K-Sample Test for Doubly Censored Tumor Times

Hwashin Hyun Shin

Tim Ramsay

Daniel Krewski

McLaughlin Centre
Institute of Population Health
University of Ottawa

Previous work:

1. **Jonckheere (Biometrika, Vol 41, 1954)**
   "A distribution free K-sample test against ordered alternatives"

   $$H_a:\ F_1(X)<F_2(X)<.........<F_K(X)$$

2. **Gehan (Biometrika, Vol 52, 1965)**
   "A generalized 2-sample Wilcoxon test for doubly censored data"
   Assuming uncensored, left-censored & right-censored data

   $$H_a:\ F_1(X)<F_2(X)$$

Current work:

"Non-parametric K-sample test for doubly censored tumor times"

1. **When:**
   a) **Tumor onset times are unknown,**
   b) **Times of death/Sacrifice are known,**
   c) **Indicators of tumor at necropsy are available.**
   ➔ **Only censored tumor times are available.**
2. **Hypotheses:**
   H_0 : **Same tumor rates**
   H_a : **Tumor incidence rates are increasing over higher dose of test agent.**
3. **Method:**
   a) **Under equal mortality assumption**
   b) **Under differential mortality assumption**
4. **Example:** **from Simulation**
   based on Portier, Hedges, Hoel 1986, from NTP experiments
5. **Results:**
   Comparable Type I error & Higher power
6. **Question:**
   How to adjust differential mortality rates among K treatment groups?

Simulated Data

Case 1:	**Same Tumor Rates & Same Mortality Rates**							
	Group 1		***Group2***		***Group 3***		***Group 4***	
	Death	**Tumor**	**Death**	**Tumor**	**Death**	**Tumor**	**Death**	**Tumor**
	85.2	1	92.5	0	94.4	0	84.7	0
	86.3	0	92.5	0	95.1	0	86.4	0
	89.4	0	93.9	0	95.2	1	87.2	0
	91.2	0	95.4	0	95.7	1	88.0	0
	92.6	0	95.5	0	95.7	0	88.8	1
Average	**83.5 weeks**	**18%**	**90.6 weeks**	**12%**	**88.7 weeks**	**14%**	**81.7 weeks**	**16%**
Case 2:	**Same Tumor Rates & Differential Mortality Rates**							
	90.8	0	92.8	0	94.1	1	86.2	1
	92.3	1	94.1	1	94.8	0	87.4	0
	93.9	0	94.2	0	96.9	1	88.5	1
	94.5	0	95.3	0	98.5	0	88.8	0
	95.3	0	96.2	0	99.1	0	92.0	0
Average	**87.0 weeks**	**20%**	**88.6 weeks**	**16%**	**90.3 weeks**	**10%**	**83.1 weeks**	**22%**
Case 3:	**Differential Tumor Rates & Same Mortality Rates**							
	98.3	1	93.1	1	89.0	1	94.9	1
	98.6	1	95.5	1	90.2	0	95.6	1
	98.8	0	98.4	1	94.1	0	97.6	1
	99.9	1	99.3	0	94.7	1	98.2	1
	100.8	0	99.6	0	95.0	1	99.3	1
Average	**89.2 weeks**	**28%**	**85.0 weeks**	**34%**	**86.9 weeks**	**30%**	**87.3 weeks**	**46%**
Case 4:	**Differential Tumor Rates & Differential Mortality Rates**							
	96.2	0	90.4	0	91.2	1	79.5	0
	96.5	1	91.2	1	91.8	0	80.3	0
	96.7	0	93.8	1	92.2	0	80.5	1
	97.0	1	94.4	0	93.5	1	81.4	1
	97.2	0	94.6	0	95.7	0	85.6	1
Average	**87.2 weeks**	**14%**	**87.2 weeks**	**16%**	**80.5 weeks**	**34%**	**78.5 weeks**	**26%**

Test Statistic

1. Under same mortality rate assumption:

$$\phi_{kh}(i, j) = \begin{cases} 1 & \text{if } X_{ki} \leq X_{hj},\ \delta_{ki} = 1, \delta_{hj} = 0, \\ -1 & \text{if } X_{ki} \geq X_{hj},\ \delta_{ki} = 0, \delta_{hj} = 1, \\ 0 & \text{otherwise,} \end{cases}$$

where X_{ki} = i-th death time in group k,

δ_{ki} = tumor indicator corresponding to X_{ki}.

$$S = \sum_{k=1}^{K-1} \sum_{h=k+1}^{K} \left[\left(\sum_{i=1}^{N_k} \sum_{j=1}^{N_h} \phi_{kh}(i, j) \right) / N_k N_h \right]$$

Then S has asymptotically a normal distribution.

2. Under differential mortality rate assumption:

$$\phi_{kh}(i, j, s, t) = \begin{cases} 1 & \text{if } X_{ki} \leq X_{hj}, X_{ki} \in A_s, X_{hj} \in A_t, \delta_{ki} = 1, \delta_{hj} = 0, \\ -1 & \text{if } X_{ki} \geq X_{hj}, X_{ki} \in A_s, X_{hj} \in A_t, \delta_{ki} = 0, \delta_{hj} = 1, \\ 0 & \text{otherwise,} \end{cases}$$

where $A_1, .., A_T$ are disjoint time intervals.

$$S = \sum_{k=1}^{K-1} \sum_{h=k+1}^{K} \left[\left(\sum_{i=1}^{N_k} \sum_{j=1}^{N_h} \sum_{s} \sum_{t} w_k(s) w_h(t) \phi_{kh}(i, j, s, t) \right) / N_k N_h \right]$$