

Survival after recurrence of breast cancer - A multistate model compared to Kaplan-Meier

Content

The poster.....	1
Data Overview	3
Kategorische Variablen	3
Numerische Variablen	3
Events in Frequencies	4
Multistate Cox Model	5

The poster

Onkologischer Schwerpunkt Stuttgart

Survival after recurrence of breast cancer A multistate model compared to Kaplan-Meier

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Background

- Kaplan-Meier Estimator (KM) as non-parametric method is well known with very few restrictions
- Complex adjustments e.g. for age/grade/... need further assumptions (A)
- Multistate Models (MS) allow for more complexity and deeper insights

Data

- Focus on female patients of 4 OSP centers
- Diagnosis: 2003-2024 with ICD C50/D05
- Model adjustment (following Putter) for:

Case	n	%
Complete	10428	83.1
Incomplete	2115	16.9
Total	12543	100

Center: A/B/C/D, Age, Tumor size, Grading 1/2/3, Nodal status 0/1, Chemo y/n, Treatment: BCT, BCT+RT, MAS, MAS+RT, BCT+MAS, BCT+MAS+RT, Adjuvant: y/n

Further information see QR-Code

Directed Acyclic Graph (DAG)

- DAG illustrates possible state transitions
- S: Start with Diagnosis C50/D05
- LR: Locoregional recurrent event
- DM: Distant metastasis
- T: Death as only absorbing event type

Variable	N	Mean	sd	Median	Min	Max
Age at Diag	12543	60.03	12.86	59.92	18.23	100.41
Tumor Size (mm)	10635	23.78	13.89	16.00	0.00	173.00

Kaplan-Meier Estimation

- Unadjusted or stratified, usually unbiased (A: independent censoring)
- Competing events lead to biased estimates
- Crossing curves can be an indicator for non-proportional hazards (A)
- Test: Schoenfeld-Residual, here $\chi^2: 5.95$, df: 4, p = 0.2
- Therefore, for centers in this case the baseline hazards are proportional "enough"

Multistate Model

- Allows to adjust for competing events
- Gives insight to each variables impact in every state
- Cumulated Hazards Higher value corresponds with higher probability of transition
- Able to plot for each transition
- Here transitions 1,4,7,8 (see DAG)

Variable	coef	exp(coef)	sel(coef)
age_diag.1	0.01	1.01	0.00
age_diag.2	0.02	1.02	0.00
age_diag.3	0.09	1.10	0.00
age_diag.5	0.05	1.05	0.01
Chemo.2	0.77	2.16	0.11
Chemo.3	-0.22	0.80	0.08
Chemo.4	0.66	1.93	0.24

Prediction with a Multistate Model

- Similar to adjusted KM: In both cases "average" patient or patient with specific covariates
- Stratified by center, probability to be in a certain state, starting at diagnosis
- While difference in KM seems huge MS model give more context
- Probability to transit to LR rather small
- Probability to transit into state Death overall comparable

Key points

- KM often used but assumptions rarely questioned
- Choose method according to data and research question
- Here: „Pure“ KM and adjusted → 600 patients
- Adjusted KM → misleading survival curve
- Also be aware: adjusted KM curves are often a subset/“average“ patient
- MS models are more flexible and incorporate all data → 12.543 patients
- More complex to interpret
- Allow to understand connections better and the effect of variables in different states

Adjusted survival after Local Recurrence (Censored/Deceased)

- Adjusted or stratified, unbiased only if assumptions are kept
- Most common adjustment: Cox proportional hazard model
- We gain global baseline hazards adjusted by covariates
- Proportional hazards are "forced"
- Sometimes with anomalies e.g. a survival of more than 100%

Cumulative Hazards - transitions to Death

All Estimators in leftside table are p<0.01 and show a brief excerpt (120 Coefficients in total (8*(3+2+1+1+5+1+1+1)))

Age has for transitions 3 the largest hazard ratio compared to other transitions

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Further information
QR Code contains:
<https://osp-stuttgart.de/biometric.html>

Members of OSP Stuttgart

Diakonie Klinikum
Klinikum Stuttgart
Marienhospital Stuttgart
R3
AS

This PDF serves as addendum for the poster.

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Data Overview

Kategorische Variablen

Variable	Kategorie	n	Prozent
sex	weiblich	12543	100
Center	A	4122	32,9
Center	B	3221	25,7
Center	C	3147	25,1
Center	D	2053	16,4
Grading	G1	1356	10,8
Grading	G2	7423	59,2
Grading	G3	3479	27,7
Grading		285	2,3
NodalStatus	0	8760	69,8
NodalStatus	1	3568	28,4
NodalStatus		215	1,7
Chemo	no	7586	60,5
Chemo	yes	4957	39,5
treat	BCT	898	7,2
treat	BCT+RT	8066	64,3
treat	MAS	1289	10,3
treat	MAS+RT	1025	8,2
treat	BCT-MAS	610	4,9
treat	BCT- MAS+RT	514	4,1
treat		141	1,1
adjuvant	no	2621	20,9
adjuvant	yes	9922	79,1

BCT – Breast Conserving Therapy

RT – Radio Therapy

MAS – Mastectomy

Numerische Variablen

Variable	n	mean	sd	median	min	max
age_diag	12543	60,0257812	12,9612292	59,9151266	18,2258727	100,40794
TumorSize (mm)	10625	23,7773976	13,8940935	16	0	173

Events in Frequencies

n = 12543

from	Start	LR	DM	LR+DM	Death	no event
Start	0	0,04783545	0,06202663	0	0,1260464	0,76409153
LR	0	0	0	0,26	0,13333333	0,60666667
DM	0	0	0	0,09640103	0,70822622	0,19537275
LR+DM	0	0	0	0	0,75241158	0,24758842
Tod	0	0	0	0	0	1

Multistate Cox Model

For the corresponding transition, see the DAG at the poster.

term	coef	exp(coef)	se(coef)	robust_se	z	Pr(> z)
age_diag.1	0,0090885 9	1,0091300 2	0,0038603 1	0,0041355 8	2,1976563 1	0,0279736 1
age_diag.2	0,0171496 9	1,0172975 9	0,0033330 3	0,0035473 4	4,8345166 9	1,3347E-06
age_diag.3	0,0911372 7	1,0954193 6	0,0030915 8	0,0033155 3	27,487968 7	2,445E-166
age_diag.4	0,0097259 3	1,0097733 8	0,0067087 2	0,0077689 1	1,2519041 2	0,2106048
age_diag.5	0,0505451 4	1,0518443 5	0,0115627 3	0,0125062 8	4,0415795 9	5,3092E-05
age_diag.6	- 0,0061284 9	0,9938902 5	0,0106532 4	0,0113934	- 0,5378979 1	0,5906475 3
age_diag.7	0,0128461 7	1,0129290 4	0,0040937 9	0,0046196 2	2,7807849 1	0,0054227 7
age_diag.8	0,0154431 5	1,0155630 1	0,0055242 9	0,0055767 4	2,7692080 5	0,0056192 7
TumorSize.1	- 0,0095407 8	0,9905045 9	0,0034323	0,0033983	- 2,8075118 5	0,0049925 8
TumorSize.2	0,0201897 3	1,0203949 2	0,0028878 3	0,0029019 8	6,9572131	3,4707E-12
TumorSize.3	0,0134937 7	1,0135852 2	0,0023633 5	0,0024116 5	5,5952365 4	2,2032E-08
TumorSize.4	0,0158939 3	1,0160209 1	0,0068697 7	0,0069395 2	2,2903490 5	0,0220010 9
TumorSize.5	0,0150083 6	1,0151215 5	0,0101904 3	0,0095749	1,5674696	0,1170049 7
TumorSize.6	-0,0027043	0,9972993 6	0,0109231	0,0109525 5	- 0,2469104 1	0,8049775 6
TumorSize.7	0,0131856 6	1,0132729 7	0,0044364 7	0,0048241 7	2,733251	0,0062712 5
TumorSize.8	0,0098332 4	1,0098817 5	0,0061185 2	0,0049080 5	2,0034938 6	0,0451243 1
Grading1.1	0,5196579 6	1,6814524 3	0,2418586 7	0,2333167 4	2,2272639 2	0,0259296 4
Grading1.2	0,8688348 4	2,3841313 4	0,2582237 2	0,2575840 4	3,3730150 9	0,0007435
Grading1.3	- 0,0001659 9	0,9998340 2	0,0937809 3	0,0914830 2	- 0,0018144 2	0,9985523
Grading1.4	11,584477 8	107417,44	159,25966 1	0,4447257 8	26,048586 4	1,396E-149
Grading1.5	0,8764708 1	2,4024061 7	0,7448565 4	0,7045471 4	1,2440201 1	0,2134921 6

Grading1.6	- 0,8779514 7	0,4156334 8	0,7886955	0,8102975	- 1,0834927 5	0,2785897 7
Grading1.7	- 0,1131442 7	0,8930218 2	0,3645844 2	0,3514552 1	- 0,3219308 3	0,7475051
Grading1.8	- 0,2135307 4	0,8077273 3	0,5414520 9	0,5675281 2	- 0,3762469 7	0,7067333
Grading2.1	1,211999	3,3601949 6	0,2491822 1	0,2437829 9	4,9716306 8	6,6392E-07
Grading2.2	1,0936104 3	2,9850318 8	0,2647527 1	0,2645081 5	4,1345055 9	3,5572E-05
Grading2.3	0,0869819 5	1,0908769 9	0,1107354 8	0,1092139 1	0,7964365 3	0,4257783 5
Grading2.4	12,044803	170212,50 6	159,25966 8	0,4569678 7	26,358095 9	4,145E-153
Grading2.5	0,9495733 3	2,5846066 4	0,7637957 7	0,7251225 1	1,3095350 2	0,1903531 8
Grading2.6	- 0,5790295 3	0,5604419 9	0,8171621	0,7995622 6	- 0,7241831 7	0,4689532 9
Grading2.7	0,2009183 2	1,2225249 1	0,3730481 3	0,3661466 3	0,5487373 1	0,5831857 4
Grading2.8	0,1849134 5	1,2031143 1	0,5469590 8	0,5760172 4	0,3210206 8	0,7481947 2
NodalStatus. 1	- 0,7789866 7	0,4588707 6	0,1158679 3	0,1295100 7	- 6,0148733 9	1,8003E-09
NodalStatus. 2	0,7074040 4	2,0287179 4	0,0928363 2	0,0987902 9	7,1606634 8	8,0288E-13
NodalStatus. 3	0,360892	1,4346085 2	0,0659773	0,0668633 9	5,3974526 6	6,7594E-08
NodalStatus. 4	0,4650264 1	1,5920562 3	0,1910899 2	0,2022819 6	2,2989020 4	0,0215105
NodalStatus. 5	0,4596083	1,5834536 2	0,2856989 3	0,2810335 5	1,6354214 6	0,1019607 3
NodalStatus. 6	0,6921429 4	1,9979925 4	0,3013846 4	0,3296632 1	2,0995456 3	0,0357688 3
NodalStatus. 7	0,3630655 3	1,4377300 7	0,1073357 6	0,1179622 8	3,0778104 6	0,0020852 8
NodalStatus. 8	0,2182682 8	1,2439207 4	0,1647288 7	0,1581697	1,3799626 4	0,1675981 5
Chemo.1	0,1329881 3	1,1422364 4	0,1140022	0,1181844 6	1,1252590 3	0,2604792 9
Chemo.2	0,7684754	2,1564759 8	0,1070927 7	0,1120949 3	6,8555766 1	7,1025E-12
Chemo.3	- 0,2226641 5	0,8003836 2	0,0772834 3	0,0776325 1	- 2,8681816 9	0,0041283 8
Chemo.4	0,6596460 9	1,9341077 2	0,2379444 7	0,2592951	2,5439974 9	0,0109591 9

Chemo.5	0,3390673 9	1,4036379 3	0,2995276 6	0,2790768 7	1,2149605 5	0,2243811 4
Chemo.6	- 0,4410633 3	0,6433519 6	0,3741033 6	0,3860384 6	- 1,1425372 9	0,2532307 5
Chemo.7	- 0,2187547 8	0,8035187 3	0,1299562 6	0,1449780 5	- 1,5088820 4	0,1313289 3
Chemo.8	0,1107564 2	1,1171227 6	0,2040059 9	0,1985573 3	0,5578057 3	0,5769770 5
Center1.1	0,0635545 4	1,0656176	0,1288528 9	0,1231787 6	0,5159536 8	0,6058867 6
Center1.2	- 0,1113721 2	0,8946057 9	0,1090739 9	0,1097602 9	- 1,0146850 5	0,3102559 8
Center1.3	0,0026451 1	1,0026486 1	0,0758024 6	0,0748349 8	0,0353458 6	0,9718039 6
Center1.4	- 1,1400421 6	0,3198055 4	0,2602509 6	0,2550764 2	- 4,4694140 8	7,8434E-06
Center1.5	- 0,6699731 7	0,5117223 1	0,3688902 3	0,3586255 4	- 1,8681691 4	0,0617385
Center1.6	- 1,0361164 8	0,35483	0,4621100 4	0,4550614 4	- 2,2768716 2	0,0227938 9
Center1.7	- 0,1660304 7	0,8470204 3	0,1352472 5	0,1546561 1	- 1,0735461 3	0,2830261 5
Center1.8	- 0,2940070 4	0,7452712 5	0,2396985	0,2425363 4	- 1,2122185 2	0,2254287 5
Center2.1	- 0,0383010 7	0,9624231 4	0,1272503 9	0,1289375 8	- 0,2970512 9	0,7664273 5
Center2.2	- 0,1425907 9	0,8671088 3	0,1005646 3	0,1030333 1	- 1,3839290 2	0,1663801 9
Center2.3	- 0,2076966 4	0,8124534 6	0,0696341 3	0,0688302 5	- 3,0175197 6	0,0025485 2
Center2.4	- 0,7761084 1	0,4601934 2	0,2510892 8	0,2702080 1	- 2,8722627 2	0,0040754 4
Center2.5	- 0,4510154 5	0,636981	0,3296579 2	0,3106527 2	- 1,4518316 3	0,1465484 3
Center2.6	- 0,3617920 5	0,6964271 7	0,3050348 6	0,3130443 2	-1,1557215	0,2477950 9

Center2.7	- 0,2679556 2	0,7649417 3	0,1172831	0,1251749	- 2,1406497 4	0,0323022 9
Center2.8	- 0,3854372 5	0,6801531 8	0,1949343 4	0,1820926 3	-2,1167097	0,0342844 9
Center3.1	0,5026613	1,6531148 5	0,1293537 1	0,1311012 8	3,8341447 5	0,000126
Center3.2	- 0,2292269 6	0,7951480 5	0,1254830 3	0,1259417 2	- 1,8201034 4	0,0687432 5
Center3.3	- 0,0107085 8	0,9893485 6	0,0954237 8	0,0925397 9	- 0,1157186 2	0,9078755 5
Center3.4	- 0,6557156 4	0,5190704 6	0,2487223 4	0,2676254 9	- 2,4501240 5	0,0142807
Center3.5	- 0,7315069 9	0,4811833	0,3905669	0,3763993 4	- 1,9434332 7	0,0519638 3
Center3.6	0,1848355 1	1,2030205 4	0,3693155	0,3990733	0,4631618	0,6432484
Center3.7	- 0,2914129 4	0,7472070 6	0,1663219 1	0,1947067 3	- 1,4966762 4	0,1344775 2
Center3.8	- 0,7743750 2	0,4609918	0,2128561 4	0,2186476 4	- 3,5416572 8	0,0003976 2
treat1.1	- 1,0617644 8	0,3458450 3	0,2858476 8	0,4114438 8	- 2,5805815 6	0,0098634 1
treat1.2	1,7578389 6	5,7998900 7	0,3186954 1	0,3555845 2	4,9435194 2	7,6725E-07
treat1.3	- 0,7478353 9	0,4733901 5	0,1339440 6	0,1401347 7	- 5,3365443 5	9,4735E-08
treat1.4	0,0323060 2	1,0328335 2	0,5323389 7	0,6064914 2	0,0532670 6	0,9575191 2
treat1.5	- 0,0216814 3	0,9785519 2	0,5655323 2	0,5819515 5	- 0,0372564 2	0,9702805 6
treat1.6	- 0,2059900 1	0,8138412 1	0,8171259 5	0,9172447 6	- 0,2245747 4	0,8223101 1
treat1.7	0,1492501	1,1609633 1	0,3860874 2	0,4970458 1	0,3002743 4	0,7639679
treat1.8	- 0,3243326 4	0,7230097	0,4285722 8	0,5668897 8	- 0,5721264 6	0,5672363
treat2.1	- 0,5085783 4	0,6013498 8	0,2706734 5	0,2694255 9	- 1,8876393 2	0,0590743 9

treat2.2	0,4683006	1,5972774 7	0,3039602 1	0,3081724 7	1,5196055 7	0,1286101 4
treat2.3	-0,0058136	0,9942032 7	0,1115619 8	0,1145459 1	- 0,0507534 4	0,9595219 9
treat2.4	- 0,0788667 6	0,9241630 5	0,6245462 9	0,6176807 1	- 0,1276820 8	0,8984005 7
treat2.5	- 0,6268742 7	0,5342591 5	0,6403584 8	0,6443653 9	- 0,9728552 7	0,3306252 4
treat2.6	0,6710371 1	1,9562651 2	0,8242759 2	0,9276902	0,7233418 1	0,4694699 1
treat2.7	0,4786302	1,6138622 1	0,4040119 4	0,5127932 4	0,9333785 2	0,3506245 6
treat2.8	- 0,5284742 4	0,5895037 2	0,4586913 7	0,6184588 7	- 0,8545018 3	0,3928269 9
treat3.1	1,1509782 3	3,1612838 5	0,2948014 1	0,4186985 2	2,7489426 9	0,0059787 8
treat3.2	2,3906736 6	10,920848 4	0,3200481 1	0,3553156 5	6,7283094	1,7165E-11
treat3.3	- 0,6069119 8	0,5450313 4	0,1623056 3	0,1685941 2	- 3,5998406 8	0,0003184 1
treat3.4	0,4820863	1,6194495 4	0,5197495 2	0,5813557 5	0,8292449 1	0,4069658 4
treat3.5	- 0,5451033 1	0,5797818 8	0,6017127 2	0,5798961 8	- 0,9400015 5	0,3472167 6
treat3.6	0,0330035	1,0335541 6	0,8246485 2	0,9509476 9	0,0347059 1	0,9723142 5
treat3.7	- 0,0581381 8	0,9435195 6	0,3924080 1	0,5044802 9	- 0,1152437 1	0,9082519 6
treat3.8	-0,6909545	0,5010975 4	0,4143650 2	0,5583080 1	- 1,2375865 9	0,2158693 9
treat4.1	0,3438007 9	1,4102976 6	0,2597083 1	0,2677324 2	1,2841208 7	0,1990996 7
treat4.2	-0,1171428	0,8894581 7	0,4035982 1	0,4057913 2	- 0,2886774 4	0,7728282 2
treat4.3	- 0,4559723 6	0,6338313 6	0,1603191 6	0,1695011 1	- 2,6900848 5	0,0071433 9
treat4.4	- 1,0739813 1	0,3416456 1	0,6577277 8	0,6415469 5	- 1,6740494 2	0,0941208 9
treat4.5	- 0,3104272 3	0,7331336 7	0,5328948 2	0,4588817 1	- 0,6764863 8	0,4987318 9

treat4.6	-12,919256	2,4504E-06	393,00534 8	1,0848126 1	- 11,909205 2	1,0598E-32
treat4.7	- 0,1573271 3	0,8544245	0,5774845 5	0,6558771 1	- 0,2398728 8	0,8104288
treat4.8	- 0,9440753 4	0,3890391 3	0,5758753 1	0,6935803 6	- 1,3611621 5	0,1734624 5
treat5.1	2,3798483 3	10,803264 2	0,2775605 5	0,3977411	5,9834106 4	2,1851E-09
treat5.2	1,9530635 8	7,0502535 7	0,3398510 1	0,3735399 1	5,2285272 6	1,7087E-07
treat5.3	- 1,2547277 9	0,2851534 6	0,2444138 8	0,2330097 1	- 5,3848735 3	7,2496E-08
treat5.4	- 0,0558249 1	0,9457047	0,5275167 8	0,6062549 7	- 0,0920815 7	0,9266332 3
treat5.5	- 1,2608708 8	0,2834071 1	0,6029737 1	0,6125157 8	- 2,0585116 7	0,0395410 4
treat5.6	0,7080608 8	2,0300509 3	0,8445839 4	0,9362742 5	0,7562537 2	0,4494970 9
treat5.7	-0,1304132	0,8777326 7	0,4193976 3	0,5244632 5	- 0,2486603 3	0,8036235 4
treat5.8	- 0,5967517 1	0,5505972 4	0,4194559 1	0,5733207 3	- 1,0408688 9	0,2979364
adjuvant.1	- 0,0919518 7	0,9121490 5	0,2312407 1	0,3819087 5	- 0,2407692 1	0,8097339 9
adjuvant.2	- 1,3796872 2	0,2516572 5	0,1763995 8	0,2050627 7	- 6,7281215 3	1,7187E-11
adjuvant.3	0,1740552	1,1901212 6	0,1165475 9	0,1195398 1	1,4560438 5	0,1453805
adjuvant.4	- 0,2914769 3	0,7471592 5	0,2511329 4	0,2679717 9	- 1,0877149 8	0,2767209 5
adjuvant.5	- 0,2577286 9	0,7728048 7	0,3704332 1	0,3743509 8	- 0,6884680 5	0,4911580 8
adjuvant.6	- 0,0940503 8	0,9102369	0,4350872 3	0,4734646 3	- 0,1986428 8	0,8425421 1
adjuvant.7	0,2573581 1	1,2935082 6	0,1868416 3	0,1798447	1,4310019	0,1524296 7
adjuvant.8	- 0,0840248 3	0,9194084 2	0,2370412 7	0,2495683	- 0,3366807 2	0,7363576

