

# **Prognosis of survival for breast cancer patients**

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# Outline

- **Introduce the data and outcomes requested by the medics.**
- **Work through the stages of the analyses.**

**Imputation**

**Fractional Polynomials**

**Producing a simple score**

**Fitting Splines**

- **Illustrate the menu call developed for everyday use.**

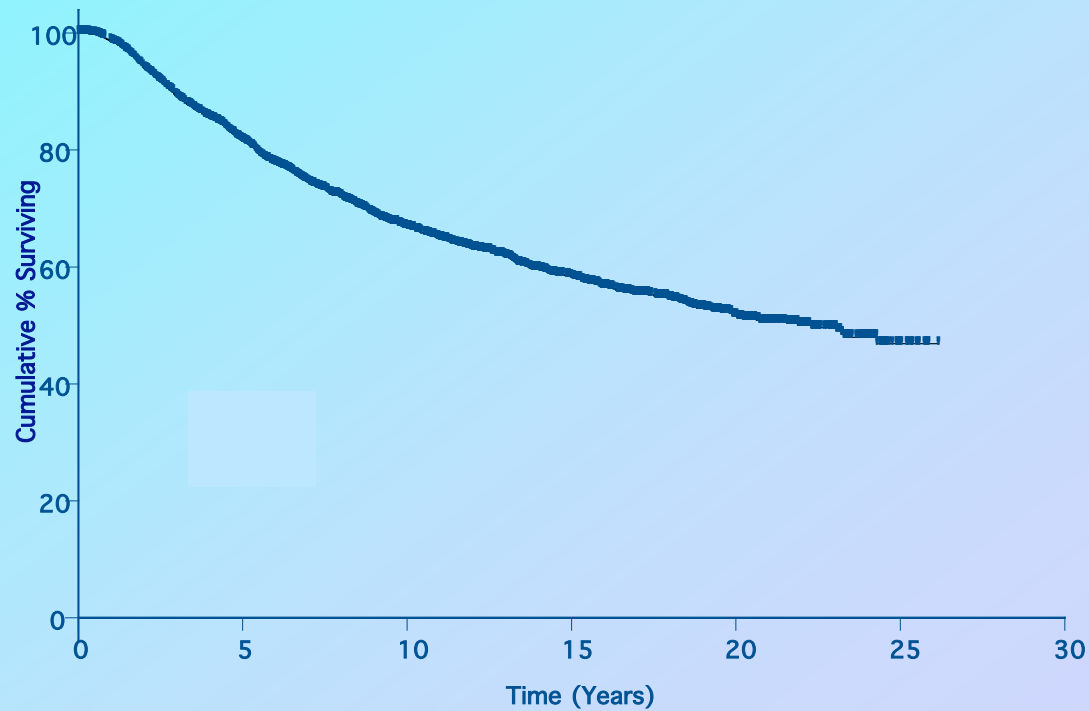
# The Problem

- **Over 8000 patients with invasive Breast Cancer with 3083 operable stage 1 and 2 disease.**
- **Time of relapse-free survival**
- **Time to a distant relapse**
- **Overall survival**
  - **Death from breast cancer**
  - **All-cause mortality**

# The Problem

- **Kaplan-Meier Curves**

Overall Survival for Stage 1 and 2 patients



# The Problem

## Factors affecting outcome

- **Histological type ( $x_4$ )**  
Ductal ( Grade I, II & III), Lobular, others (Mucoid, Medullary, Tubular)
- **Tumour Size ( $x_3$ )**  
( $\leq 2.0$  cms, 2.0 - 5.0 cms,  $>5.0$  cms)
- **Axilla Nodal status ( $x_5$ )**  
(All negative, 1-3, 4 - 9,  $\geq 10$  positive)
- **Age ( $x_1$ )**  
(Under 40, 41-50, 51-60, 61-70, Over 70)

# The Problem

## Factors affecting outcome

- Postmenopausal status ( $x_2$ )
- Type of surgery ( $x_{11}$ )
- Progesterone receptor status ( $x_{6a}$ )
- Oestrogen receptor status ( $x_{7a}$ )
- Adjuvant treatment  
Chemotherapy ( $x_8$ )
- Hormonal therapy ( $x_9$ )
- Radiotherapy ( $x_{10}$ )

## The Task

- **Given the information on the prognostic factors for a new patient**
- **To provide estimates of the probabilities of being relapse-free or surviving after 5, 10, 15, 20 years.**

# Prognostic Factors

|                                | Code     | Mean | % missing |
|--------------------------------|----------|------|-----------|
| Age (years)                    | $x_1$    | 55   | 0         |
| Postmenopausal status          | $x_2$    | 0.55 | 2.0       |
| Clinical tumour size (mm)      | $x_3$    | 28   | 1.1       |
| Histology Ductal Grade 2       | $x_{4a}$ | 0.39 | 0         |
| Histology Ductal Grade 3       | $x_{4b}$ | 0.34 | 0         |
| Histology Lobular              | $x_{4x}$ | 0.13 | 0         |
| Histology Other                | $x_{4y}$ | 0.03 | 0         |
| No of positive lymph nodes     | $x_5$    | 2.8  | 0         |
| Progesterone receptor positive | $x_{6a}$ | 0.52 | 13.7      |
| Oestrogen receptor positive    | $x_{7a}$ | 0.70 | 11.5      |
| Chemotherapy (any type)        | $x_8$    | 0.20 | 0         |
| Hormonal therapy               | $x_9$    | 0.35 | 0         |
| Radiotherapy                   | $x_{10}$ | 0.42 | 0         |
| Impalable tumour               | $x_{3x}$ | 0.07 | 1.1       |

# Imputation

**van Buuren S., H. C. Boshuizen and D. L. Knook. 1999. Multiple imputation of missing blood pressure covariates in survival analysis. *Statistics in Medicine* 18:681-694.**

**mvisamp imputes missing values using "switching regression", an iterative multivariable regression technique.**

**mvisamp varlist [if exp] [in range] [weight], gen(name)  
[ cc(ccvarlist) cmd(cmdlist) seed(#) ]**

# Imputation

**Impute x6a and x7a on complete variables and transformed year and survival time**

```
mvisamp x6a x7a x1 x4a x4b x4x x4y x5 yr_1 yr_2  
yr_3 lnt _d, gen(z1) seed(101)
```

**Impute x3 on these variables and completed x6a, x7a**

```
mvisamp x3 z1_1 z1_2 x1 x4a x4b x4x x4y x5 yr_1  
yr_2 yr_3 lnt _d if x3>0, gen(z2) seed(103)
```

# Cox's Proportional Hazards model

## Fractional Polynomials

- For the continuous variables, the Fractional Polynomials, based on  $X^{-2}$ ,  $X^{-1}$ ,  $X^{-0.5}$ ,  $X^{0.5}$ ,  $X^2$ ,  $X^3$ , and  $\log_e(X)$  are compared with the linear polynomial to determine if one or more of these polynomials provides a better fit.
- All other factors are (0,1) variables, including the interaction of Hormone Therapy with ER status.

# Cox's Proportional Hazards model

## Fractional Polynomials

**mfracpol** selects the fractional polynomial (FP) model which best predicts the outcome variable, **yvar**, from the RHS variables, **xvarlist**. After execution, **mfracpol** leaves variables in the data named **Ivar1\_\_1**, **Ivar2\_\_2**, ...**Ivar2\_1**, **Ivar2\_2** etc. The new variables contain the best-fitting fractional polynomial powers of **var1**, **var2**, .

```
mfracpol regression_cmd yvar xvarlist [in range] [if exp]  
[weight]      [, alpha(alpha_list) df(df_list)  
select(select_list)      regression_cmd_options ]
```

# Cox's Proportional Hazards model

## Fractional Polynomials

\* Force in ER and hormon, since know ER x hormon is significant.

```
mfracpol cox _t x1 ix2 ix3 ix3x x4a x4b x4x x4y x5 ix6a ix7a  
x7ah hormon chemo rt yr, dead(_d) sel(.05, ix7a hormon  
x7ah:0.9999) df(ix3 x5:2)
```

# Cox's Proportional Hazards model

## Fractional Polynomials

-> gen double lx1\_\_1 =  $X^{-2-.0327}$  if e(sample)

(where:  $X = x1/10$ )

-> gen double lix3\_\_1 =  $\ln(X)+1.243$  if e(sample)

(where:  $X = (ix3+1)/100$ )

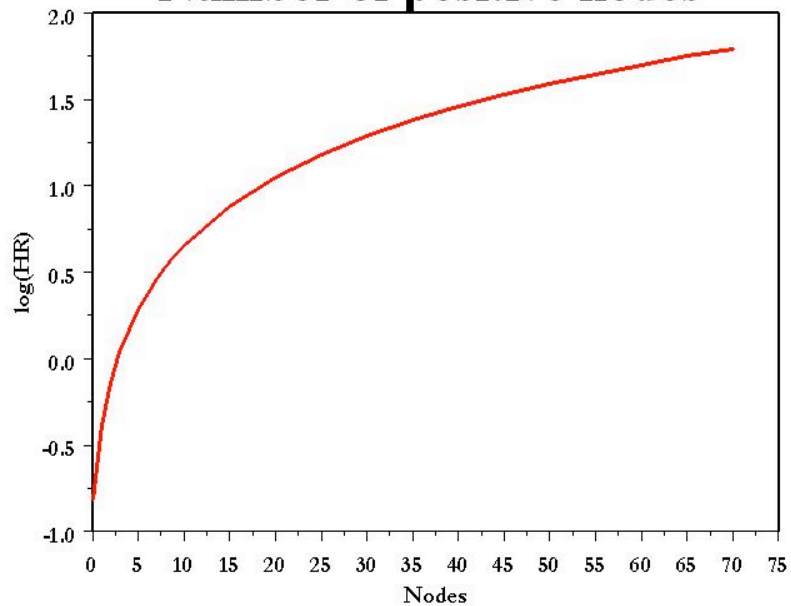
-> gen double lx5\_\_1 =  $\ln(X)+.974$  if e(sample)

(where:  $X = (x5+1)/10$ )

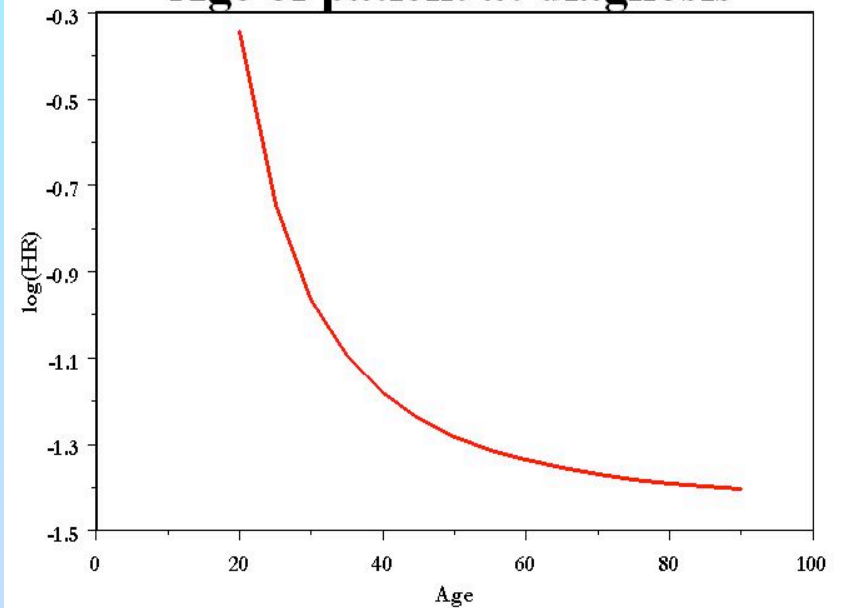
# Cox's Proportional Hazards model

## Fractional Polynomials

### Number of positive nodes



### Age of patient at diagnosis



# Cox's Proportional Hazards model

## Fractional Polynomials

Final multivariable fractional polynomial model for \_t

| Variable | -----Initial----- |        |        | -----Final----- |    |        |
|----------|-------------------|--------|--------|-----------------|----|--------|
|          | df                | Select | Alpha  | Status          | df | Powers |
| x1       | 4                 | 0.0500 | 0.0500 | in              | 2  | -2     |
| ix2      | 1                 | 0.0500 | 0.0500 | out             | 0  |        |
| ix3      | 2                 | 0.0500 | 0.0500 | in              | 2  | 0      |
| ix3x     | 1                 | 0.0500 | 0.0500 | in              | 1  | 1      |
| x4a      | 1                 | 0.0500 | 0.0500 | in              | 1  | 1      |
| x4b      | 1                 | 0.0500 | 0.0500 | in              | 1  | 1      |
| x4x      | 1                 | 0.0500 | 0.0500 | in              | 1  | 1      |
| x4y      | 1                 | 0.0500 | 0.0500 | out             | 0  |        |
| x5       | 2                 | 0.0500 | 0.0500 | in              | 2  | 0      |
| ix6a     | 1                 | 0.0500 | 0.0500 | in              | 1  | 1      |
| ix7a     | 1                 | 0.9999 | 0.0500 | in              | 1  | 1      |
| x7ah     | 1                 | 0.9999 | 0.0500 | in              | 1  | 1      |
| hormon   | 1                 | 0.9999 | 0.0500 | in              | 1  | 1      |
| chemo    | 1                 | 0.0500 | 0.0500 | in              | 1  | 1      |
| rt       | 1                 | 0.0500 | 0.0500 | out             | 0  |        |
| yr       | 4                 | 0.0500 | 0.0500 | out             | 0  |        |

# Cox's Proportional Hazards model

## Fractional Polynomials

| _t      | _d | Coef.     | Std. Err. | z     | P> z  | [95% Conf. Interval] |
|---------|----|-----------|-----------|-------|-------|----------------------|
| Ix1__1  |    | 4.707014  | 1.439364  | 3.27  | 0.001 | 1.885911 7.528116    |
| Iix3__1 |    | .5143961  | .0655541  | 7.85  | 0.000 | .3859123 .6428798    |
| ix3x    |    | 1.320571  | .2790599  | 4.73  | 0.000 | .7736239 1.867518    |
| x4a     |    | 1.122357  | .1557526  | 7.21  | 0.000 | .8170873 1.427626    |
| x4b     |    | 1.420355  | .1588664  | 8.94  | 0.000 | 1.108983 1.731728    |
| x4x     |    | 1.028325  | .1704158  | 6.03  | 0.000 | .6943161 1.362334    |
| Ix5__1  |    | .6070695  | .0299867  | 20.24 | 0.000 | .5482966 .6658423    |
| ix6a    |    | -.1314727 | .066974   | -1.96 | 0.050 | -.2627393 -.000206   |
| ix7a    |    | .1902246  | .0781319  | 2.43  | 0.015 | .037089 .3433603     |
| x7ah    |    | -.708684  | .1504531  | -4.71 | 0.000 | -1.003567 -.4138013  |
| hormon  |    | -.0381773 | .1254731  | -0.30 | 0.761 | -.2841 .2077454      |
| chemo   |    | -.3198936 | .0782234  | -4.09 | 0.000 | -.4732086 -.1665787  |

Deviance:16524.958.

# Cox's Proportional Hazards model

## Fractional Polynomials

- . global model `e(fp\_fvl) `
- . stcox \$model, nolog sca(sca\*) sch(sch\*)
- . stphtest, rank detail

| Test of proportional hazards assumption |          |        |    |           |
|---|----------|--------|----|-----------|
|   | rho      | chi2   | df | Prob>chi2 |
| Ix1__1                                  | -0.08739 | 10.11  | 1  | 0.0015    |
| Ix3_1__1                                | 0.03250  | 1.23   | 1  | 0.2666    |
| x4a                                     | -0.06038 | 4.17   | 1  | 0.0412    |
| x4b                                     | -0.11912 | 16.27  | 1  | 0.0001    |
| x4x                                     | -0.01873 | 0.40   | 1  | 0.5268    |
| Ix5__1                                  | -0.14572 | 23.72  | 1  | 0.0000    |
| ix6a                                    | 0.06161  | 4.59   | 1  | 0.0321    |
| ix7a                                    | 0.08467  | 8.35   | 1  | 0.0039    |
| x7ah                                    | 0.03161  | 1.14   | 1  | 0.2847    |
| hormon                                  | -0.01300 | 0.19   | 1  | 0.6609    |
| chemo                                   | 0.11522  | 16.23  | 1  | 0.0001    |
| global test                             |          | 145.80 | 11 | 0.0000    |

## Simple scoring system

- A scoring system was developed so that a unit increase in the score was approximately an increase of 0.1 in the  $\log_e(\text{HR})$ .
- For the (0,1) binary variables the scores were taken to the nearest 0.1 of the  $\log_e(\text{HR})$ , but for the continuous variables the cut-off points were selected to have an increment of approximately 0.2 in the  $\log_e(\text{HR})$ .

# Simple scoring system

| Node status | Score | Tumour size               | Score |
|-------------|-------|---------------------------|-------|
| 0           | 0     | $\leq 11\text{mm}$        | 0     |
| 1           | 4     | 12 – 19                   | 2     |
| 2           | 6     | 20 – 27                   | 4     |
| 3 – 4       | 8     | 28 – 38                   | 6     |
| 5 – 6       | 10    | $\geq 39$                 | 8     |
| 7 – 9       | 12    |                           |       |
| 10 – 14     | 14    |                           |       |
| 15 – 20     | 16    | ER <sup>+</sup> and HT    | 0     |
| 21 – 29     | 18    | ER <sup>+</sup> and no HT | 8     |
| 30 – 42     | 20    | ER <sup>-</sup>           | 7     |
| 43 – 52     | 22    |                           |       |
| $\geq 53$   | 24    |                           |       |

## Simple scoring system

### Fitting splines

`stpm [varlist] [if exp] [in range] , model_complexity  
scale(hazardlnormalodds) stratify(strat_varlist)`

`stpm` fits spline-based distributional models to right- or interval-censored survival-time data.

`varlist` is a set of covariates.

`model_complexity` given by defining the number of degrees of freedom to use or by defining the knot positions

`scale` specifies the scale of model

`stratify`

`stpm guysrisk, st(guysrisk) sc(h) knots(0.643 1.614)  
nolog`

## Simple scoring system

| <b>Score</b> | <b>1</b>     | <b>2</b>     | <b>5</b>     | <b>10</b>    | <b>20</b>    |
|--------------|--------------|--------------|--------------|--------------|--------------|
| <b>10</b>    | <b>0.989</b> | <b>0.973</b> | <b>0.942</b> | <b>0.914</b> | <b>0.881</b> |
| <b>14</b>    | <b>0.984</b> | <b>0.960</b> | <b>0.914</b> | <b>0.873</b> | <b>0.827</b> |
| <b>18</b>    | <b>0.976</b> | <b>0.940</b> | <b>0.873</b> | <b>0.815</b> | <b>0.751</b> |
| <b>22</b>    | <b>0.964</b> | <b>0.911</b> | <b>0.815</b> | <b>0.735</b> | <b>0.650</b> |
| <b>26</b>    | <b>0.947</b> | <b>0.869</b> | <b>0.735</b> | <b>0.628</b> | <b>0.522</b> |
| <b>30</b>    | <b>0.921</b> | <b>0.809</b> | <b>0.629</b> | <b>0.497</b> | <b>0.376</b> |
| <b>34</b>    | <b>0.884</b> | <b>0.727</b> | <b>0.498</b> | <b>0.348</b> | <b>0.229</b> |
| <b>38</b>    | <b>0.830</b> | <b>0.619</b> | <b>0.350</b> | <b>0.204</b> | <b>0.109</b> |
| <b>42</b>    | <b>0.755</b> | <b>0.485</b> | <b>0.205</b> | <b>0.092</b> | <b>0.035</b> |
| <b>46</b>    | <b>0.656</b> | <b>0.337</b> | <b>0.092</b> | <b>0.027</b> | <b>0.006</b> |

# Menu system

