Also, the adjusted tremanet effect (all pre-specified covariates retained in the model) is shown in the following with the standard error estimated by sandwich estimator :

Hazard ratio using the Sandwich Estimator

Population	HR (95% CI) p-value
Never smoked	0.67 (0.49, 0.92) p=0.0125
Oriental	0.66 (0.48, 0.91) P=0.0110
Oriental never smoked	0.37 (0.20, 0.66) P=0.0007

The need for adjustment for important prognostic factors in clinical trials is stated in the literature. Hauck et al [2] report that failure to adjust for prognostic factors in the analysis of randomized trials leads to a loss of efficiency as well as bias in the treatment effect being estimated, recommending that analyses adjust for important prognostic covariates. Further, Akawaza et al [3] report that when a trial population is heterogeneous with several strongly prognostic factors, as if often the case in advanced cancer patients, a simple logrank test can yield misleading results and should not be used. Further, the authors note that the stratified logrank test may suffer some power loss when many prognostic factors need to be considered and the number of patients within stratum is small. To address these problems, the Cox regression methods are advised.

References:

[1] ICH Topic E9. Statistical Principles for Clinical Trials. CPMP/ICH/363/96, 1996.

[2] Hauck, WW., Anderson, S., and Marcus, SM. Should We Adjust for Covariates in Nonlinear Regression Analyses of Randomized Trials? Controlled Clinical Trials, 1998, 19:249–256

[3] Akazawa, K., Nakamura, T. and Palesch, Y. Power of logrank test and Cox regression model in clinical trials with heterogeneous samples. Statistics in Medicine, 1997, 16: 583–597

サブグループ解析の頑健性に関する資料

Robustness of the subgroup analysis for non smokers, Oriental patients and non smoking Oriental patients:

In order to check the robustness of findings in the subsets of never smokers, Oriental patients and Oriental never smokers, a resampling procedure was adopted as follows:

For each subset, a given number of patients were sampled with replacement from Iressa and placebo treated patients on a 2:1 basis to reflect the trial randomization. The hazard rate amongst the sampled patients was then calculated for Iressa and placebo and the hazard ratio computed. This procedure was repeated 1000 times. The mean and spread of the resulting (log) hazard ratios was then calculated. The results are shown in Table 1.

Table 1. Results of resampling simulations in never smokers, Oriental patients and Oriental never smokers.

Subset	N[a] resampled (Iressa:placebo)	HR[b]	HR 2.5th percentile	HR 97.5th percentile
Oriental non Smokers (N=141)	20:10	0.355[c]	0.081	1.283
	40:20	0.361	0.138	0.839
	60:30	0.361	0.171	0.763
	Full resampling[d]	0.368	0.208	0.647
Orientals (N=342)	20:10	0.671	0.215	2.002
	50:25	0.681	0.339	1.368
	100:50	0.662	0.413	1.051
	150:75	0.661	0.458	1.002
	Full resampling	0.664	0.486	0.896
Non Smokers (N=375)	20:10	0.660	0.213	2.289
	50:25	0.670	0.340	1.260
	100:50	0.674	0.413	1.120
	150:75	0.673	0.438	1.001
	200:100	0.679	0.464	0.981
	Full resampling	0.681	0.496	0.930

[a] 1000 resamples per row.

[b] Hazard ratio.

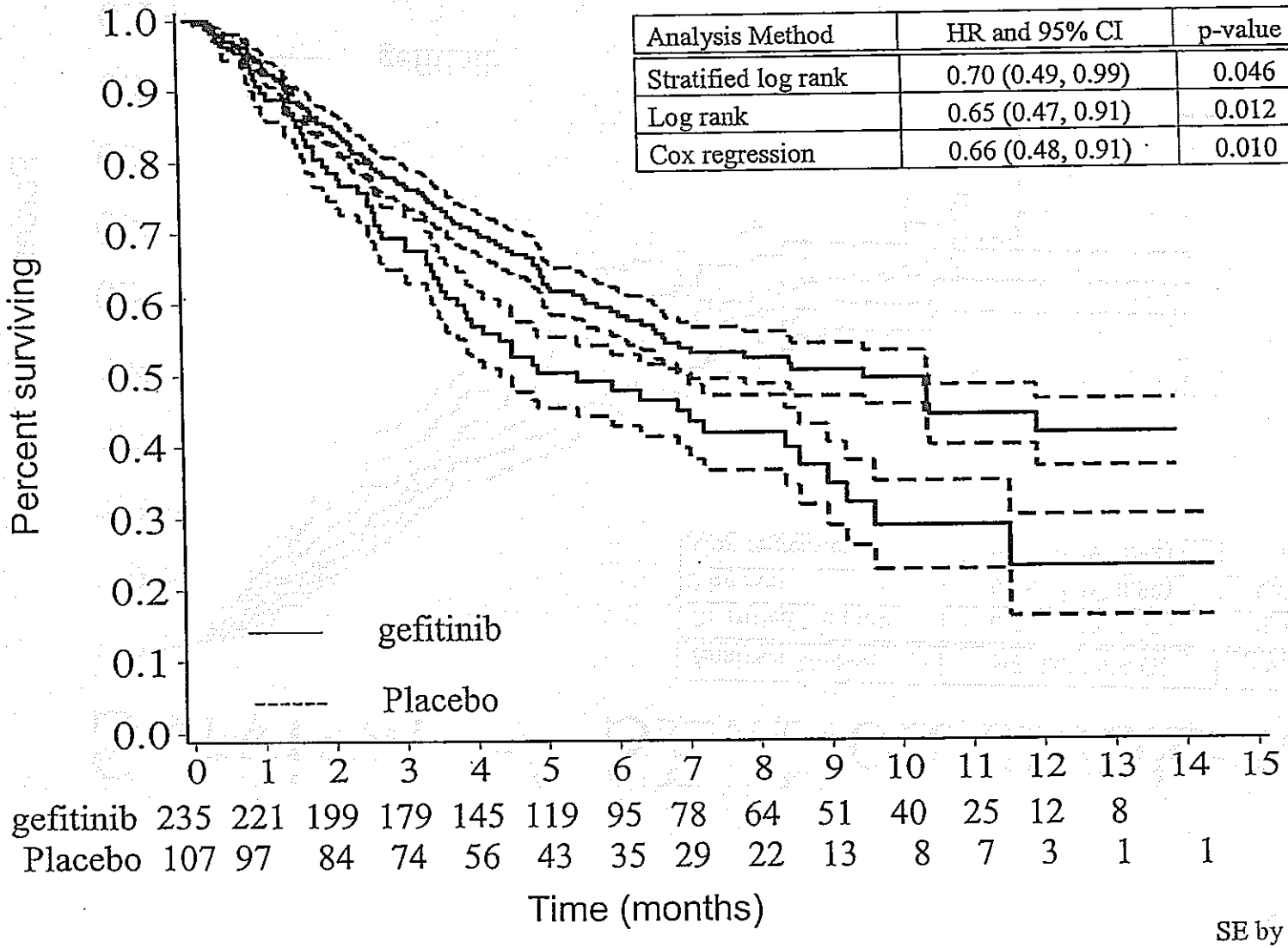
[c] Only 998 resamples returned a hazard ratio estimate; in two samples there were no deaths in the Iressa arm due to the small sample size and a hazard ratio could not be calculated.

[d] Full resampling with replacement.

The resampling results how that the findings in non smokers, Oriental and Oriental non smokers are robust. Even with small sample sizes, a treatment effect in favour of Iressa treated patients is evident. Full resampling confirms statistical significance in all three subsets.

Survival +/- SE: Orientals

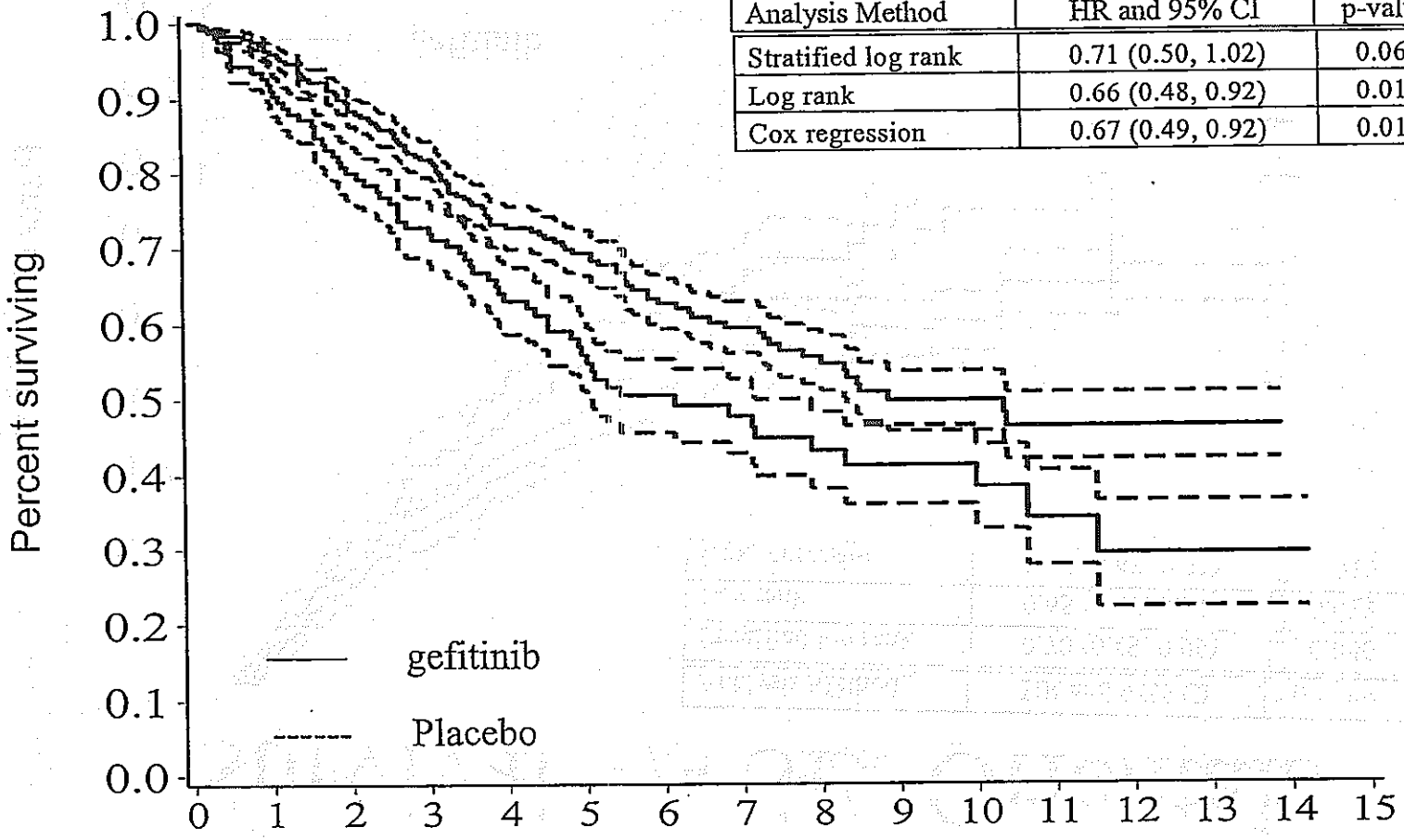
Analysis Method	HR and 95% CI	p-value
Stratified log rank	0.70 (0.49, 0.99)	0.046
Log rank	0.65 (0.47, 0.91)	0.012
Cox regression	0.66 (0.48, 0.91)	0.010



SE by Greenwoods formula

Survival +/- SE: Non-smokers

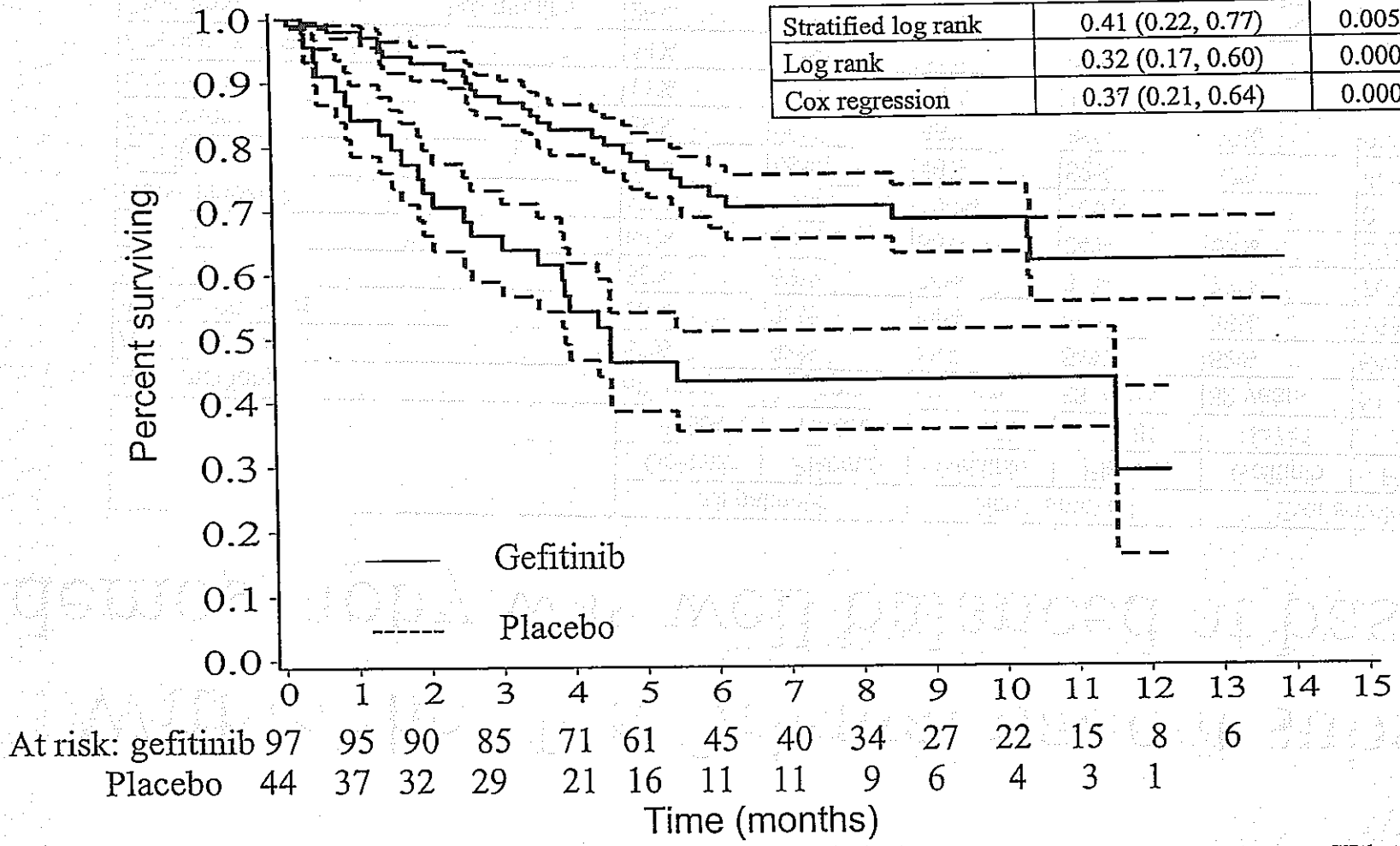
Analysis Method	HR and 95% CI	p-value
Stratified log rank	0.71 (0.50, 1.02)	0.061
Log rank	0.66 (0.48, 0.92)	0.013
Cox regression	0.67 (0.49, 0.92)	0.012



SE by Greenwoods formula

Survival +/- SE : Oriental non-smokers

Analysis Method	HR and 95% CI	p-value
Stratified log rank	0.41 (0.22, 0.77)	0.0052
Log rank	0.32 (0.17, 0.60)	0.0003
Cox regression	0.37 (0.21, 0.64)	0.0004



SE by Greenwoods formula

東洋人及び非喫煙者の患者背景に関する資料

Within the Non Oriental patient subset, demography was well balanced at baseline

		All patients		Never smoked		Ever smoked	
		Gefitinib	Placebo	Gefitinib	Placebo	Gefitinib	Placebo
		N=894	N=456	N=153	N=81	N=741	N=375
Age (median)		62 years	61 years	62 years	63 years	62 years	61 years
Age < 65 years		61%	62%	56%	54%	62%	64%
Age >= 65 years		39%	38%	44%	46%	38%	36%
Male		69%	69%	34%	37%	77%	76%
PS 0-1		64%	68%	66%	64%	63%	69%
Never smoked		17%	18%	100%	100%	0	0
2nd line		47%	45%	48%	52%	47%	44%
Refractory		89%	90%	86%	85%	89%	90%
Intolerant		11%	10%	13%	12%	11%	9%
Adenocarcinoma histology		44%	45%	71%	62%	38%	41%
Time from diagnosis to randomisation	<6 months	26%	23%	35%	21%	24%	24%
	6-12 months	36%	40%	29%	42%	38%	39%
	> 12 months	37%	37%	35%	37%	38%	37%
Best response to prior chemotherapy	CR/PR	17%	19%	11%	24%	18%	18%
	SD	37%	38%	42%	39%	36%	38%
	PD/NE	46%	43%	46%	33%	45%	44%

Within the Oriental patient subset, demography was well balanced at baseline

		All patients		Never smoked		Ever smoked	
		Gefitinib	Placebo	Gefitinib	Placebo	Gefitinib	Placebo
		N=235	N=107	N=97	N=44	N=138	N=63
Age (median)		61 years	61 years	58 years	55 years	64 years	64 years
Age < 65 years		59%	64%	68%	82%	53%	52%
Age >= 65 years		41%	36%	32%	18%	47%	48%
Male		60%	60%	21%	27%	87%	83%
PS 0-1		72%	72%	72%	70%	72%	73%
Never smoked		41%	41%	100%	100%	0	0
2nd line		54%	65%	52%	64%	55%	65%
Refractory		93%	97%	94%	100%	93%	95%
Intolerant		7%	3%	6%	0	7%	5%
Adenocarcinoma histology		64%	64%	77%	84%	55%	49%
Time from diagnosis to randomisation	<6 months	25%	32%	22%	41%	27%	25%
	6-12 months	40%	38%	38%	34%	41%	41%
	> 12 months	35%	30%	40%	25%	32%	33%
Best response to prior chemotherapy	CR/PR	21%	21%	22%	16%	21%	24%
	SD	34%	32%	35%	32%	34%	32%
	PD/NE	44%	48%	43%	52%	45%	44%

癌の組織型、性別、喫煙歴の別による有効性に関する資料　別添資料 13-1

癌の組織型、性別、喫煙歴の別による有効性

癌の組織型、性別、喫煙歴の別によるイレッサの有効性の日本及びアジア地域での報告についてを、以下の表にまとめた。

Fukuoka et al（IDEAL1 試験日本人サブセット）

	奏効	非奏効	病勢ｺﾝﾄﾛｰﾙ	非病勢ｺﾝﾄﾛｰﾙ
女性	6	10	13	3
男性	8	27	23	12
腺癌	13	25	30	8
非腺癌	1	12	6	7

[奏効率/性別]　感度（奏効例に占める女性の割合）　6/14（42.9%）
特異度（非奏効例に占める男性の割合）　27/37（73.0%）
[奏効率/組織型] 感度（奏効例に占める腺癌の割合）　13/14（92.9%）
特異度（非奏効例に占める非腺癌の割合）　12/37（32.4%）
[病勢ｺﾝﾄﾛｰﾙ率/性別]　感度（病勢ｺﾝﾄﾛｰﾙ例に占める女性の割合）　13/36（36.1%）
特異度（非病勢ｺﾝﾄﾛｰﾙ例に占める男性の割合）　12/15（80%）
[病勢ｺﾝﾄﾛｰﾙ率/組織型] 感度（病勢ｺﾝﾄﾛｰﾙ例に占める腺癌の割合）　30/36（83.3%）
特異度（非病勢ｺﾝﾄﾛｰﾙ例に占める非腺癌の割合）7/15（46.7%）

Takano et al

	奏効	非奏効
女性	17	15
男性	15	51
腺癌	31	50
非腺癌	1	16
非喫煙者	20	12
喫煙者	12	54

[性別]　感度（奏効例に占める女性の割合）　17/32（53.1%）
特異度（非奏効例に占める男性の割合）　51/66（77.3%）
[組織型] 感度（奏効例に占める腺癌の割合）　31/32（96.9%）
特異度（非奏効例に占める非腺癌の割合）　16/66（24.2%）
[喫煙歴] 感度（奏効例に占める非喫煙者の割合）　20/32（62.5%）
特異度（非奏効例に占める喫煙者の割合）　54/66（81.8%）

Kaneda et al

	奏効	非奏効
女性	14	23
男性	6	58
腺癌	20	61
非腺癌	0	20
非喫煙者	15	40
喫煙者	5	41

[性別] 感度（奏効例に占める女性の割合） 14/20 (70%)
特異度（非奏効例に占める男性の割合） 58/81 (71.6%)
[組織型] 感度（奏効例に占める腺癌の割合） 20/20 (100%).
特異度（非奏効例に占める非腺癌の割合） 20/81 (24.7%)
[喫煙歴] 感度（奏効例に占める非喫煙者の割合） 15/20 (75%)
特異度（非奏効例に占める喫煙者の割合） 41/81 (50.6%)

Hotta et al

	奏効	非奏効
女性	6	13
男性	9	28
腺癌	13	32
非腺癌	2	9
喫煙量 BI＜600	8	20
喫煙量 BI≧600	7	21

BI: Brinkman Index

[性別] 感度（奏効例に占める女性の割合） 6/15 (40%)
特異度（非奏効例に占める男性の割合） 28/41 (68.3%)
[組織型] 感度（奏効例に占める腺癌の割合） 13/15 (86.7%)
特異度（非奏効例に占める非腺癌の割合） 9/41 (22.0%)
[喫煙歴] 感度（奏効例に占める喫煙量 BI＜600 の割合） 8/15 (53.3%)
特異度（非奏効例に占める喫煙量 BI≧600 の割合） 21/41 (51.2%)

Kim et al

	奏効	非奏効
女性	10	9