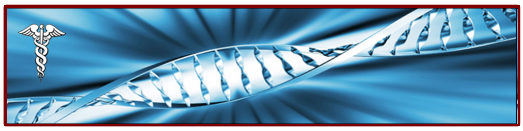


TransMedRi Workshop in Biostatistics:
Critical evaluation of statistical analysis in scientific paper

R and Data Analysis in Oncology

Paško Konjevoda, MD, PhD
Institute Ruđer Bošković
Bijenička cesta 54, HR-10001,
Zagreb, Croatia

R and BUGS

Oncology is the branch of medicine most dependent on statistics.

Therefore, the correct choice of statistical applications to analyze cancer data is essential component of any serious research.

Combination of R and BUGS - an alternative to commercial applications such as SAS and Stata.

What is R?

R is three things:

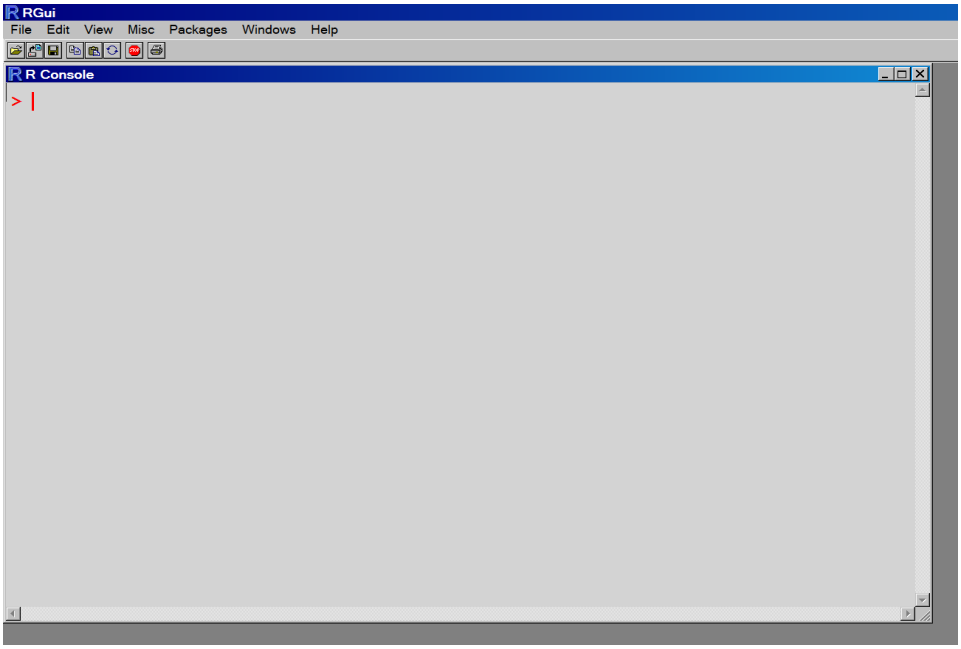
- a programming language
- a software environment
- a project
- (www.cran-r-project.org)

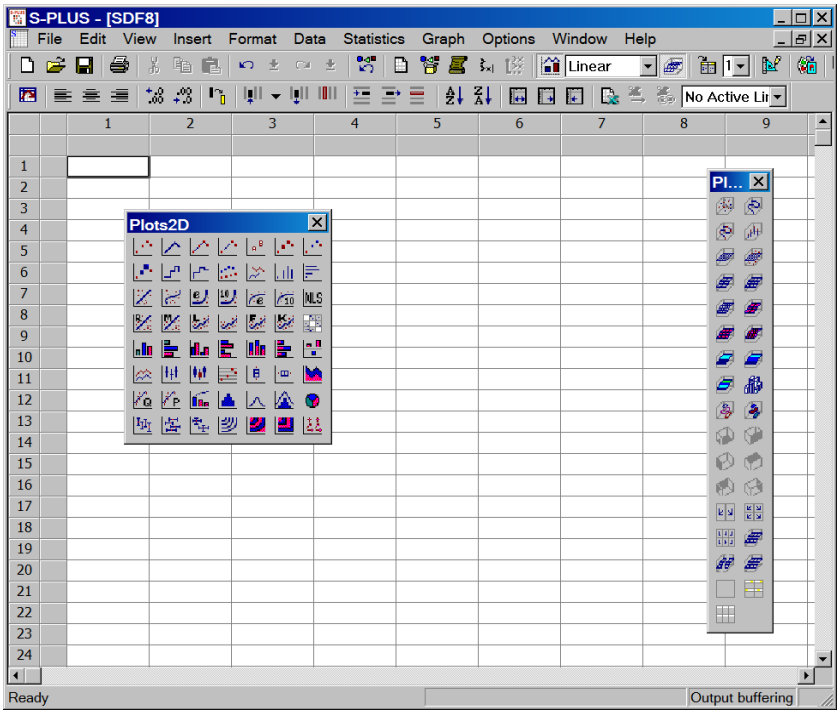
PRO

- It's free!!
- cutting edge statistics
- cutting edge graphics
- functional, object-oriented programming-language

CONTRA

- GUI
- You must invest lots of time to master R

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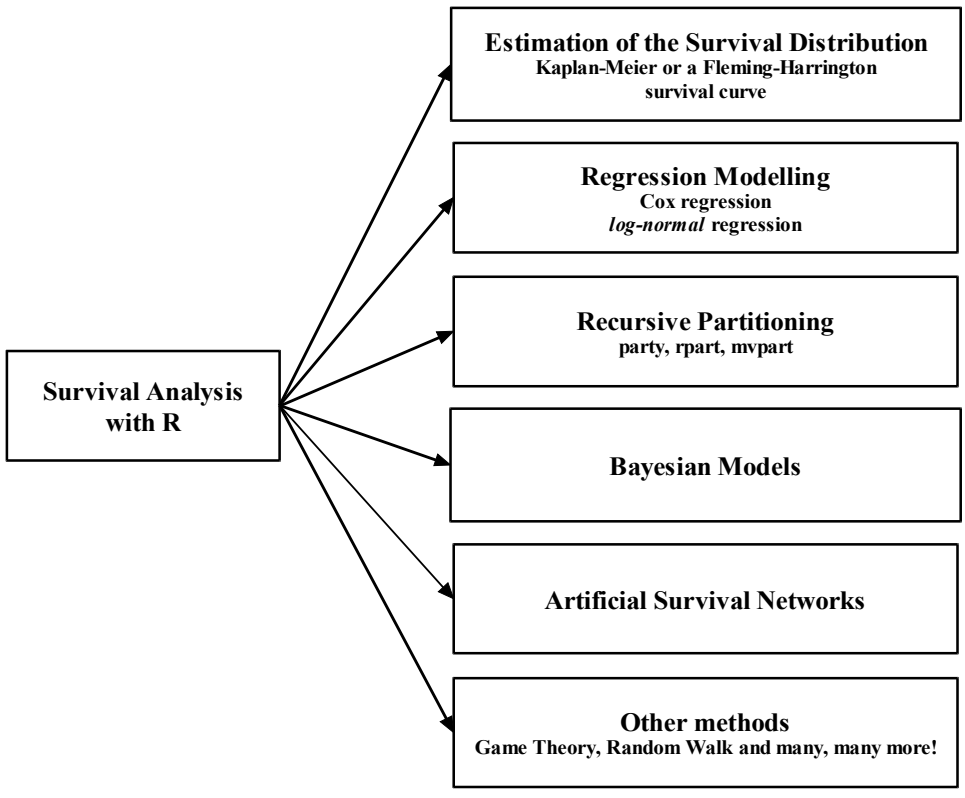
Ready
Output buffering


Survival Analysis with R
Estimation of the Survival Distribution
Kaplan-Meier or a Fleming-Harrington survival curve
Regression Modelling
Cox regression
log-normal regression
Recursive Partitioning
party, rpart, mvpart
Bayesian Models
Artificial Survival Networks
Other methods
Game Theory, Random Walk and many, many more!

R Modules for Survival Analysis

AER AIM aster aster2 bayesSurv BayHaz Biograph BMA boot bujar censReg changeLOS clinfun cmprsk (core) cmprskContin coin compeir CompetingRiskFrailty concreg condGEE CoxBoost coxme coxphf coxphw coxrobust CPE Cprob crrSC DAAG dblcens Design DPpackage DTDA eha (core)emplik Epi epiR etm exactRankTests fitdistrplus flexCrossHaz frailtyHL frailtypack gamlss.cens gbm gcmrec glmpath globalboosttest glrt gof gss ICE Icens intcox interval ipred ipw JM kinship km.ci kmi KMsurv LearnBayes lmec locfit LogicReg logspline lpc lss MAMSE maxstat mboost MCMCglmm MCMCpack mfp MixAK mixPHM MLEcens msm mspath msSurv mstate muhaz (core) multcomp mvna mvpart NADA NestedCohort nltm OrdFacReg p3state.msm pamr party pec penalized peperr PermAlgo phmm plsRcox polspline powerSurvEpi prodlim proptest pseudo quantreg randomSurvivalForest rankhazard relsurv rhosp risksetROC rms (core) rpart saws simexaft SMIR smoothSurv SMPracticals spatstat spef splinesurv superpc surv2sample survAUC survBayes survey survival (core) survivalBIV survivalROC survJamda survPresmooth survrec timereg (core) tpr TraMineR TSHRC TwoWaySurvival uniCox VGAM

BUGS
(http://www.mrc-su.cam.ac.uk/bugs/)

BUGS is an open source software package for performing **B**ayesian inference **U**sing **G**ibbs **S**ampling.

The user specifies a statistical model, of (almost) arbitrary complexity, by simply stating the relationships between related variables.

The software includes an ‘expert system’, which determines an appropriate MCMC (Markov chain Monte Carlo) scheme (based on the Gibbs sampler) for analysing the specified model.

The user then controls the execution of the scheme and is free to choose from a wide range of output types.

Prognostic factors - definition

- Prognostic factors are covariates that have an influence on the prognosis of a patient independently from the treatment.
- We use the term predictive to describe an interaction between a factor and the treatment.

From: Royston, P. and Sauerbrei, W., A new approach to modelling interactions between treatment and continuous covariates in clinical trials by using fractional polynomials, *Statistics in Medicine,* 23, 2509–2525, 2004.

From: Schumacher M, Hollander N, Schwarzer G, Sauerbrei W. Prognostic factor studies. In: Crowley J, Ankerst D, editors. Handbook of statistics in clinical oncology. Boca Raton: Chapman & Hall/CRC; 2006. p. 289–333.

Prognostic factors - AJCC criteria (I)

The American Joint Committee on Cancer (AJCC) has established three major criteria for prognostic factors.

Factors must be significant, independent, and clinically important.

From: Schumacher M, Hollander N, Schwarzer G, Sauerbrei W. Prognostic factor studies. In: Crowley J, Ankerst D, editors. Handbook of statistics in clinical oncology. Boca Raton: Chapman & Hall/CRC; 2006. p. 289–333.

Prognostic factors - AJCC criteria (II)

significant implies that the prognostic factor rarely occurs by chance;

independent means that the prognostic factor retains its prognostic value despite the addition of other prognostic factors;

and clinically important implies clinical relevance, such as being capable (at least in principle) of influencing patient management and thus outcome.

From: Schumacher M, Hollander N, Schwarzer G, Sauerbrei W. Prognostic factor studies. In: Crowley J, Ankerst D, editors. Handbook of statistics in clinical oncology. Boca Raton: Chapman & Hall/CRC; 2006. p. 289–333.

Independent prognostic factor (I)

Multivariate analysis – Cox or log-normal regression

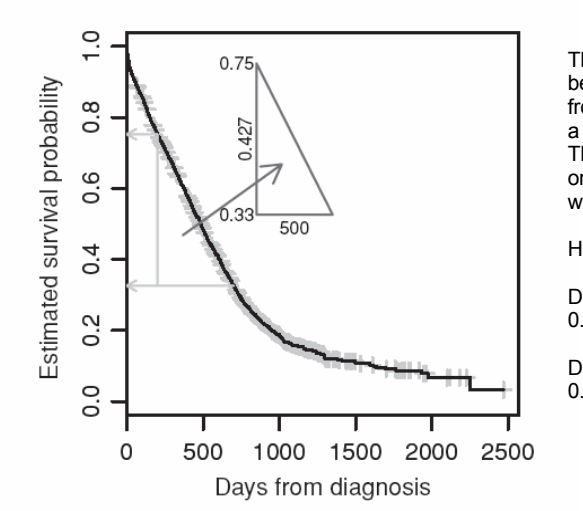
- Basic hazard
- Influence of prognostic factors on hazard
- Influence of therapy on hazard

Common mistakes

- Correlation of the new factor with established prognostic facors is not the proof of prognostic value!!
- Kaplan-Meier (and long-rank test) is not the proof of prognostic value!!

Independent prognostic factor (III)

- Hazard rate – the slope (or derivative) of the survival curve (Cox regression)



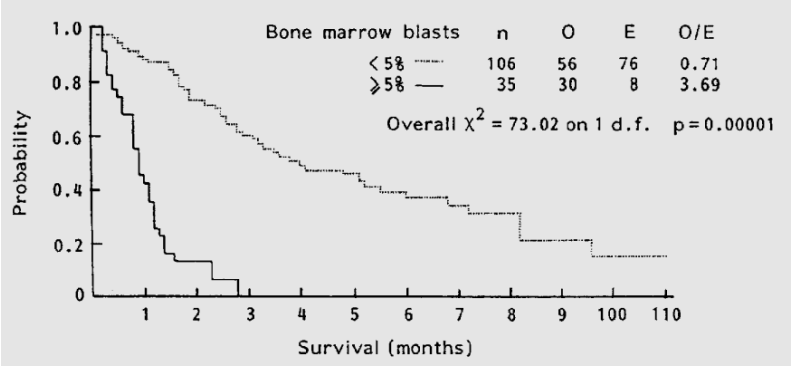
The triangle on the upper left shows the change between 200 days and 700 days, from a survival of 0.75 at day 200 to a survival of 0.33 at day 700. The difference in survival is 0.42, or more precisely 0.427, which is a reduction of 0.000854 per day.

Hazard rates at days 200 and 700 are, approximately:

Day 200
0.00854/0.752 = 0.11

Day 700
0.00854/0.326 = 0.026

Independent prognostic factor (IV)



HR = 3.69 / 0.71 = 5 .20

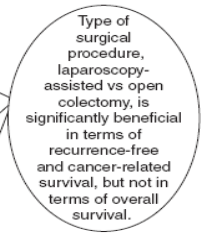
Cox proportional hazards regression
Log-normal regression

Independent prognostic factor (V)

Table 19.4 Results of a Cox proportional hazards regression analysis comparing the survival of patients with laparoscopy-assisted colectomy versus open colectomy, for the treatment of non-metastatic colon cancer. Reproduced courtesy of Elsevier (*The Lancet*, 2002, Vol No. **359**, page 2224–30

	Hazard ratio (95% CI)	p
Probability of being free of recurrence		
Lymph-node metastasis (presence *vs* absence)	0.31 (0.16–0.60)	0.0006
Surgical procedure (OC *vs* LAC)	0.39 (0.19–0.82)	0.012
Preoperative serum CEA concentrations (≥4 ng/mL *vs* <4 ng/mL)	0.43 (0.22–0.87)	0.018
Overall survival		
Surgical procedure (OC *vs* LAC)	0.48 (0.23–1.01)	0.052
Lymph-node metastasis (presence *vs* absence)	0.49 (0.25–0.98)	0.044
Cancer-related survival		
Lymph-node metastasis (presence *vs* absence)	0.29 (0.12–0.67)	0.004
Surgical procedure (OC *vs* LAC)	0.38 (0.16–0.91)	0.029

OC = open colectomy; LAC = laparoscopy-assisted colectomy; CEA = carcinoembryonic antigen.



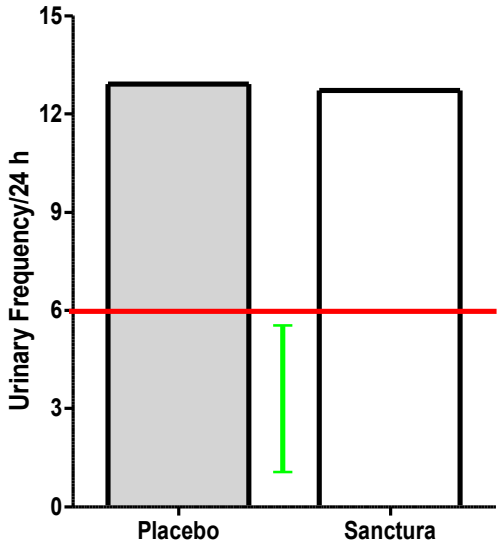
Clinically (not) important (I)

Efficacy endpoint	Placebo N=256	Sanctura N=253	P-value
Urinary frequency/24 hours [a,*]			
Mean baseline	12.9	12.7	
Mean change from baseline	-1.3 (0.2)	-2.4 (0.2)	<0.001
Urge incontinence episodes/week [b,*]			
Mean baseline	30.1	27.3	
Mean change from baseline	-13.9 (1.2)	-15.4 (1.1)	0.012
Urinary void volume/toilet void (mL) [a,c]			
Mean baseline	156.6	155.1	
Mean change from baseline	7.7 (3.1)	32.1 (3.1)	<0.001

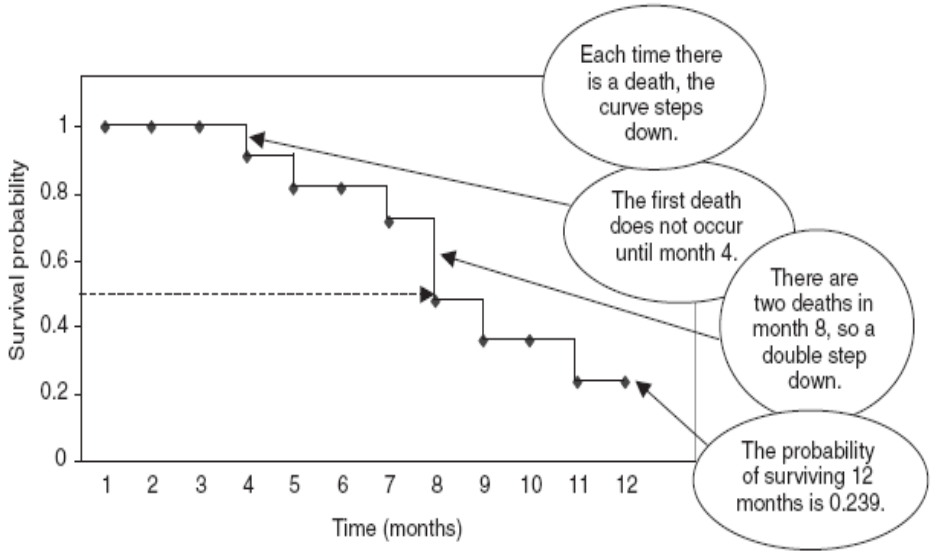
Adverse Event	Placebo (N=590)	Sanctura 20 mg BID (N=591)
Gastrointestinal disorders		
Dry mouth	34 (5.8)	119 (20.1)
Constipation	27 (4.6)	57 (9.6)
Abdominal pain upper	7 (1.2)	9 (1.5)
Constipation aggravated	5 (0.8)	8 (1.4)
Dyspepsia	2 (0.3)	7 (1.2)
Flatulence	5 (0.8)	7 (1.2)
Nervous system disorders		
Headache	12 (2.0)	25 (4.2)
General Disorders		
Fatigue	8 (1.4)	11 (1.9)
Renal and Urinary Disorders	8 (1.4)	11 (1.9)
Urinary retention	2 (0.3)	7 (1.2)
Eye Disorders		
Dry eyes NOS	2 (0.3)	7 (1.2)
Abbreviations: BID=twice daily, NOS=not otherwise specified.		

From: Drug reference Encyclopedia - http://www.theodora.com/drugs/

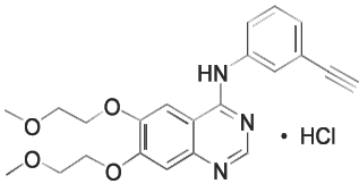
Clinically (not) important (II)

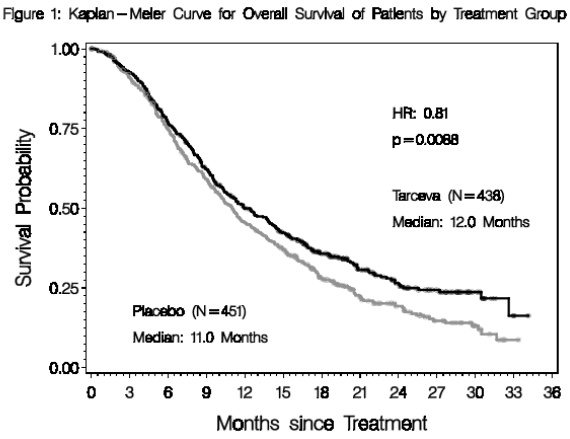


Clinically (not) important (III)



Clinically (not) important (IV)

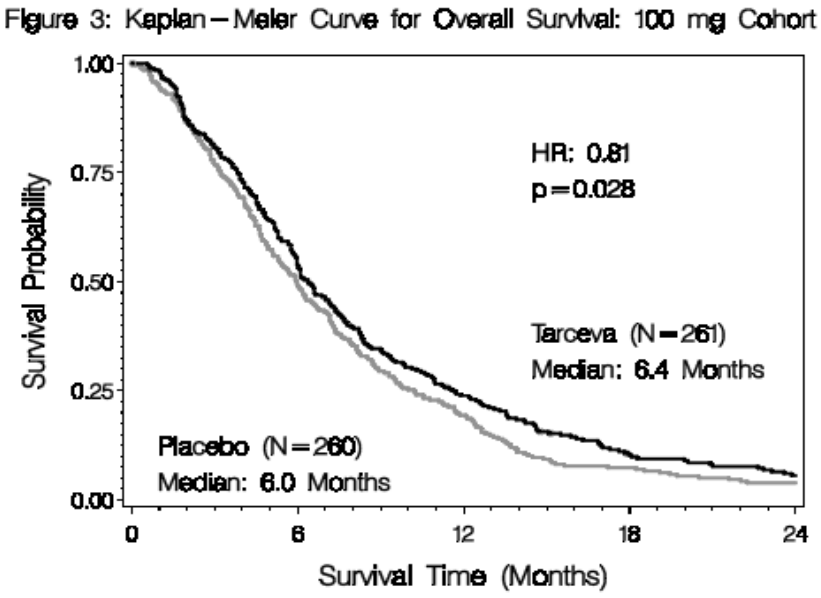




	Median in Months (95% CI)		Hazard Ratio (1) (95% CI)	p-value (2)
	TARCEVA 150 mg N = 438	Placebo N=451		
Progression-Free Survival based on investigator's assessment	2.8 (2.8, 3.1)	2.6 (1.9, 2.7)	0.71 (0.62, 0.82)	p < 0.0001
Overall Survival	12.0 (10.6, 13.9)	11.0 (9.9,12.1)	0.81 (0.70, 0.95)	0.0088

From: Drug reference Encyclopedia - http://www.theodora.com/drugs/

Clinically (not) important (V)



From: Drug reference Encyclopedia - http://www.theodora.com/drugs/

Clinically (not) important (VI)

Based on a pilot study with subsequent testing in two further studies, **Rustin et al.** proposed the following definitions for determining response of ovarian cancer to initial chemotherapy. **Response according to CA125 occurred if there was either a 50% or a 75% reduction in CA125 levels.** For the 50% response criteria, four separate samples are required, ie, two initial samples showing an elevation with two subsequent samples showing a 50% decrease. For the 75% response definition, only three samples are necessary, which must exhibit a serial decrease of at least 75%. In both definitions, the final sample must be taken at least 28 days after the previous sample. According to Rustin et al, both definitions are necessary as some responses are detected by only one of the definitions. It should be pointed out that patients with initial concentrations of CA125 less than 40 U/L cannot be evaluated using these definitions.

The above definitions were retrospectively tested in 19 phase 2 clinical trials investigating 14 different cytotoxicdrugs for recurrent ovarian cancer. Overall, responses based on CA125 were similar to those based on standard criteria, leading Rustin et al. To suggest that the 50% and 75% response criteria could substitute for standard responses in phase 2 clinical trials evaluating new treatments for ovarian cancer. As assessable disease is found in only a minority of patients with cancer of the ovary following debulking surgery, use of these definitions would increase the number of patients participating in clinical trials.

From: Duy MJ, Bonfrer JM. Kulpa J, Rustin GJS, Soletormos G, Torre GC, et all. CA125 in ovarian cancer: European group on tumor markers guidelines for clinical use. Int J Gynecol Cancer. 2005;15:679691.

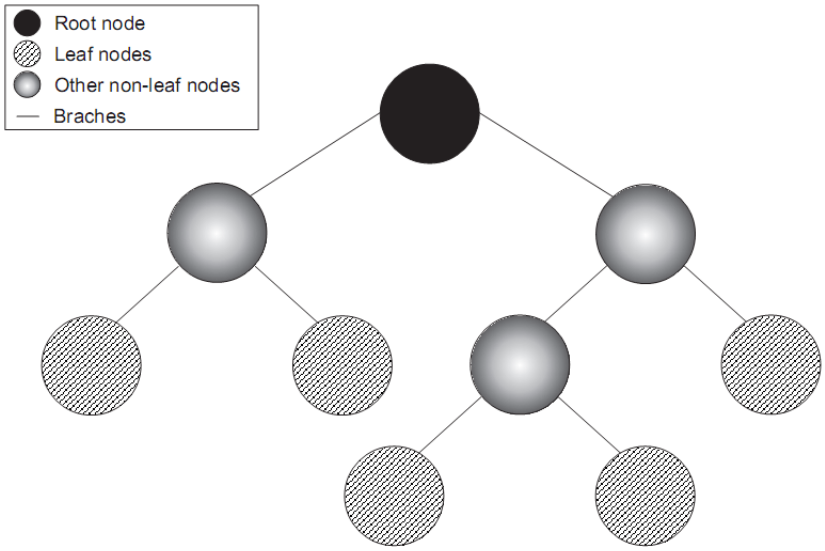
From these criteria it becomes obvious that statistical aspects will play an important role in the investigation of prognostic factors.

Requirements for Confirmatory Prognostic Factor Studies According to Simon and Altman

1) Documentation of intra- and interlaboratory reproducibility of assays
2) Blinded conduct of laboratory assays
3) Definition and description of a clear inception cohort
4) Standardization or randomization of treatment
5) Detailed statement of hypotheses (in advance)
6) Justification of sample size based on power calculations
7) Analysis of additional prognostic value beyond standard prognostic factors
8) Adjustment of analyses for multiple testing
9) Avoidance of outcome-orientated cut-off values
10) Reporting of confidence intervals for effect estimates
11) Demonstration of subset-specific treatment effects by an appropriate statistical test

From: Simon R, Altman DG. Statistical aspects of prognostic factor studies in oncology. Br J Cancer 1994;69:979–985.

Recursive partitioning (I)



From: An Evaluation of Decision Tree and Survival Analysis Techniques for Business Failure Prediction, PhD Thesis, Adrian Charles Benjamin Gepp, BCom, BIT, 24 December 2005

Recursive partitioning (II)

Module	Criterium	Model
party	log-rank test	Kaplan-Meier and long-rank tets
rpart	Gini index	Cox regression and Hazard Ratio
mvpart	Gini index	Cox regression and Hazard Ratio

Example – Matrix metaloproteinases and endometrial carcinoma

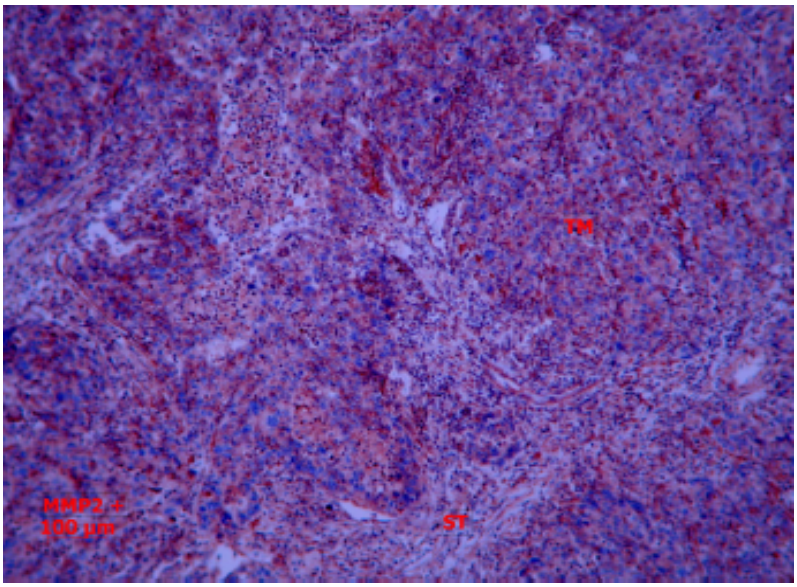
- Age
- Histology type
- Gradus
- FIGO
- LVI
- Depth of invasion
- Cervix involvement
- Size
- Estrogen receptors

- MMP-2 stroma
- MMP-2 tumor
- MMP-9 stroma
- MMP-9 tumor

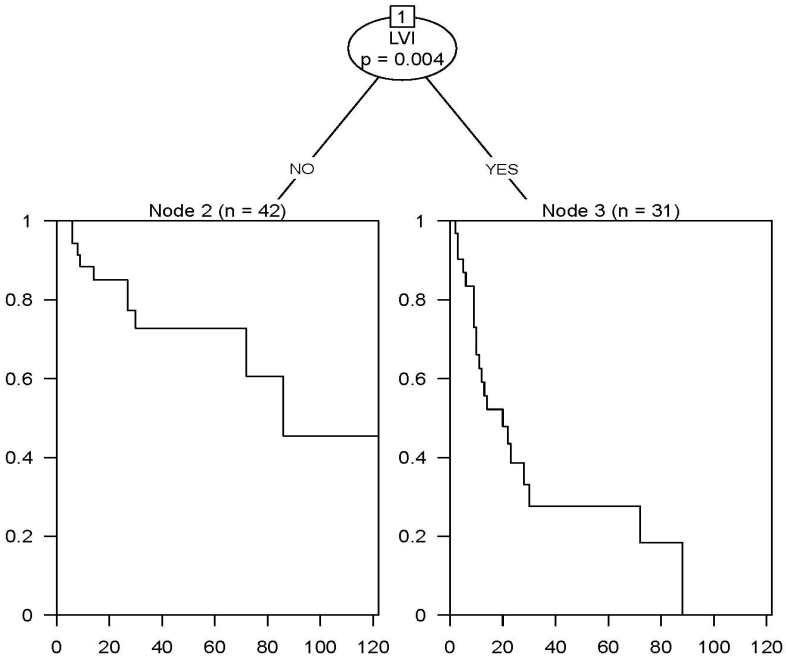
0 (null) 0-10%
1 (A) 10-25%
2 (C) 25%-50%
3 (D) > 50%

N = 73 patients
START = date of operation
END = diagnosis of recidive
TIME = months

Immunohistochemistry - MMP-2



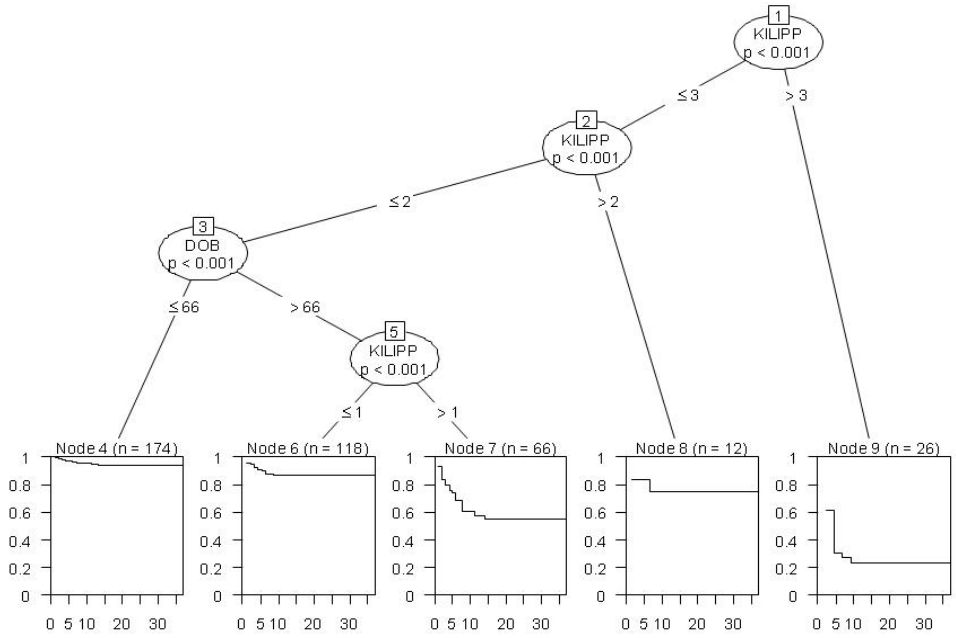
party



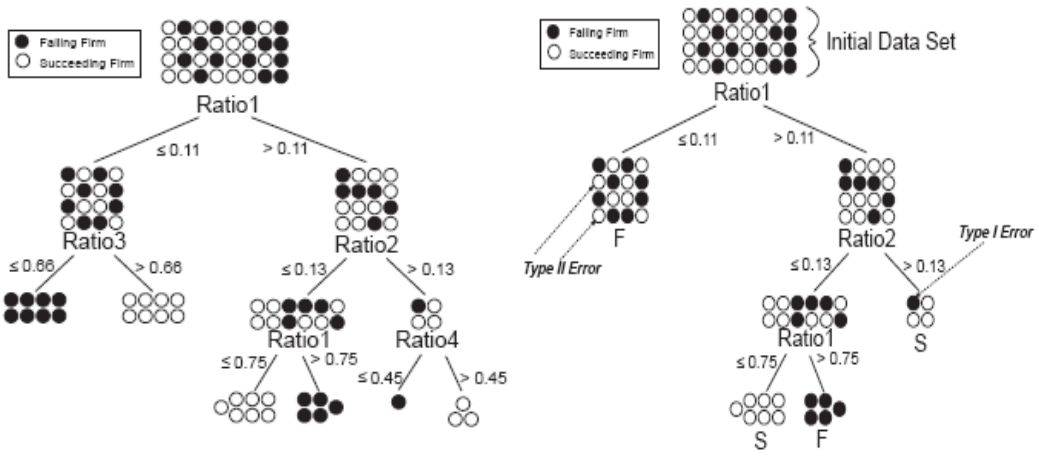
party – source code

```
# 1. working directory and data
setwd("c:\\")
endometrium <- read.table("c:\\rawdata.txt",
header = TRUE, sep = ";")
# 2. modules
library(party)
library(survival)
# 3. analysis
stree <- ctree(Surv(Time, Status) ~.,
data = endometrium)
# 4. numerical results
stree
# 5. graphics
plot(stree)
```

party – multiple splits

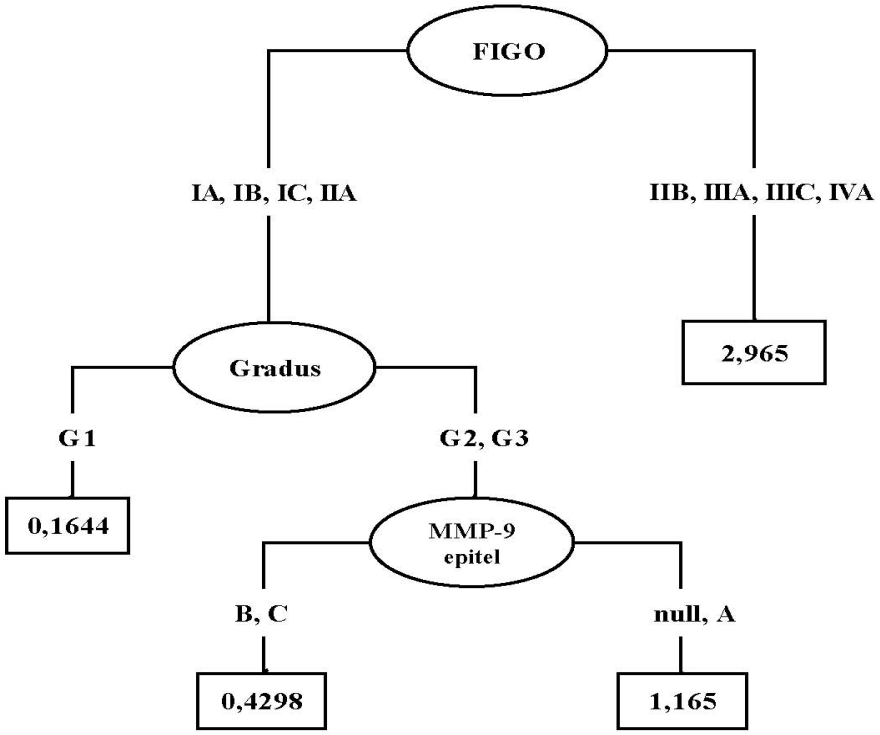


Gini Index and Prunning

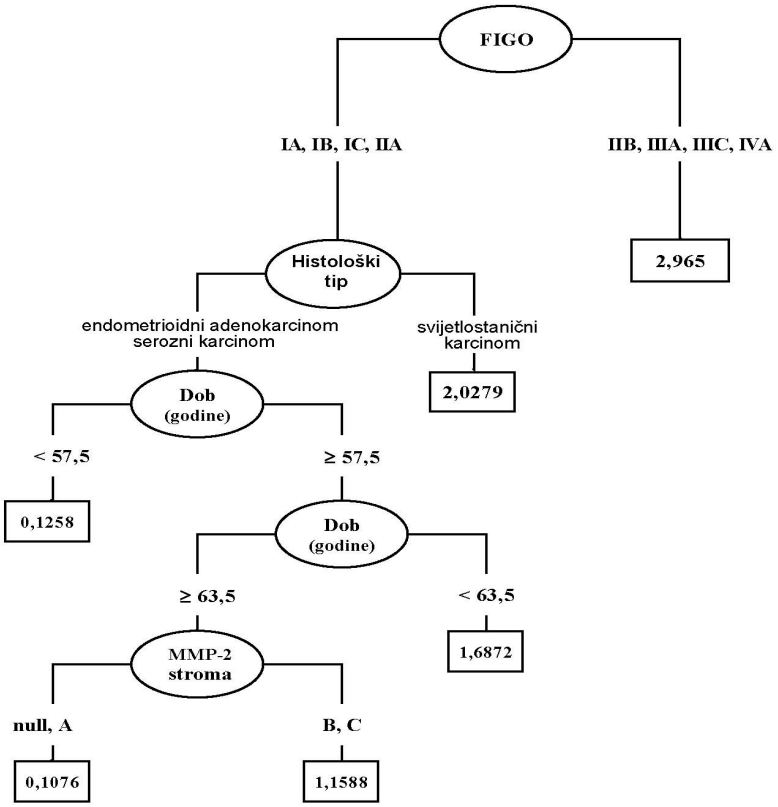


From: An Evaluation of Decision Tree and Survival Analysis Techniques for Business Failure Prediction, PhD Thesis, Adrian Charles Benjamin Gepp, BCom, BIT, 24 December 2005

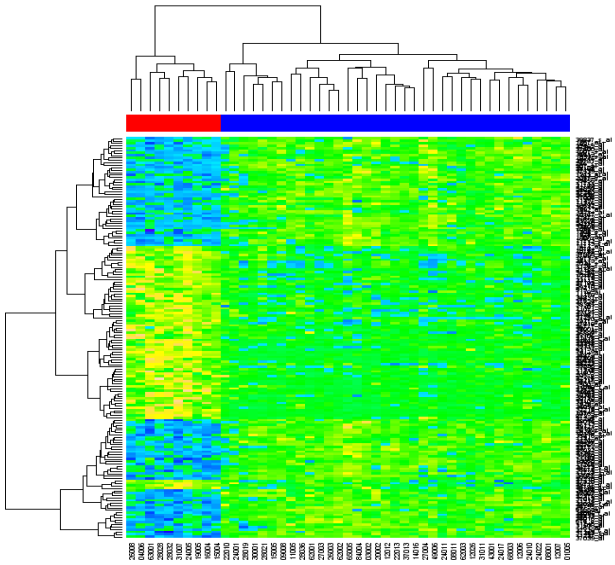
rpart



mvpart



R and Bioconductor (I)



R and Bioconductor (II)

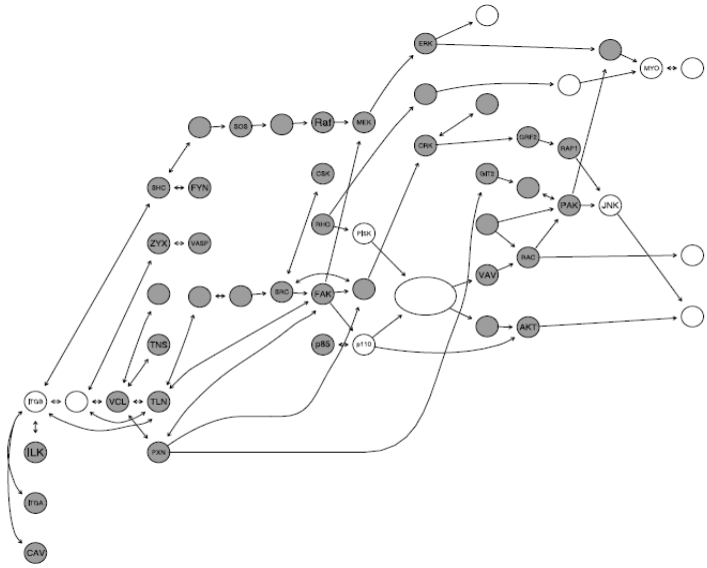


FIGURE 27.5 Integrin mediated cell adhesion network.

R and Bioconductor (III)

Replicates needed for statistics at each time point and biological condition:

- 4× for cell lines and inbred animals
- 15-100 and MORE for human samples