STATISTICAL RESEARCH

CURE RATE MODELS

Introduction

Standard survival models assume that all cases in the study population are susceptible to the event of interest if the follow-up is sufficiently long. Traditional methods of survival analysis namely, log rank test and Cox regression model assume that all individuals remain at risk. The clinical trials consist of heterogeneous population of patients which can be divided into two groups based on treatment. One group consists of those patients who respond favorably to the treatment and subsequently become immune or insusceptible to the disease and are said to be cured. The other group consists of those patients who do not respond to the treatment and remain uncured or cured but relapsed. The subjects are termed to be cured if they are censored after long follow-up period at the time of analysis. In these situations, interest often lies in estimating the proportion of subjects who do not experience the event. Failing to account for such cured subjects would lead to incorrect inferences and researchers may be interested in estimating the cured fraction. Cure models were proposed about 50 years ago, have received regular attention in statistical literature but not attained wide use or acceptance in medical literature because of their reliance on parametric forms. When the proportional hazard assumptions are valid, the use of log rank test and Cox regression analysis predictions are most valid. Parametric cure model provides a coherent statistical approach to investigate the effect of covariates on the time to failure separately from their effect on ultimate outcome.

Aims

- To construct models for estimating Cure Fraction
- To compare empirically the performance of different cure models using a cancer database

Materials and methods

A series of 1107 locally advanced breast cancer (LABC) patients who had completed the neo-adjuvant treatment protocol consisting of preoperative chemo-

radiotherapy followed by surgery between 1990 and 1999 at Cancer Institute (WIA), Chennai, formed the study group. Five prognostic variables were included in the model. Event free survival (EFS) duration was defined as the minimum time elapsed to disease progression, disease recurrence, occurrence of second malignant neoplasm or death from any cause. Patients alive without disease were censored at the date of last follow-up. EFS probability was estimated using Kaplan-Meier method. The prerequisite for the application of mixture cure model is the long term follow-up. The parametric and nonparametric cure models were used to model to estimate the cure fraction. The STATA package was used for model building.

Results

Table 22 describes the proportion and event free survival estimates. EFS probabilities for all cases together showed minimal changes after 7 years of follow up.

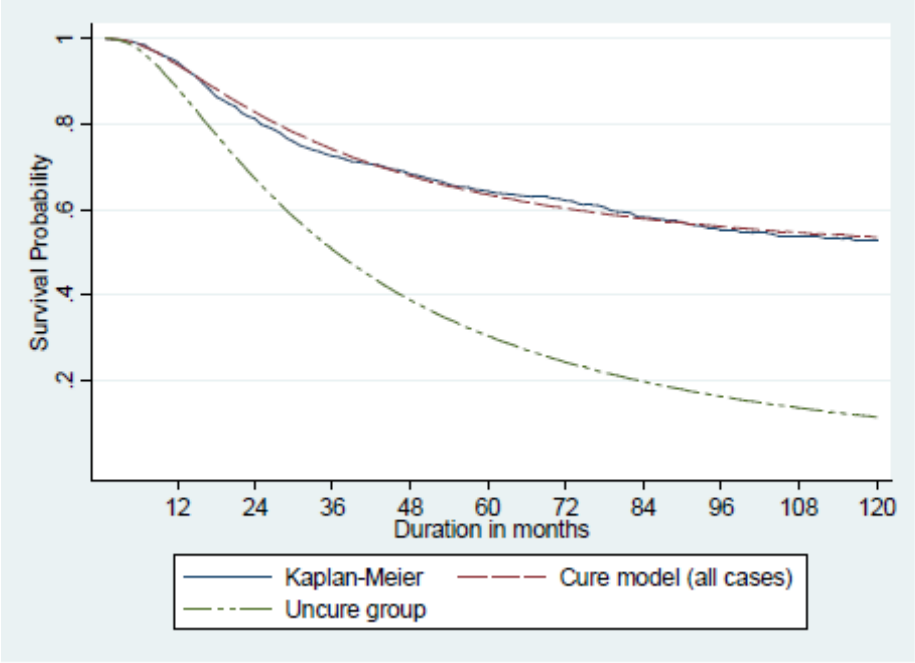
Table 22: Distribution survival (%) according to the prognostic Variables

Tumour Stage	Tumour Residue	Pathologic Node	No.	%	Survival %	
					5 years	10 years
Stage 2B	TR-	PN-	162	14.6	78.0	70.0
		PN+	32	2.9	58.0	49.0
	TR+	PN-	96	8.7	81.3	60.8
		PN+	76	6.9	61.0	46.8
Stage 3A	TR-	PN-	122	11.0	84.1	78.8
		PN+	57	5.1	46.5	38.6
	TR+	PN-	98	8.9	67.0	57.5
		PN+	107	9.7	50.3	28.6
Stage 3B	TR-	PN-	89	8.0	64.5	57.4
		PN+	38	3.4	50.1	45.1
	TR+	PN-	85	7.7	63.0	47.4
		PN+	145	13.1	42.0	28.7
All Stages			1107	100.0	64.2	52.6

TR: Tumour Residue; PN: Pathologic Node

The survival percentages were 64.2, 55.3, 53.7 and 52.6 for the years 5, 8, 9 and10 respectively. The same was observed for factors of tumor residue, pathologic node and tumor stage. The survival differences in the factors were significant ($p<0.001$) for tumor residue, pathologic node and tumor stage. The maximum follow up duration was 15 years with a median follow-up duration of 82 months among those without experiencing any event and 27 months among those experiencing any event. The number of events was the maximum in the second year and decreased gradually. Event free survival probabilities for all cases together showed minimal changes after 7 years of follow up survival percentages were 64.2, 55.3, 53.7 and 52.6 for the years 5, 8, 9 and 10 respectively. The same was observed for factors of tumor residue, pathologic node and tumor stage. The estimation of survival cure models is similar to that obtained by the Kaplan-Meier estimates (Fig. 33).

Fig. 33: Comparison of Kaplan Meier and cure models model survival estimates



The cure fraction was estimated to be 47.5% log normal kernel. The survival time was restricted to 10 years as we expected maximum failure within this period. While Kaplan-Meier method estimates the survival of all the cases in the dataset, the cure model estimates also the survival of the uncured.

The estimates of the cure fraction scale and shape parameters are given in Table 23. The stage parameter estimates are significant and also the reduction in the deviance was significant when we include stage (Model 2).

Table 23: Cure proportional hazard (PH) model estimates

Model	Model 1*			Model 2@		
	Coef.	SE	p value	Coef.	SE	p value
Cure PH model						
Cure fraction (π)						
Tumour Residue	0.216	0.104	0.037	0.185	0.104	0.075
Path. Node	0.796	0.101	<0.001	0.740	0.102	<0.001
Stage 3A				0.226	0.124	0.07
Stage 3B				0.494	0.121	<0.001
Constant	-0.898	0.092	<0.001	-1.102	0.117	<0.001
Scale (λ)						
Constant	-5.975	0.234	<0.001	-6.006	0.235	<0.001
Shape (γ)						
Constant	0.403	0.044	<0.001	0.407	0.043	<0.001
-2LogL	5225.8			5208.6		

*Model 1 includes factors of tumour residue (TR) and pathologic node (PN)
@Model 2 includes factors of TR, PN and tumour stage; PH: proportional hazard
TR negative, PN negative and tumour stage 2B served as reference categories

The lognormal and the Weibull are the two most commonly used parametric cure models. The cure fraction estimates under lognormal and Weibull are given in Table 24. The Weibull model has given consistently higher vales when compared to lognormal.

Table 24: Cure fraction estimates

PN	Lognormal cure model		Weibull cure model	
	TR-	TR+	TR-	TR+
PN-	62.5	54.8	66.5	60.3
PN+	34.7	27.1	40.5	32.6

TR: Tumour Residue; PN: Pathologic Node

The cure fraction estimates under PH and non-proportional hazard models are presented in Table 25. Under stage 2 the non-PH estimates are lower than PH estimates.

Table 25: Cure fraction under PH and non-PH models

Stage	PN	PH Model		Non PH Model	
		TR-	TR+	TR-	TR+
All stages	PN-	62.9	46.6	62.5	54.8
	PN+	43.7	27.4	34.7	27.1
Stage 2B	PN-	68.2	61.8	52.9	40.1
	PN+	42.5	36.1	30.1	17.3
Stage 3A	PN-	62.1	55.7	68.3	55.5
	PN+	36.5	30.0	45.5	32.7
Stage 3B	PN-	52.4	46.0	59.7	46.9
	PN+	26.7	20.3	36.9	24.1

TR: tumour residue; PN: pathologic node; PH: proportional hazard

Conclusion

Two models of different sets of covariates are considered wherein the difference in the covariates of the models and compared. The comparison of the Weibull and lognormal kernels suggests that Weibull model assumption seems to be better. The models under the PH and non-PH assumptions found to have similar results. The cure fraction is sensitive to the model specifications. Cox model is the most widely used in the analysis of survival data. The PH assumption, which is the basic for application of the model, is not always tested. The test for PH revealed some departure in the prognostic variables. The Cox model identifies the prognostic factors and their hazards in comparison to the reference group and is valid only under proportional hazards assumption. The cure rate estimates under parametric kernels and the Cox model with Weibull kernel yield similar results.

The study is in progress.

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