Beyond Hazard Ratio: Measures of Treatment Effect on Survival

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Outline

- Hazard
- PH assumption
- Non-PH in cancer clinical trials
- Restricted Mean Survival Time
- Semi-parametric AFT model
- Conclusions

Hazard (function)

- Hazard – “speed of events”

- Depends on time (in general) – thus, function of time

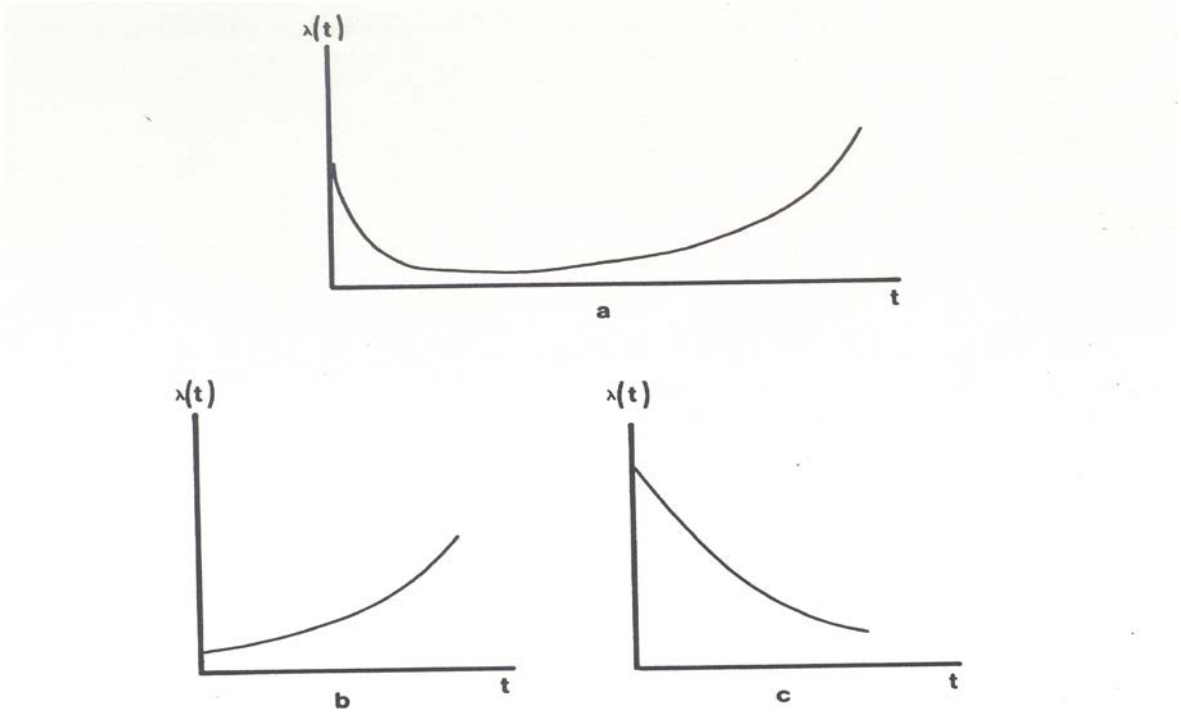
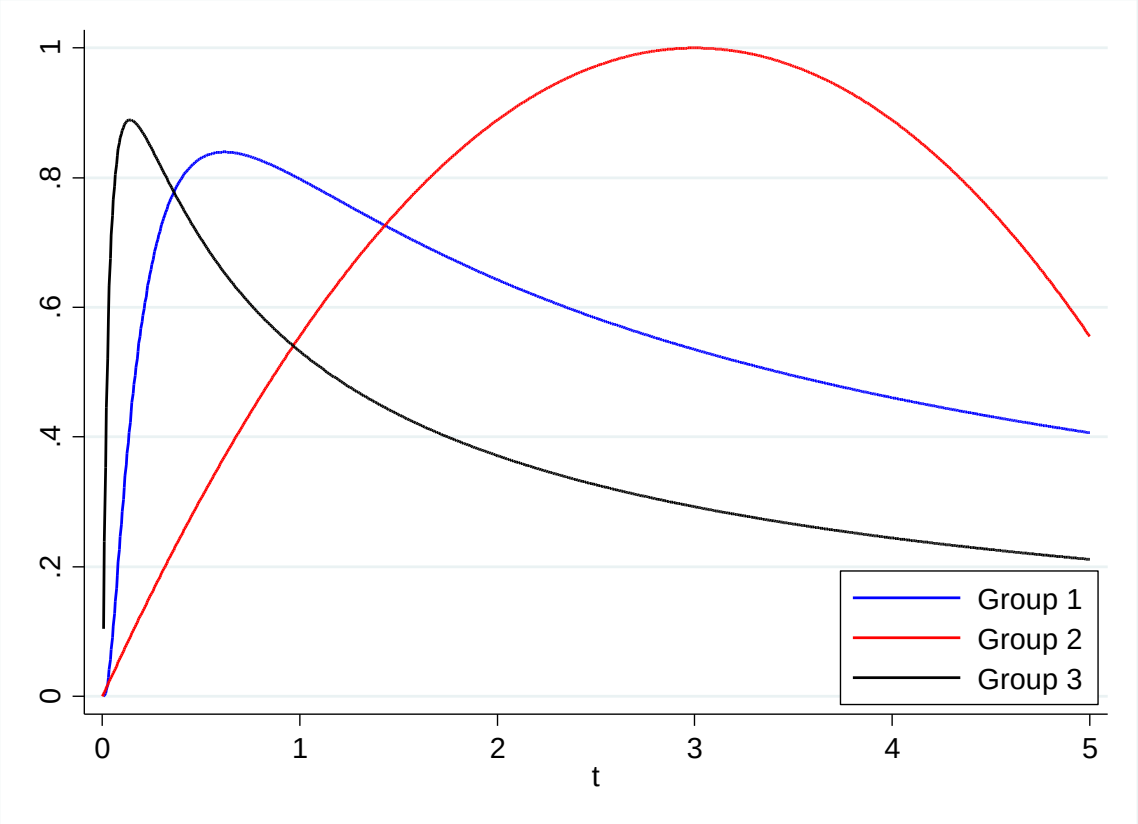


Figure 1.1 Some types of hazard functions: (a) hazard for human mortality; (b) positive aging; (c) negative aging.

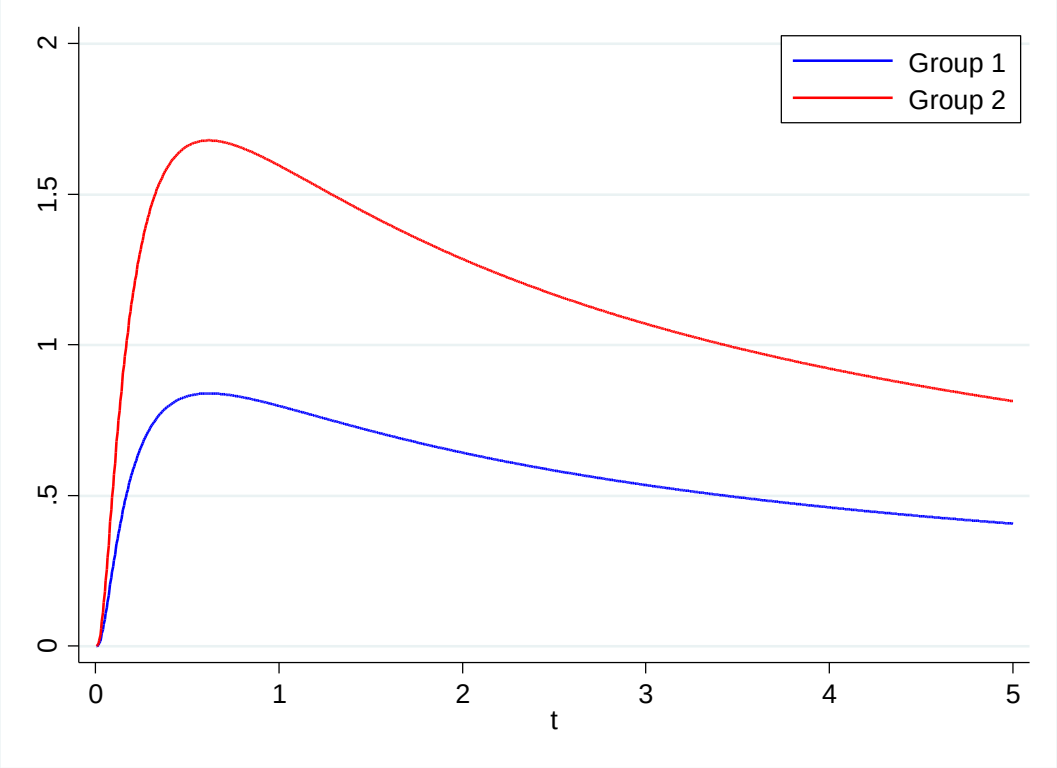
Arbitrary Hazard Functions

- Which group lives (on average) longer ?



Proportional Hazard Functions/Model

- Hazard ratio = 2
- Group 2 lives (on average) longer
- By how much?



Adjuvant Trials of Gastric Cancer

JAMA®

Online article and related content current as of May 6, 2010.

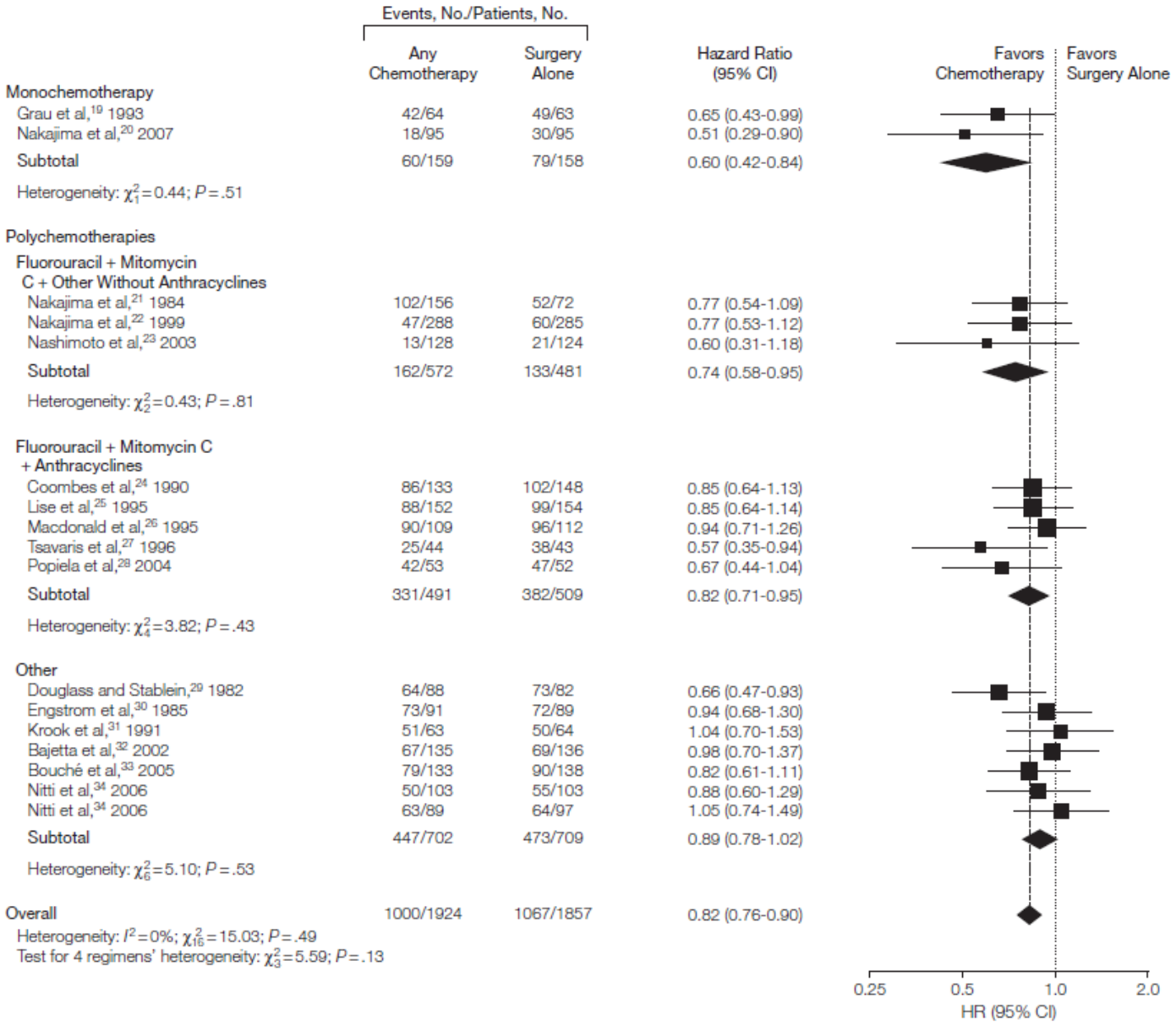
Benefit of Adjuvant Chemotherapy for Resectable Gastric Cancer: A Meta-analysis

The GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group

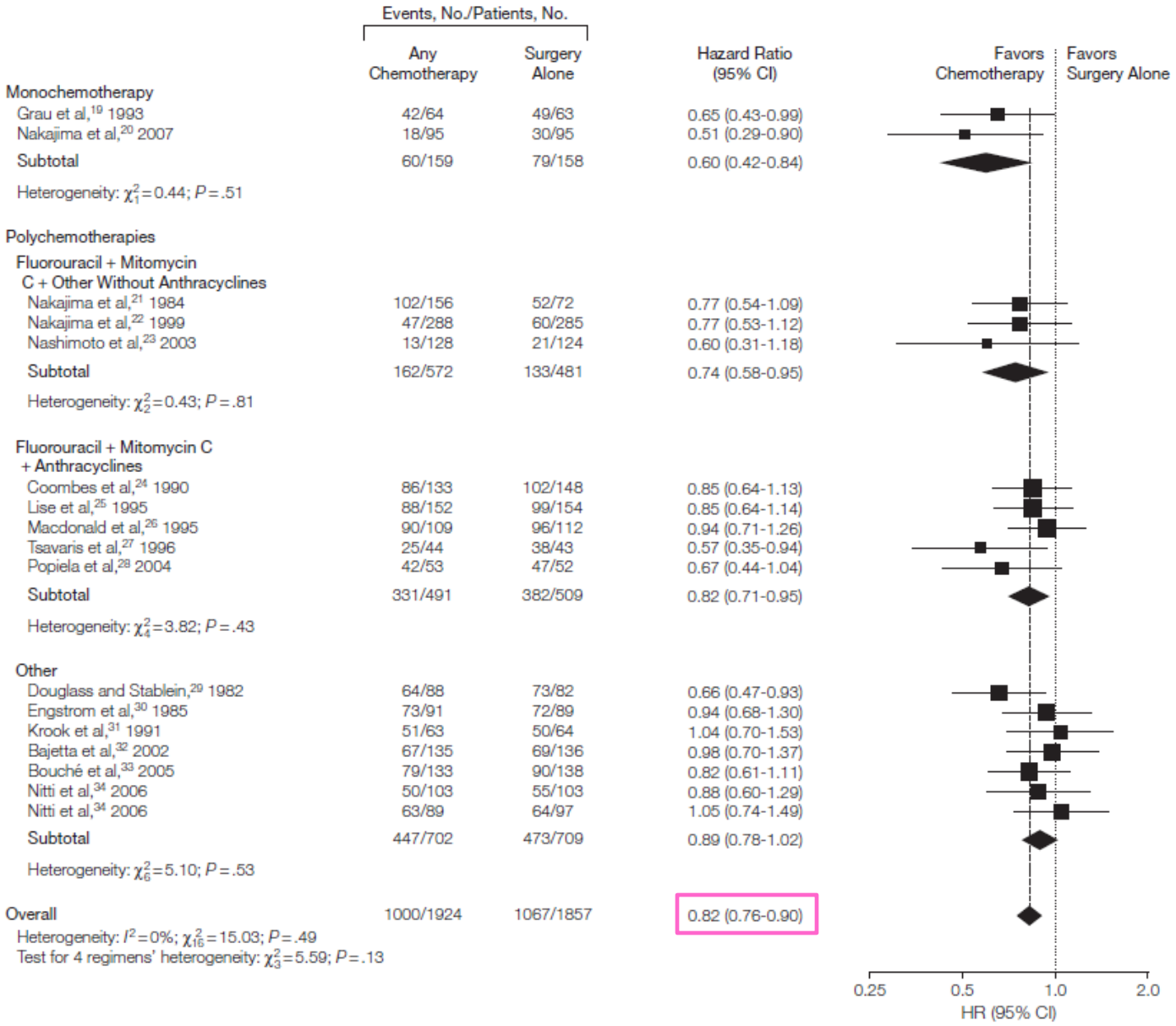
JAMA. 2010;303(17):1729-1737 (doi:10.1001/jama.2010.534)

- 17 trials, 3838 patients
- Surgery vs. surgery + adj. chemotherapy

Adjuvant Trials of Gastric Cancer

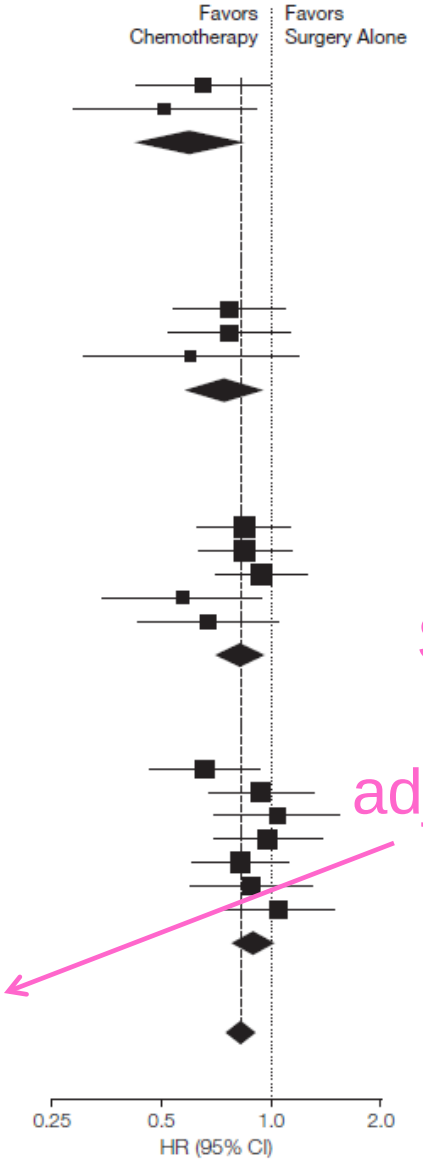


Adjuvant Trials of Gastric Cancer



Adjuvant Trials of Gastric Cancer

	Events, No./Patients, No.		Hazard Ratio (95% CI)
	Any Chemotherapy	Surgery Alone	
Monochemotherapy			
Grau et al,[19] 1993	42/64	49/63	0.65 (0.43-0.99)
Nakajima et al,[20] 2007	18/95	30/95	0.51 (0.29-0.90)
Subtotal	60/159	79/158	0.60 (0.42-0.84)
Heterogeneity: $\chi^2_1=0.44$; $P=.51$			
Polychemotherapies			
Fluorouracil + Mitomycin C + Other Without Anthracyclines			
Nakajima et al,[21] 1984	102/156	52/72	0.77 (0.54-1.09)
Nakajima et al,[22] 1999	47/288	60/285	0.77 (0.53-1.12)
Nashimoto et al,[23] 2003	13/128	21/124	0.60 (0.31-1.18)
Subtotal	162/572	133/481	0.74 (0.58-0.95)
Heterogeneity: $\chi^2_2=0.43$; $P=.81$			
Fluorouracil + Mitomycin C + Anthracyclines			
Coombes et al,[24] 1990	86/133	102/148	0.85 (0.64-1.13)
Lise et al,[25] 1995	88/152	99/154	0.85 (0.64-1.14)
Macdonald et al,[26] 1995	90/109	96/112	0.94 (0.71-1.26)
Tsavaris et al,[27] 1996	25/44	38/43	0.57 (0.35-0.94)
Popiela et al,[28] 2004	42/53	47/52	0.67 (0.44-1.04)
Subtotal	331/491	382/509	0.82 (0.71-0.95)
Heterogeneity: $\chi^2_4=3.82$; $P=.43$			
Other			
Douglass and Stablein,[29] 1982	64/88	73/82	0.66 (0.47-0.93)
Engstrom et al,[30] 1985	73/91	72/89	0.94 (0.68-1.30)
Krook et al,[31] 1991	51/63	50/64	1.04 (0.70-1.53)
Bajetta et al,[32] 2002	67/135	69/136	0.98 (0.70-1.37)
Bouché et al,[33] 2005	79/133	90/138	0.82 (0.61-1.11)
Nitti et al,[34] 2006	50/103	55/103	0.88 (0.60-1.29)
Nitti et al,[34] 2006	63/89	64/97	1.05 (0.74-1.49)
Subtotal	447/702	473/709	0.89 (0.78-1.02)
Heterogeneity: $\chi^2_6=5.10$; $P=.53$			
Overall	1000/1924	1067/1857	0.82 (0.76-0.90)
Heterogeneity: $I^2=0\%$; $\chi^2_{16}=15.03$; $P=.49$			
Test for 4 regimens' heterogeneity: $\chi^2_3=5.59$; $P=.13$			



So, how much longer do the adjuvant-treatment patients live?

Proportional Hazards Model

- *Semi-parametric:* hazards do not have to be specified.
- Ubiquitous in cancer clinical trials and data analyses...
- ... despite non-intuitive interpretation of the hazard ratio...
- ... despite the strong nature of the PH assumption.

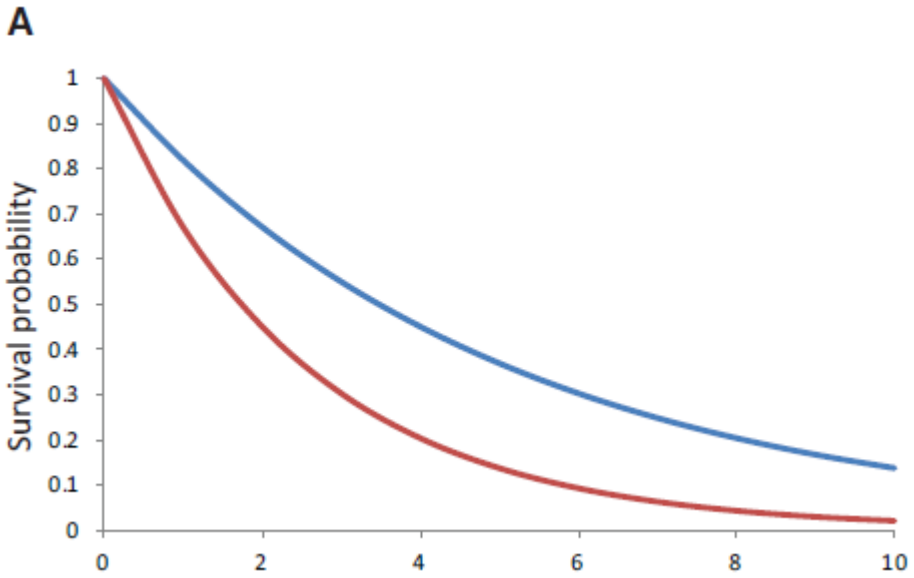
Survival Curves Under the PH Assumption

REVIEW

Understanding and Communicating Measures of Treatment Effect on Survival: Can We Do Better?

Everardo D. Saad, John R. Zalcberg, Julien Péron, Elisabeth Coart, Tomasz Burzykowski, Marc Buyse

JNCI J Natl Cancer Inst (2018) 110(3): djx179



- No overlapping fragments, no crossing !

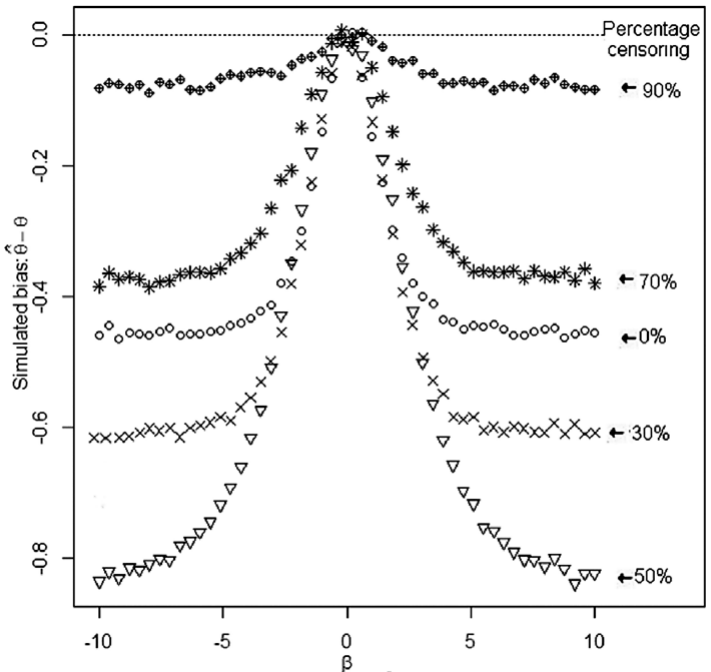
PH is a Very Strong Assumption

- In randomized clinical trials, omitting a prognostic factor causes a bias towards 0 in the estimated treatment effect.
  - Even if the distribution of the factor is balanced at baseline!

Bias and Sensitivity Analysis When Estimating Treatment Effects from the Cox Model with Omitted Covariates

Biometrics 69, 850–860
December 2013

Nan Xuan Lin,[1,2] Stuart Logan,[1] William Edward Henley[1,2,*]



Violations of the proportional hazards assumption in randomized phase III oncology clinical trials.

Rifaquat Rahman, Geoffrey Fell, Lorenzo Trippa, Brian Michael Alexander

DOI:
10.1200/JCO.2018.36.15_suppl.2543
Journal of Clinical Oncology 36, no. 15_suppl (May 2018) 2543-2543.

"We performed a PubMed search for randomized phase III trials in breast cancer, lung cancer, prostate cancer and colorectal cancer published in high-impact journals between 2014 and 2016. (...)

We identified 157 publications with 115 KM curves of overall survival (OS) and 139 KM curves of a non-survival time-to-event outcome.

There was evidence of non-proportionality of hazards in a total of 62 (24%) time-to-event outcomes including 20 of 115 (18%) OS KM curves and 42 of 139 (30%) non-survival KM curves. (...)"

Statistical Challenges in the Design of Late-Stage Cancer Immunotherapy Studies

Rosemarie Mick[1] and Tai-Tsang Chen[2,3]

The past several years have witnessed a revival of interest in cancer immunology and immunotherapy owing to striking immunologic and clinical responses to immune-directed anti-cancer therapies and leading to the selection of "Cancer Immunotherapy" as the 2013 Breakthrough of the Year by *Science*. But statistical challenges exist at all phases of clinical development. In phase III trials of immunotherapies, survival curves have been shown to demonstrate delayed clinical effects, as well as long-term survival. These unique survival kinetics could lead to loss of statistical power and prolongation of study duration. Statistical assumptions that form the foundations for conventional statistical inference in the design and analysis of phase III trials, such as exponential survival and proportional hazards, require careful considerations. In this article, we describe how the unique characteristics of patient response to cancer immunotherapies will impact our strategies on statistical design and analysis in late-stage drug development. *Cancer Immunol Res; 3(12); 1292–8. ©2015 AACR.*

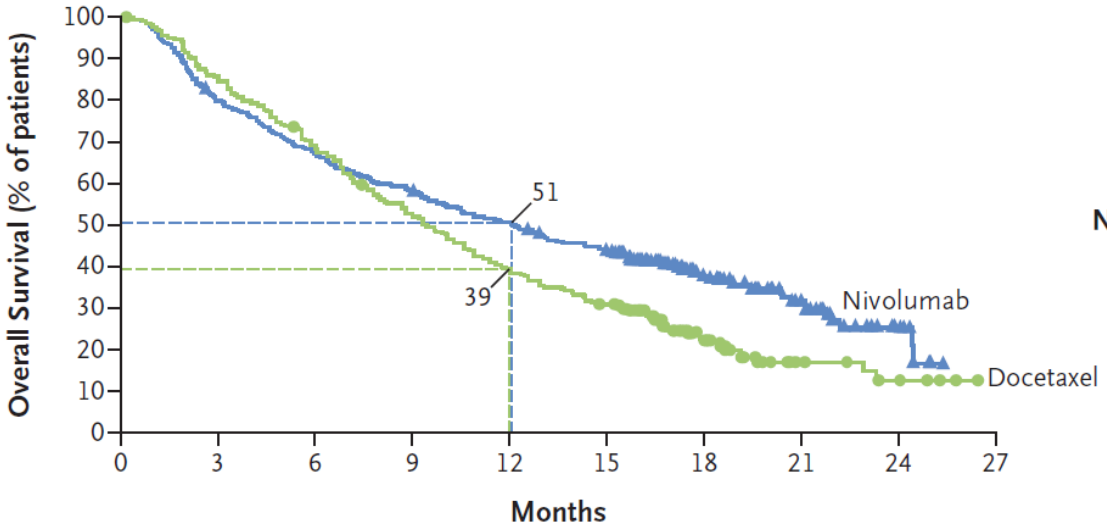
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhäufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crinò, G.R. Blumenschein, Jr., S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, and J.R. Brahmer

A **Overall Survival**



No. at Risk										
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate (95% CI)
		mo	%
Nivolumab	190/292	12.2 (9.7–15.0)	51 (45–56)
Docetaxel	223/290	9.4 (8.1–10.7)	39 (33–45)

Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P=0.002

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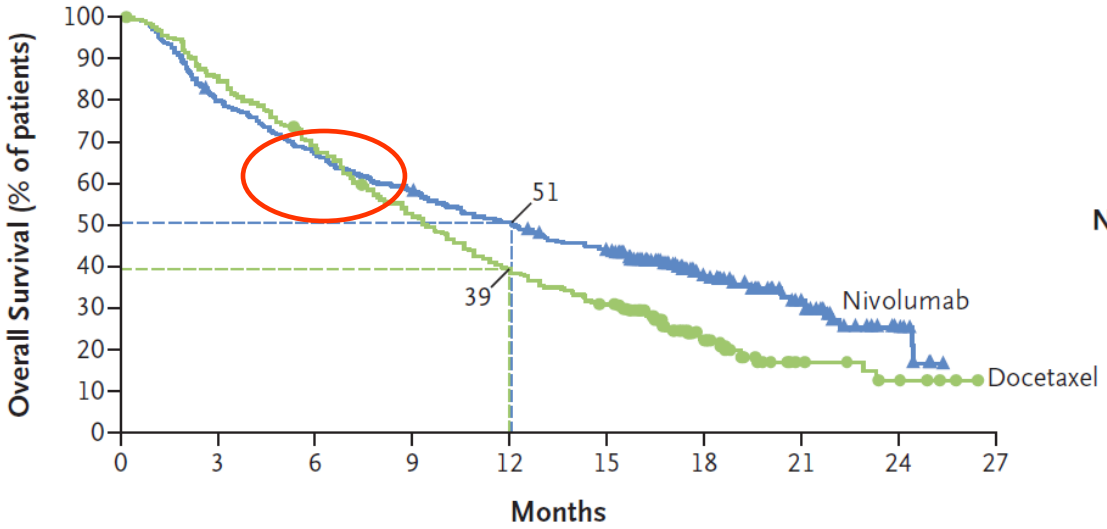

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Hazard ratio for deat[illegible] (96% CI, 0.59–0.89)
P[illegible]

Why Not Working Directly With the Mean Survival Time?

Non-parametric Estimation of the Mean Survival Time

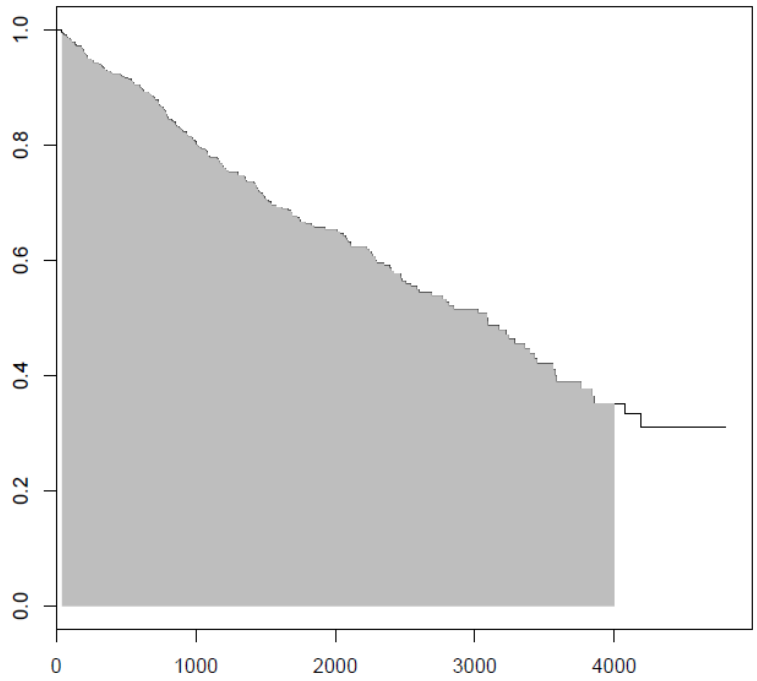
- Mean survival time = area under survival curve

  (only if the curve reaches 0 ! – rarely happens in practice)

Restricted Mean Survival Time (RMST)

- RMST(*t*) = area under survival curve until time *t*

  = mean survival time until time *t*



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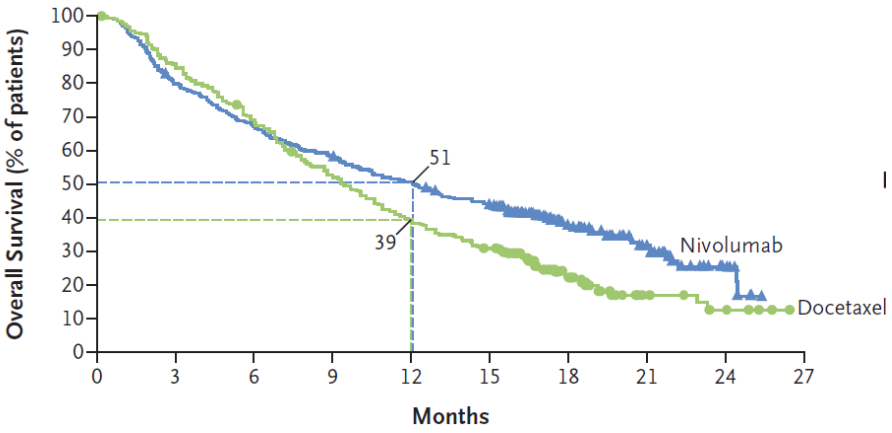
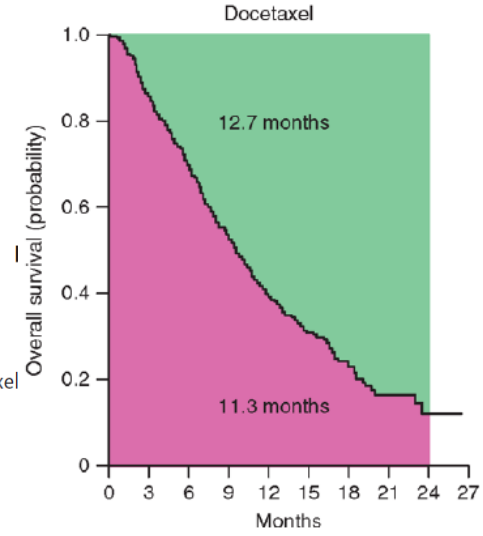
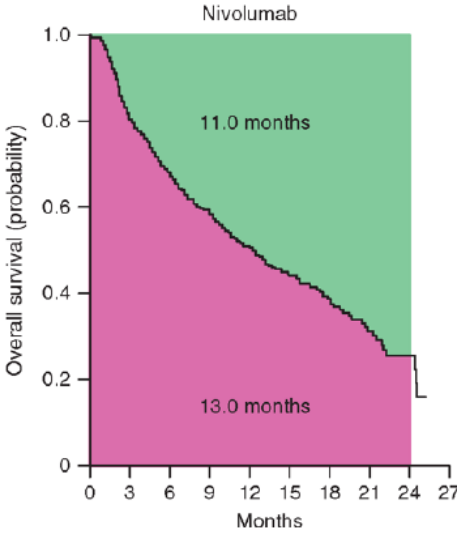


JAMA Oncology | Original Investigation

Interpretability of Cancer Clinical Trial Results Using Restricted Mean Survival Time as an Alternative to the Hazard Ratio

Kyongsun Pak, BPharm; Hajime Uno, PhD; Dae Hyun Kim, MD; Lu Tian, ScD; Robert C. Kane, MD; Masahiro Takeuchi, ScD; Haoda Fu, PhD; Brian Claggett, PhD; Lee-Jen Wei, PhD





RMST @24 mths:
Nivo 13, Docetaxel 11.3
ΔRMST = 1.7 mths
95% CI: (0.4-3.1), *p*=0.01

Accelerated Failure-time Model (AFT)

- *Assumption*: treatment effect is expressed as *shortening or lengthening of the time* to event.

- Mean (time) ratio:

$$\mathrm{MR} = \frac{mean\ \ time\ \ for\ experimental}{mean\ \ time\ \ for\ control}$$

- Simple interpretation: relative change of the mean time !

Semi-parametric AFT Model

- Does not assume any particular distribution of the failure time.
- Thus, the same advantage as the PH model.
- But: less vulnerable to omission of prognostic factors.

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JAMA®

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JAMA. 2010;303(17):1729-1737 (doi:10.1001/jama.2010.534)

- 17 trials, 3838 patients
- Surgery vs. surgery + adj. chemotherapy

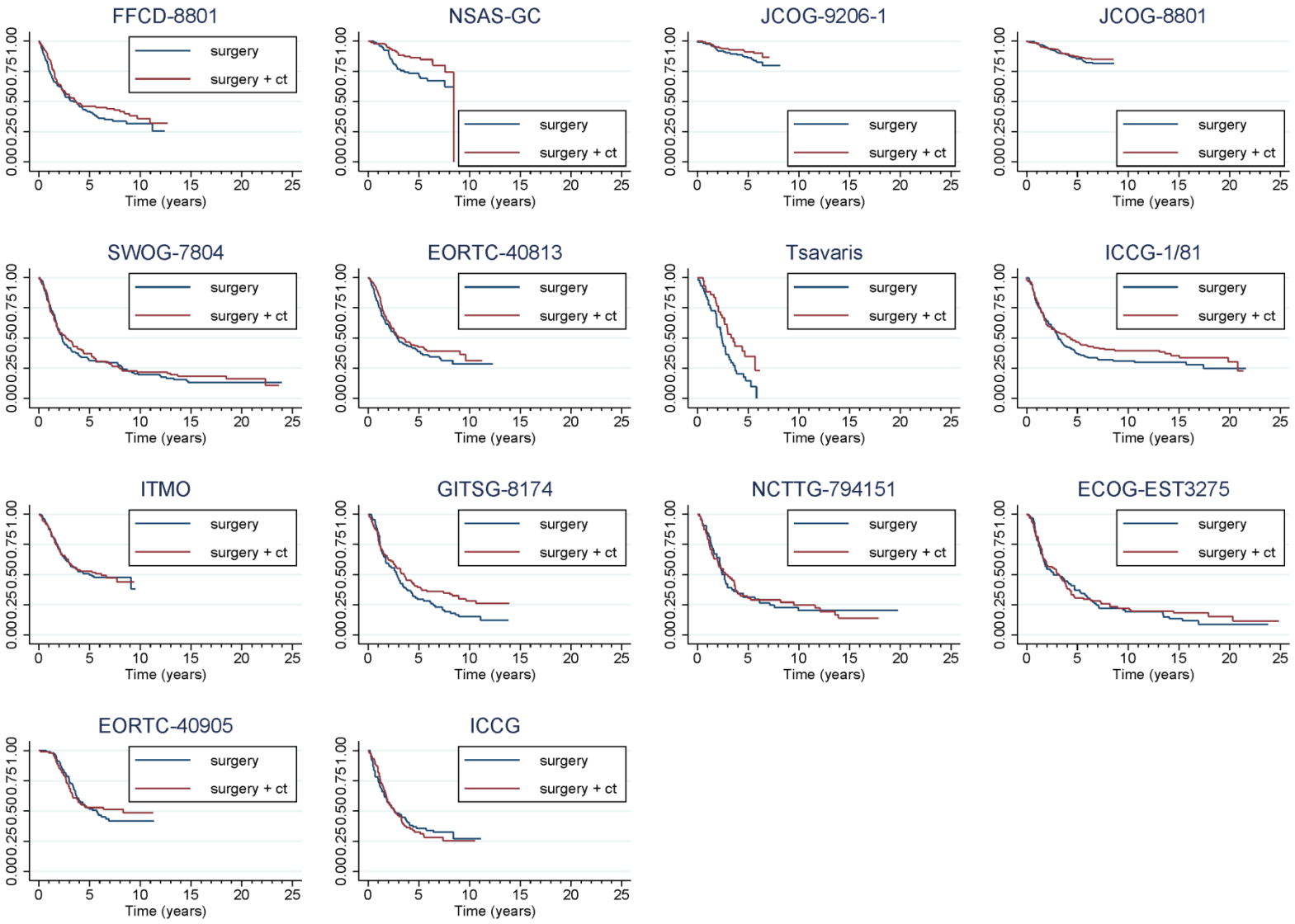
Disease-Free Survival as a Surrogate for Overall Survival in Adjuvant Trials of Gastric Cancer: A Meta-Analysis

J Natl Cancer Inst;2013;105:1600–1607

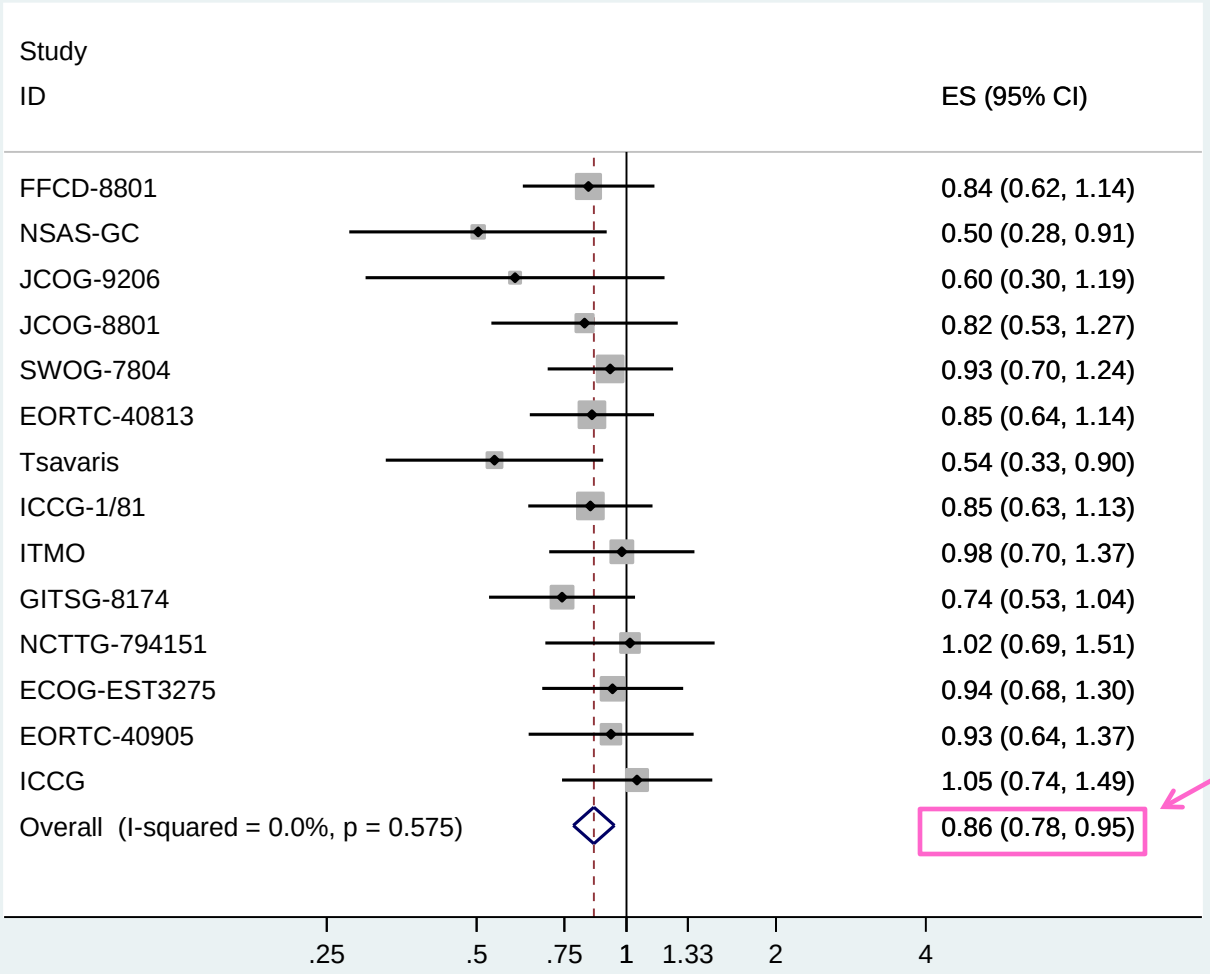
Koji Oba, Xavier Paoletti, Steven Alberts, Yung-Jue Bang, Jacqueline Benedetti, Harry Bleiberg, Paul Catalano, Florian Lordick, Stefan Michiels, Satoshi Morita, Yasuo Ohashi, Jean-pierre Pignon, Philippe Rougier, Mitsuru Sasako, Junichi Sakamoto, Daniel Sargent, Kohei Shitara, Eric Van Cutsem, Marc Buyse, Tomasz Burzykowski; on behalf of the GASTRIC group

- 14 trials, 3288 patients
- Surgery vs. surgery + adj. chemotherapy

Adjuvant Trials of Gastric Cancer: HR



Adjuvant Trials of Gastric Cancer: HR

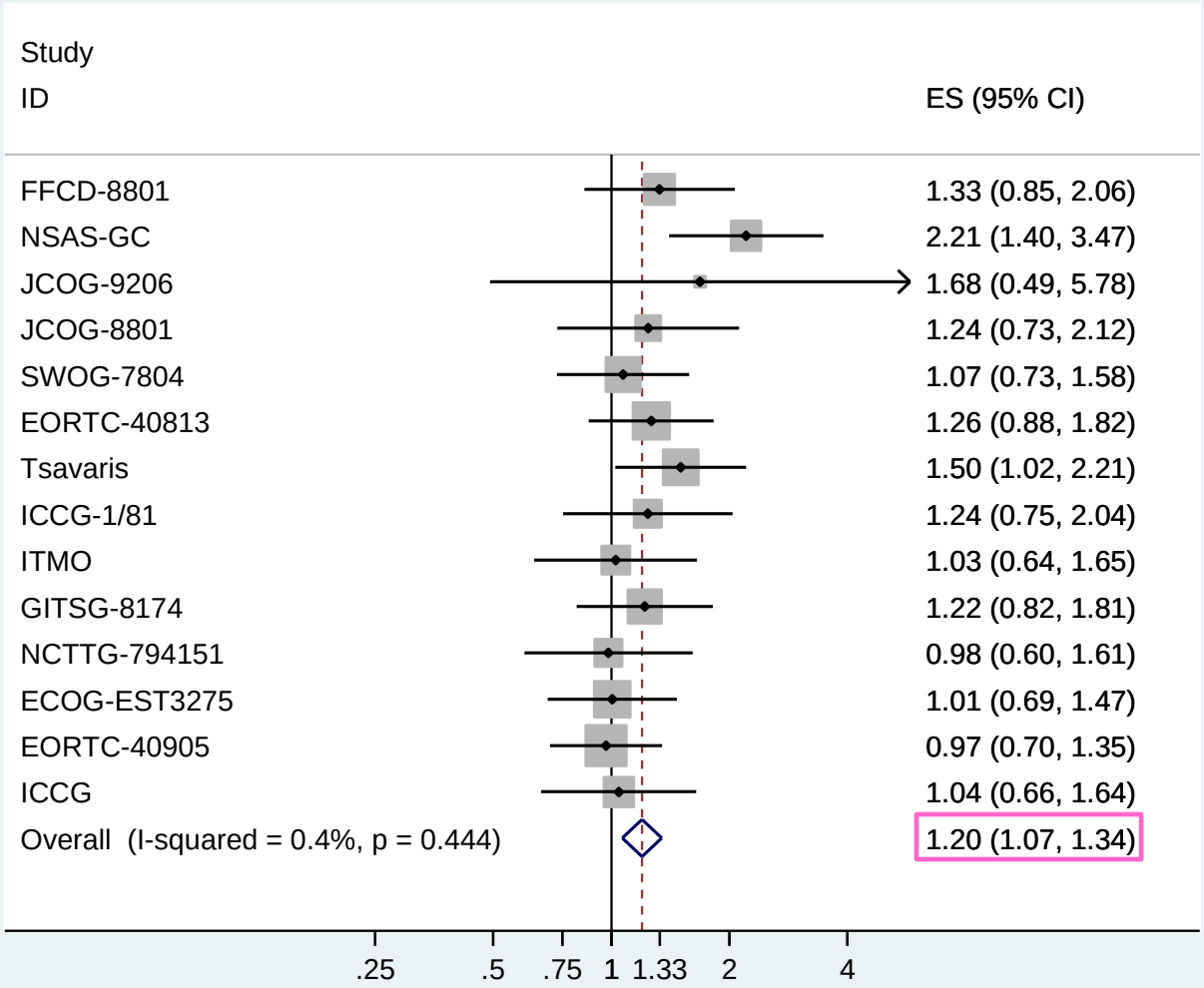


Hazard of adjuvant-treatment patients is 14% smaller.

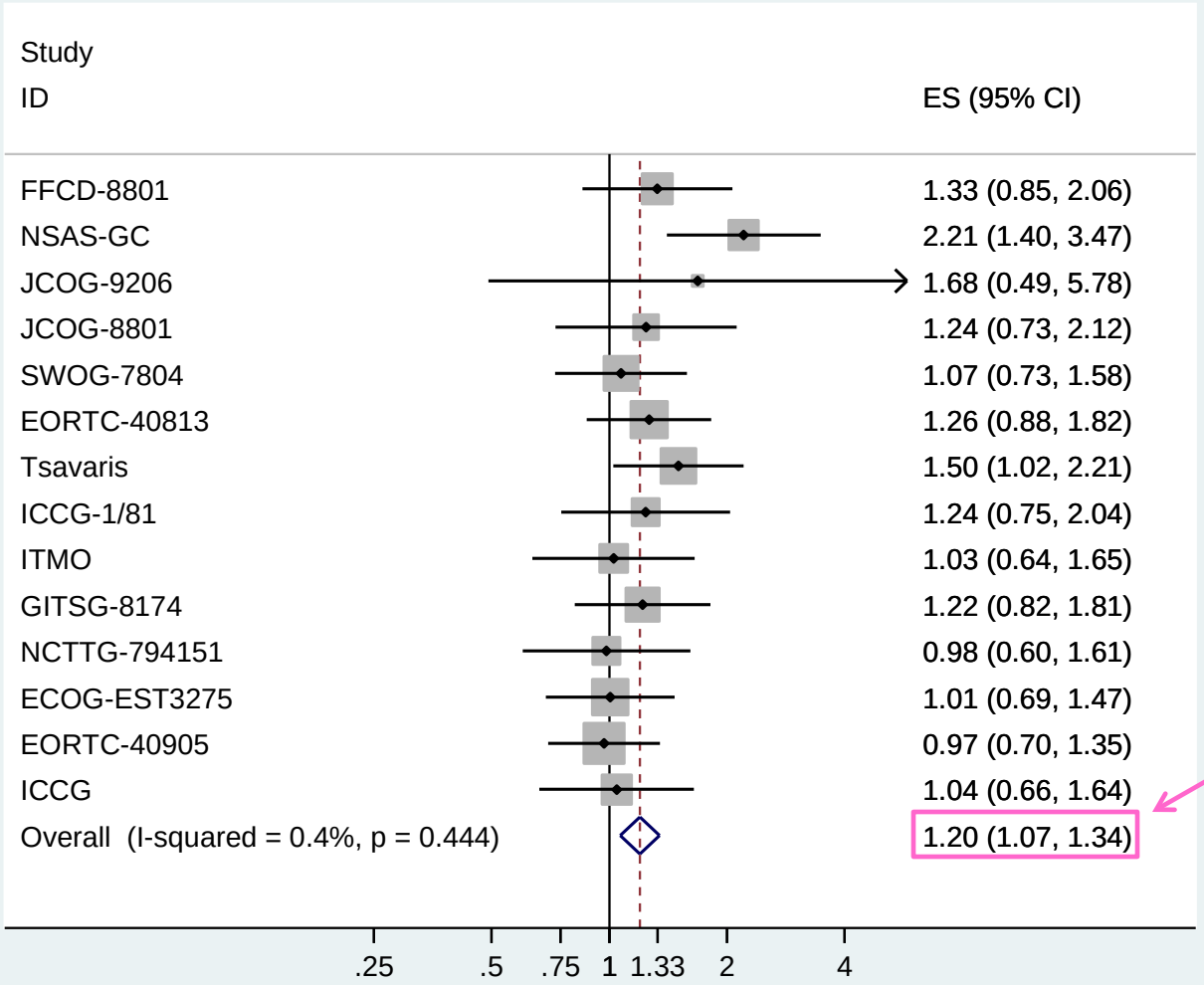
Adjuvant Trials of Gastric Cancer: MR

Trial	HR	95% CI	MR	95% CI
FFCD-8801	0.84	(0.62, 1.14)	1.33	(0.85, 2.08)
NSAS-GC	0.50	(0.28, 0.91)	2.21	(1.39, 3.50)
JCOG-9206-1	0.60	(0.30, 1.19)	1.68	(0.48, 5.92)
JCOG-8801	0.82	(0.53, 1.27)	1.24	(0.72, 2.14)
SWOG-7804	0.93	(0.70, 1.24)	1.07	(0.72, 1.59)
EORTC-40813	0.85	(0.64, 1.14)	1.26	(0.87, 1.83)
Tsavaris	0.54	(0.33, 0.90)	1.50	(1.01, 2.22)
ICCG-1/81	0.85	(0.63, 1.13)	1.24	(0.75, 2.06)
ITMO	0.98	(0.70, 1.37)	1.03	(0.63, 1.67)
GITSG-8174	0.74	(0.53, 1.04)	1.22	(0.81, 1.83)
NCTTG-794151	1.02	(0.69, 1.51)	0.98	(0.59, 1.63)
ECOG-EST3275	0.94	(0.68, 1.30)	1.01	(0.68, 1.48)
EORTC-40905	0.93	(0.63, 1.37)	0.97	(0.69, 1.36)
ICCG	1.05	(0.74, 1.49)	1.04	(0.66, 1.66)

Adjuvant Trials of Gastric Cancer: MR



Adjuvant Trials of Gastric Cancer: MR



Mean survival time of adjuvant-treatment patients is 20% longer.

Conclusions

- Empirical evidence against the PH assumption
- Semi-parametric AFT modelling practically feasible
- Natural interpretation of the mean (time) ratio
- A serious alternative to the semi-parametric PH model

Acknowledgements

- The GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group for permission to use their data.

  The investigators who contributed to GASTRIC are listed in references (1,2).

  (1) The GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group (2010). Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. Journal of the American Medical Association 303:1729-37.

  (2) The GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group (2013). Role of chemotherapy for advanced / recurrent gastric cancer: an individual-patient-data meta-analysis. European Journal of Cancer 49:1565-77.

- Chen Hu, Johns Hopkins University, USA