

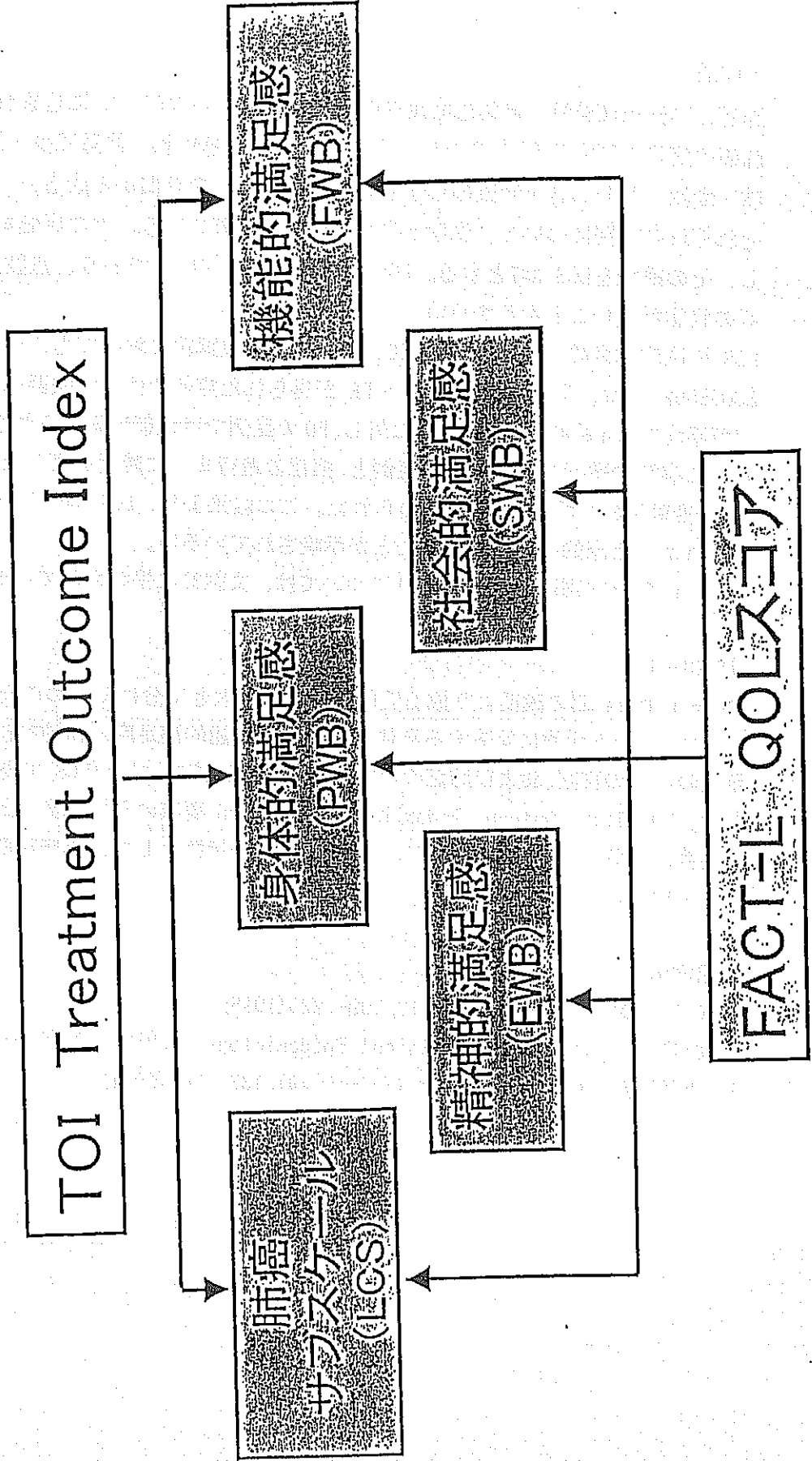
Tumour burden

	Iressa N=1129	Placebo N=563
Histology	48%	48%
Adenocarcinoma	35%	33%
Squamous cell carcinoma		
Time from diagnosis to randomisation	26%	25%
< 6 months	37%	39%
6-12 months		
> 12 months	37%	36%
Stage at diagnosis	34%	30%
IIIB		
IV	48%	50%
Metastatic disease	79%	80%

Prior cancer therapy

	Iressa N=1129	Placebo N=563
2 nd line	49%	49%
Refractory to prior chemotherapy	90%	91%
Received prior platinum	96%	96%
Received prior platinum and docetaxel	27%	28%
Best response to prior chemotherapy	CR/PR	19%
	SD	37%
	PD/NE	44%

FACT-L・TOI・LCS



【LCS】

肺癌ワスケール(LCS)は、肺癌患者用のQOL 調査票であるFACT- L に含まれる設問のうち、肺癌の症状に関する7項目を抜粋したものである。息切れ・体重減少・思考の明瞭さ・咳・食欲・胸苦しさ・呼吸のしやすさに関する7つの設問から成る。

それぞれの設問について、患者自身が5段階で評価を行う。その評価を0～4にスコア化し、その総和をLCSスコアとする。LCSスコアの幅は0～28点であり、点数が高いほど、患者の状態が良いことを示す1)2)。

LCSの臨床的意義については、ECOGの無作為比較試験においても、検討されている。ECOG5592では、化学療法にてCR・PRが得られた症例では、治療開始12週後のLCSスコアが平均で2.4ポイント上昇したのに対し、PDの症例では改善は認められなかった。また、早期に病態の進行が認められた症例と、病態の進行までに時間を要した症例とでは、LCSスコアの変動に3.1ポイントの差が認められた。この結果より、LCSスコアで2～3ポイントの変動があれば、臨床的に意義があることが示唆されている2)。

FACT- Lの日本語版(LCSを含む)については、文献3)に掲載されている。

【FACT- L】

FACT- Lは44個の設問より成る質問票であり、大きく分けて5つの要素より成る。

すなわち、全身状態に関連する身体的満足度/機能的満足度/精神的満足度/社会的満足度の4つの要素、および肺癌の症状に関連する肺癌ワスケール(LCS)である。

なお、TOI(Trial Outcome Index)は、FACT- Lの5要素のうち、身体的満足度、機能的満足度、肺癌ワスケールの3要素より成り、QOLの指標として、臨床試験での使用が推奨されている。

引用文献

- 1) Cella, D. F. : Lung Cancer, 12, 199- 220 (1995)
- 2) Cella, D. : Journal of Clinical Epidemiology, 55, 285- 295 (2002)
- 3) 小林国彦 : QOL 評価法マニュアル(インターメディカ), 138- 149 (2001)

Validity of analysis on Hazard ratio as a function of smoke exposure in Oriental patients:

All Oriental subjects are used in this analysis. The curve results from a Cox regression analysis where terms are fitted for randomized treatment, smoke exposure (a, being the number of pack smoked per day multiplied by the number of years smoked) and randomized treatment by smoke exposure interaction. Non smokers were included with zero pack year exposure. To avoid unnecessary loss of information, smoke exposure was not split into arbitrary categories but rather was fitted as a continuous variable.

The model fitted is therefore as follows

$$\lambda_0(t)e^{\beta_1 X + \beta_2 S + \beta_{12} XS}$$

Where $\lambda_0(t)$ is the baseline hazard, being the same for both treatments, x is the treatment indicator, being 1 for Iressa, 0 for placebo and S denotes smoking exposure in pack years. In terms of the parameters, β_1 relates to treatment, β_2 relates to smoking exposure and β_{12} relates to treatment by smoking exposure interaction.

The log hazard ratio, Iressa to placebo, as a function of smoke exposure is therefore given by

$$\text{Log (HR)} = \beta_1 + \beta_{12}S$$

And the estimated variance of log hazard ratio is given by

$$\text{Variance Log (HR)} = \text{Var} (\beta_1) + S^2 \text{Var} (\beta_{12}) + 2S \text{Cov} (\beta_1, \beta_{12})$$

Hence, the parameter estimates and their covariance matrix can then used to plot the hazard ratio, Iressa: placebo, and its 95% CI as a function of smoke exposure. Results of the analysis are given below:

Analysis of survival by smoking exposure in Oriental patients

- Model

$$\text{Log (HR)} = \beta_1 + \beta_{12} \times \text{Smoke exposure}$$

- $\beta_1 = -0.46386$

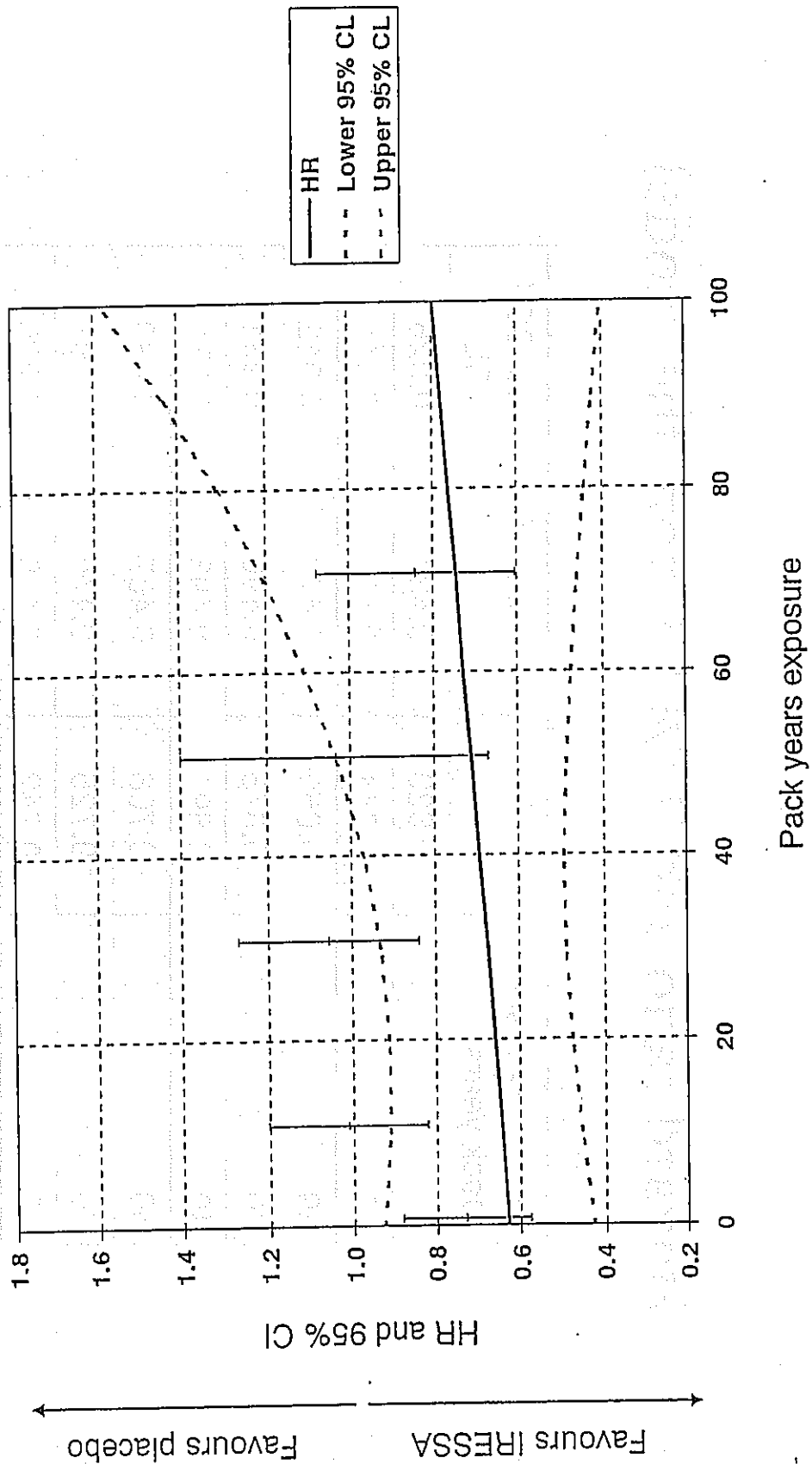
$$\beta_{12} = 0.002372$$

- $\text{Var}(\beta_1) = 0.03895$

$$\text{Var}(\beta_{12}) = 0.000017571$$

$$\text{Cov}(\beta_1, \beta_{12}) = -0.00046396$$

Plot of hazard ratio as a function of smoke exposure



Hazard ratio and 95% CI from the model

Smoke Exposure (pack years)	HR	Lower 95% CL	Upper 95% CL
0	0.629	0.427	0.926
10	0.644	0.455	0.911
20	0.659	0.477	0.912
30	0.675	0.490	0.931
40	0.691	0.493	0.971
50	0.708	0.487	1.030
60	0.725	0.475	1.107
70	0.742	0.459	1.200
80	0.760	0.441	1.310
90	0.778	0.422	1.437
100	0.797	0.402	1.580

The vertical bars are hazard ratio estimates +/- SE for a simple categorisation of the data in to [1] zero smoke exposure (N=141), [2] 0 to 20 pack years smoke exposure (N=65), [3] 20 to 40 pack years smoke exposure (N=51), [4] 40 to 60 pack years smoke exposure (N=28) and [5] greater than 60 years smoke exposure (N=39).

The difference in log likelihood between the Cox model with treatment as the only covariate and with smoking exposure and smoking exposure by treatment interaction was 4.645 on 2 degrees of freedom, $p=0.10$. The difference in log likelihood between the model with treatment as the only covariate and with smoking exposure and smoking exposure by treatment interaction with smoke exposure categorised as in [1]-[5] was 21.423 8 degrees of freedom, $p=0.01$.

Given the skewed distribution for smoke exposure, a better continuous model fit may be obtained by considering smoke exposure on a different scale. The results of an analysis looking at smoke exposure as a curvilinear continuous factor (i.e. at the square root of smoke exposure) are provided below:

Analysis of survival by smoking exposure in Oriental patients

- Model

$$\text{Log (HR)} = \beta_1 + \beta_{12} \times \sqrt{\text{Smoke exposure}}$$

- $\beta_1 = -0.58784$

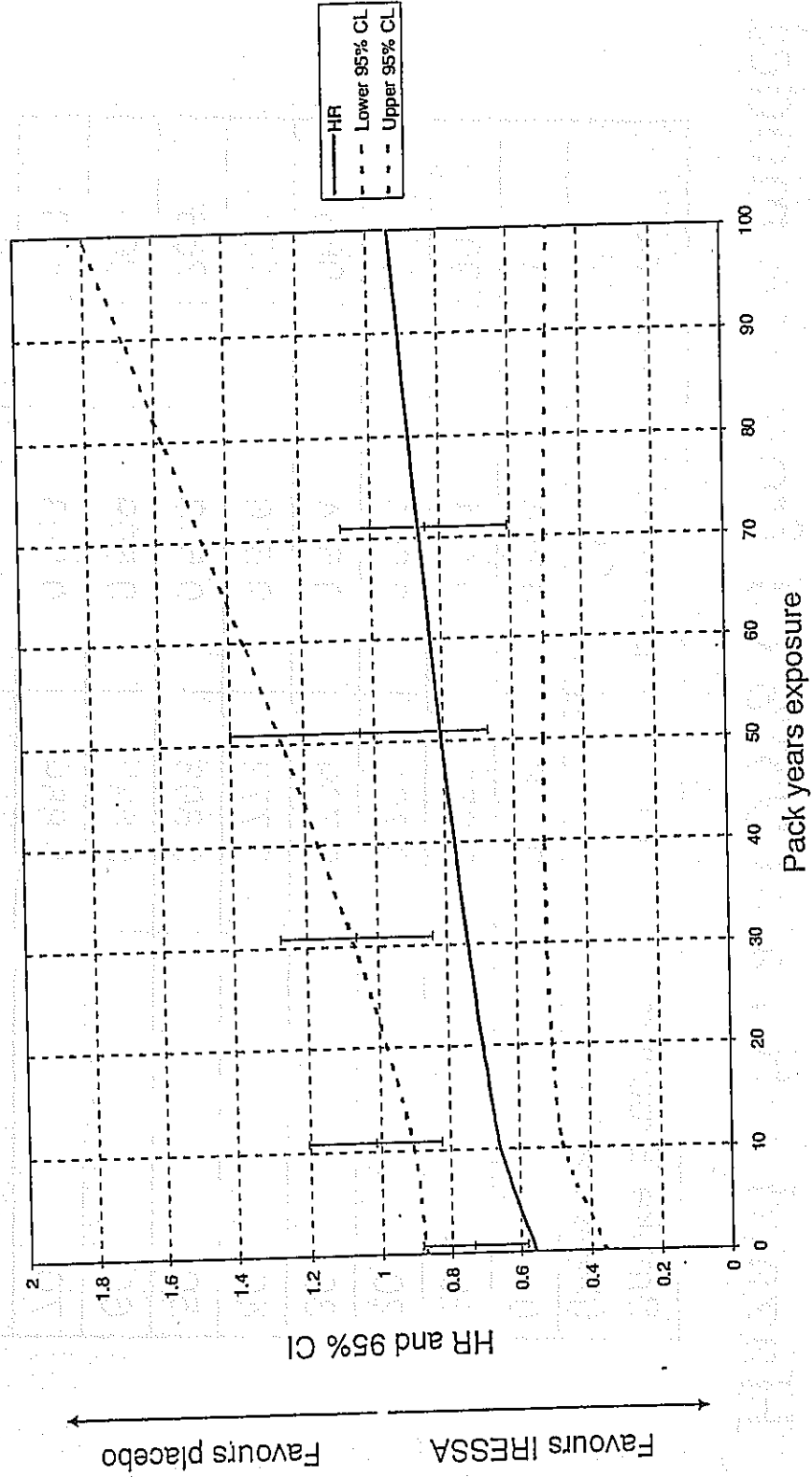
- $\beta_{12} = 0.052109$

- $\text{Var}(\beta_1) = 0.05318$

$$\text{Var}(\beta_{12}) = 0.002067$$

$$\text{Cov}(\beta_1, \beta_{12}) = -0.00738$$

Plot of hazard ratio as a function of smoke exposure



Hazard ratio and 95% CI from the model

Smoke Exposure (pack years)	HR	Lower 95% CL	Upper 95% CL
0	0.556	0.354	0.873
10	0.655	0.474	0.905
20	0.701	0.504	0.976
30	0.739	0.514	1.063
40	0.772	0.516	1.157
50	0.803	0.513	1.256
60	0.832	0.509	1.360
70	0.859	0.503	1.466
80	0.885	0.497	1.576
90	0.911	0.491	1.688
100	0.935	0.485	1.804