma \geq 0$ and $\widehat{S}(t)$ is the pooled estimate of the survival function at time t.

A hazard ratio model

- The hazard ratio (HR)

$$\lambda(t) = h_1(t)/h_0(t) = \begin{cases} 1 & t \le t_1 \\ \dfrac{\lambda - 1}{t_2 - t_1}(t - t_1) + 1 & t_1 < t \le t_2 \\ \lambda & t > t_2 \end{cases} \tag{2}$$

- $h_0(t)$ and $h_1(t)$ are the hazard functions of the control and the experimental groups respectively.
- Discussed by clinicians in cancer immunotherapy research (Hoos et al. 2010, JNCI, and others.)

Weight functions

- Set weight w_1 to w_2 at time t_1 and t_2

$$w(t) = \frac{e^{a(t-\tau)}}{1 + e^{a(t-\tau)}} \tag{3}$$

- Motivated by Schoenfeld (1981) and Xu et al. (2017, Stat Med), the weighted log-rank test (1) with weight proportional to the logarithm of the HR at the event time would asymptotically maximize its power.
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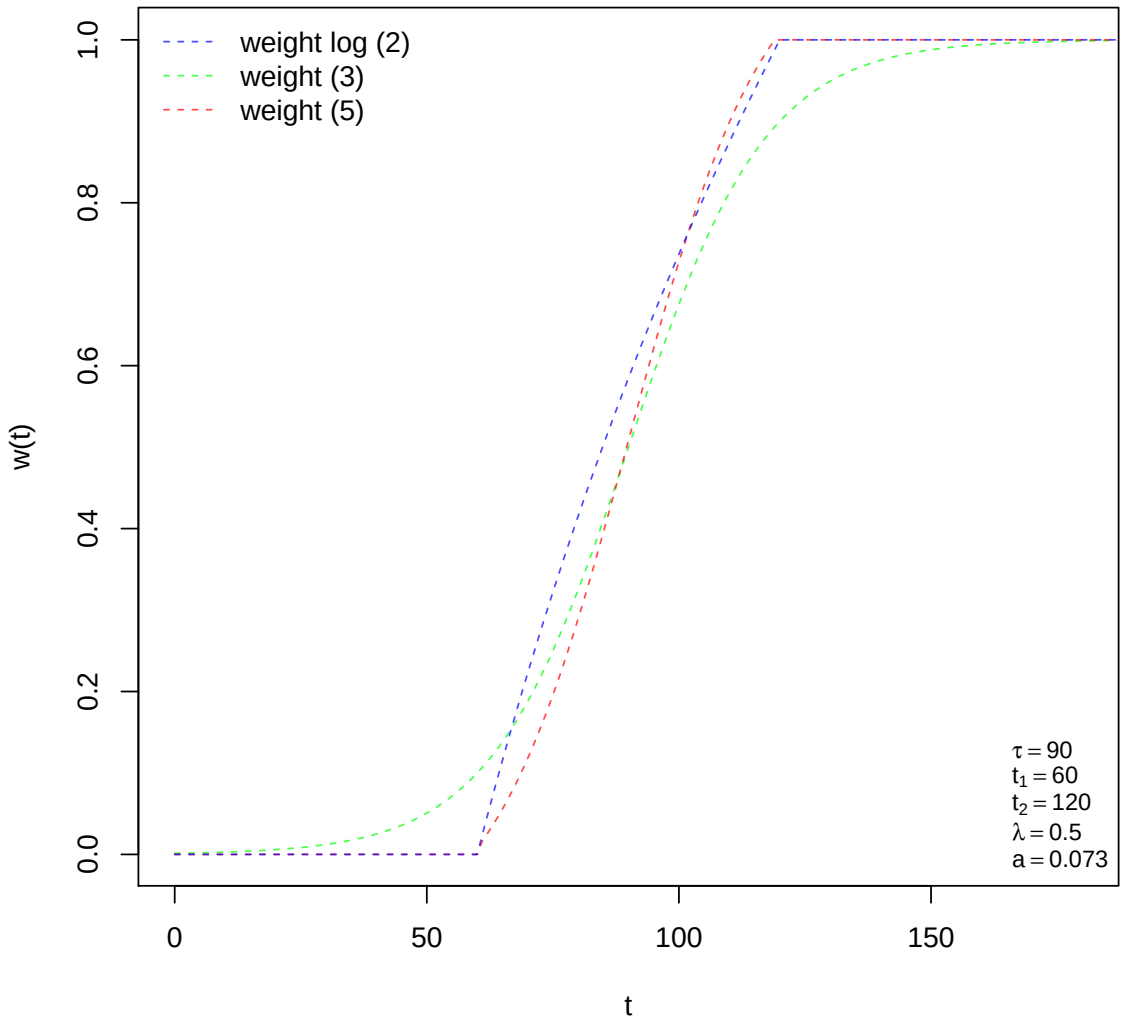
$$w_a(t) = \begin{cases} 0 & t \leq t_1 \\ \dfrac{w(t) - w(t_1)}{w(t_2) - w(t_1)} & t_1 < t \leq t_2 \\ 1 & t > t_2 \end{cases} \tag{4}$$

Three weight functions



Test statistic

Theorem Test statistic (1) with weight functions (3) and (4) is asymptotically normally distributed with mean μ and unit variance.

Schoenfeld approximation of μ (Schoenfeld, 1981, Biometrika) using the Taylor expansion when $\log(h_1(t)/h_0(t)) \sim O(n^{-1/2})$,

$$\mu = \frac{n^{1/2} \int w(t) \log(h_1(t)/h_0(t)) \pi(t)(1-\pi(t)) V(t) dt}{[\int (w(t))^2 \pi(t)(1-\pi(t)) V(t) dt]^{1/2}} \qquad (5)$$

Test statistic

- The integration is over the range from 0 to ∞;
- $$V(t) = P_0 f_0(t)(1 - H_0(t)) + P_1 f_1(t)(1 - H_1(t))\,;$$
- $$\pi(t) = \frac{P_1(1 - F_1(t))(1 - H_1(t))}{P_0(1 - F_0(t))(1 - H_0(t)) + P_1(1 - F_1(t))(1 - H_1(t))}\,.$$

Sample size and power

- The key is to assess (analytically or numerically)

$$\mu = \frac{n^{1/2} \int w(t) \log(h_1(t)/h_0(t)) \pi(t)(1-\pi(t)) V(t) dt}{[\int (w(t))^2 \pi(t)(1-\pi(t)) V(t) dt]^{1/2}} = n^{1/2} R$$

- R programs to numerically evaluate R.
- Sample size

$$n = [(Z_{1-\alpha/2} + Z_{1-\beta})/R]^2$$

- Power

$$1 - \beta = \Phi(\mu - Z_{1-\alpha/2}) + \Phi(-\mu - Z_{1-\alpha/2})$$

Estimation through a connection between weighted log-rank test and weighted Cox regression

If we use weight (3) or (4) in the weighted Cox regression (WCR)

- Our weighted log-rank test is the score test from the weighted Cox regression.
- $\exp(\hat{\beta})$ obtained from WCR with censoring correction, using weight $w(t)\widehat{G}(t)^{-1}$, provides an estimate of the average hazard ratio (AHR).
- Schemper et al. (2009, Stat Med) discussed how AHR could be estimated in connection with WCR.

Average hazard ratio (AHR)

- We compare three AHR's as estimands of the treatment effect in our study.
- The AHR-CR is estimated using uniform one weight with censoring correction.
- The AHR-WCR is estimated using the Prentice weight $S(t)$ with censoring correction.
- The WCR using weights (3) and (4) show a similar performance so we focus on the latter. The estimator is denoted as AHR-WCR2.

Simulation algorithm

1. n subjects are randomized with $1:1$ ratio to the two arms. Generate subjects' enrollment times U from a uniform distribution with rate $1/A$, A is the enrollment period.
2. For subjects in the control arm, their event time T_0 follows an exponential (h_0) distribution.
3. For subjects in the experimental arm, their event time T_1 could be
   - Under the null: type I error rate is controlled.
   - Under various delayed scenarios.

Simulation algorithm

4. Then we have the observed survival time $Z = min\{T, B - U\}$ and the event indicator $\delta = I\{T \leq B - U\}$, where $T = T_0 \cup T_1$. We assume the cause to loss-of-follow-up is administrative censoring.
5. Apply the proposed weighted log-rank tests using weights (3) and (4), the standard log-rank test, or tests in the Fleming-Harrington $G^{\rho,\gamma}$ class.
6. Repeat steps 1 through 5 for 10,000 simulation replicates to evaluate the empirical type I error rate or power.

Empirical power for 3 transition periods

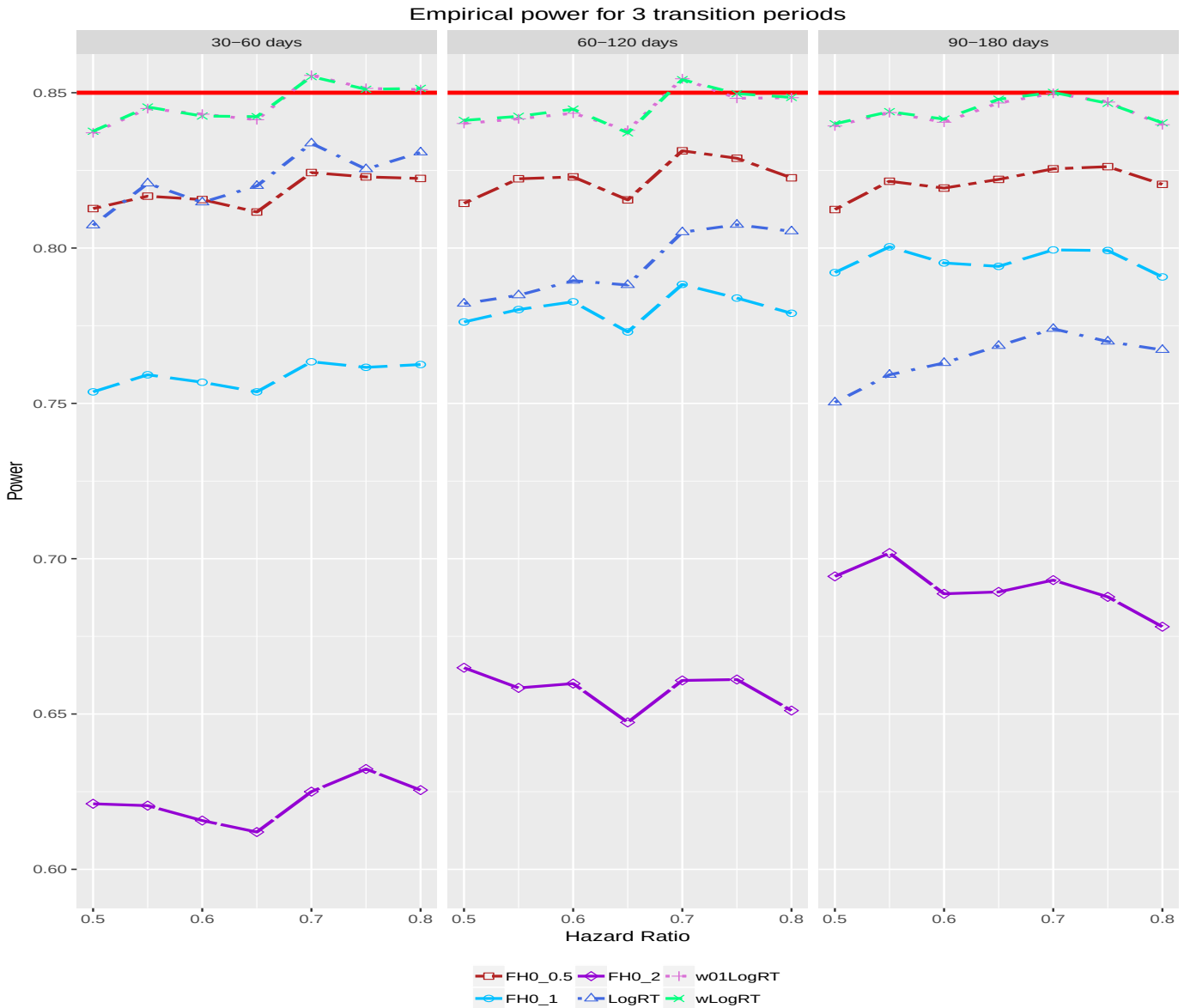


Table 1: Empirical power of 5 tests: wLogRT using weight (3), w01LogRT using weight (4), 3 tests in the $G^{\rho,\gamma}$ class with $(\rho = 0, \gamma = 0.5)$ (FH0_0.5), $(\rho = 0, \gamma = 1)$ (FH0_1), and $(\rho = 0, \gamma = 2)$ (FH0_2), and the standard log-rank test (LogRT).

Transition period used	Center (days)	Width (days)	Sample size	Empirical power(%)					
				wLogRT	w01LogRT	FH0_0.5	FH0_1	FH0_2	LogRT
Correct center, correct width									
90 - 180	135	90	232	85.0	84.8	82.4	80.7	71.4	74.9
Wrong center, correct width									
0 - 90	45	90	198	73.2	72.8	75.6	74.1	64.0	67.5
45 - 135	90	90	214	79.9	79.7	78.8	77.0	67.8	71.2
135 - 225	180	90	252	86.3	86.2	85.1	83.6	74.5	77.6
180 - 270	225	90	276	87.9	87.5	88.3	87.3	78.5	82.2
Correct center, wrong width									
125 - 145	135	20	226	83.6	83.4	80.8	79.1	70.0	73.9
110 - 160	135	50	228	84.3	84.3	81.8	80.2	70.7	74.6
40 - 230	135	190	240	85.4	85.6	83.4	81.7	73.2	75.9
Wrong center, wrong width									
30 - 70	50	40	196	72.5	72.1	74.9	72.9	63.7	67.4
0 - 100	50	100	200	74.3	73.8	76.0	74.3	65.1	68.1
200 - 240	220	40	268	86.5	86.2	87.4	85.9	77.8	80.6
170 - 270	220	100	274	87.7	87.4	87.9	86.5	78.1	81.2

Note: The sample size is calculated using the NESA method for the weighted log-rank tests to have 85% power to detect HR 0.5 under various specifications of the transition period. Simulation set-up: there is a delayed treatment effect with the transition period 90-180 days (centered at 135 days with width 90 days); the enrollment period is $A = 1$ year and the maximum follow-up is $B = 3$ years; the control group hazard rate is 0.31 (equivalently survival rate 40% at the end of year 3); nominal $\alpha = 0.05$ is used; the number of simulation replicates is 10,000.

Table 2: Re-analysis of the overall survival data from the trial of nivolumab, Ferris et al. (2016)

Transition period	P-values		AHR-WCR2	
	wLogRT	w01LogRT	Estimate	CI
0 - 4	0.000419	0.000330	0.605	(0.405-0.804)
1 - 3	0.000396	0.000458	0.602	(0.4-0.804)
2 - 2	0.002319	0.002646	0.639	(0.424-0.854)
0 - 5	0.000331	0.000225	0.593	(0.388-0.799)
1 - 4	0.000192	0.000145	0.576	(0.372-0.779)
1.5 - 3.5	0.000152	0.000137	0.569	(0.365-0.773)
2 - 3	0.000132	0.000133	0.561	(0.356-0.766)
2.5 - 2.5	0.000121	0.000124	0.555	(0.35-0.76)
2 - 4	0.000083	0.000059	0.542	(0.334-0.751)
3 - 3	0.000087	0.000087	0.538	(0.327-0.749)
2 - 5	0.000136	0.000104	0.547	(0.325-0.769)
3.5 - 3.5	0.000050	0.000056	0.531	(0.308-0.755)
LogRT		0.006976		
AHR-CR			0.685	(0.489-0.881)
AHR-WCR			0.731	(0.533-0.928)

Discussion

- The regularity condition $\log(h_1(t)/h_0(t)) \sim O(n^{-1/2})$ under which Schoenfeld (1981) derived the Schoenfeld approximation (10) does not appear to be stringent in practice.
- Usually the true transition period is not known in practice. Investigators should lean toward later-centered, wider transition period to be conservative when they design a trial.
- Further research on treatment effect estimator is needed.
- Software: we have R programs to implement our methods.

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Thank You!

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