

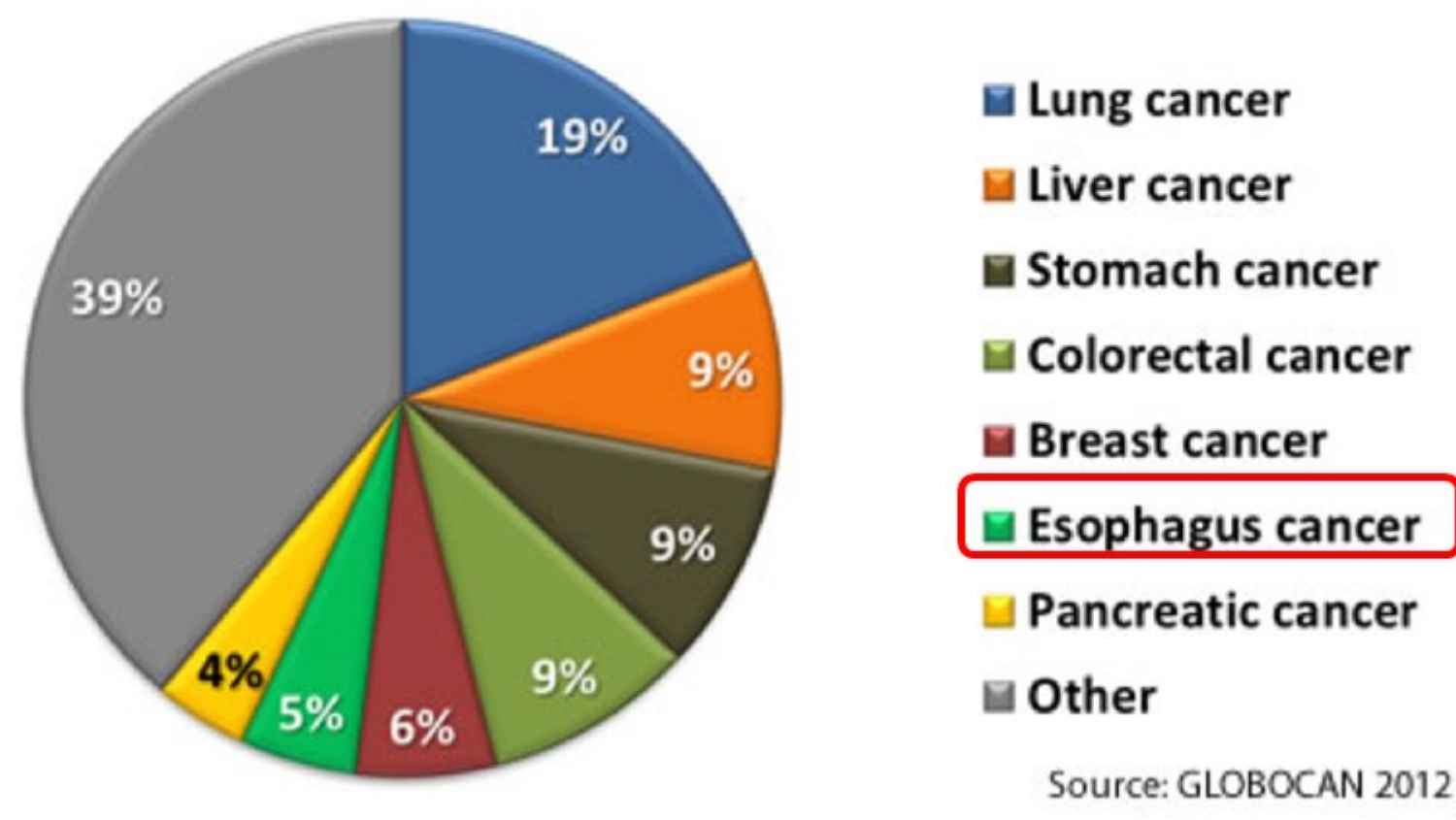
Serum biomarkers of chemoradiosensitivity in esophageal cancer is identified by the targeted metabolomics approach.



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Fujigaki S¹, Nishiumi S¹, Kobayashi T¹, Yoshida M^{1,2,3}.

Esophageal Cancer

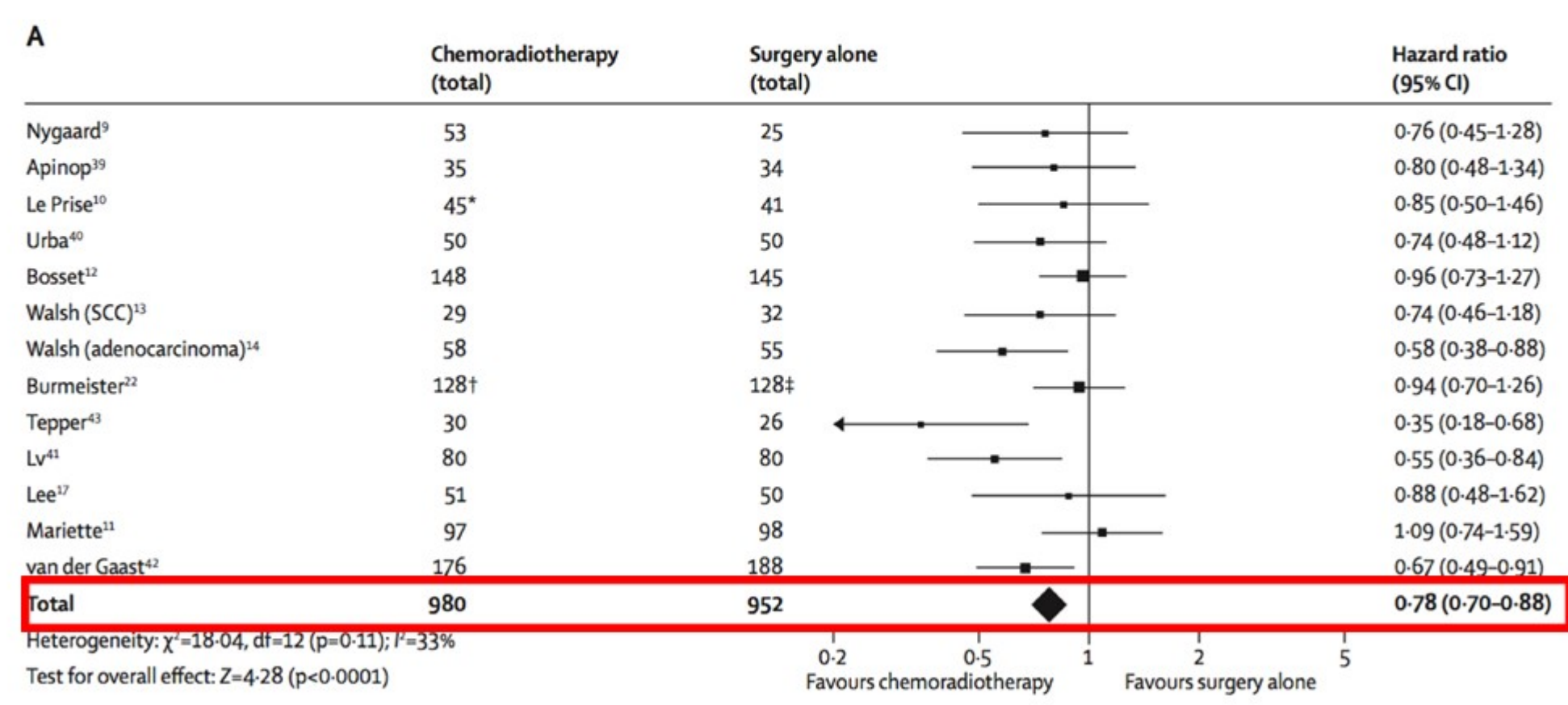
Most Common Causes of Cancer Death Worldwide in 2012



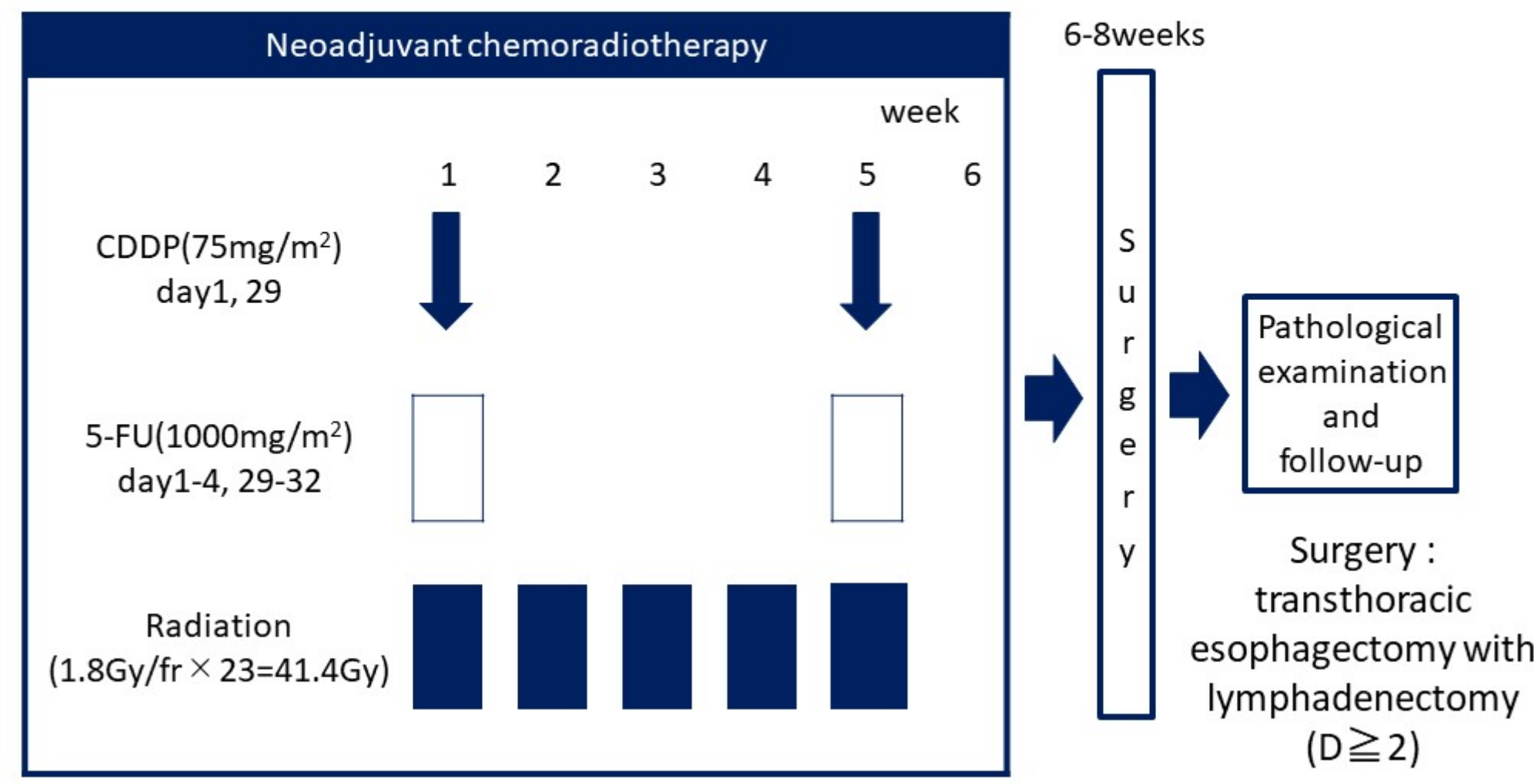
Esophageal Cancer

Sjoquist KM, Burmeister BH, Smithers BM et al. *Lancet Oncol.* 2011;12(7):681.

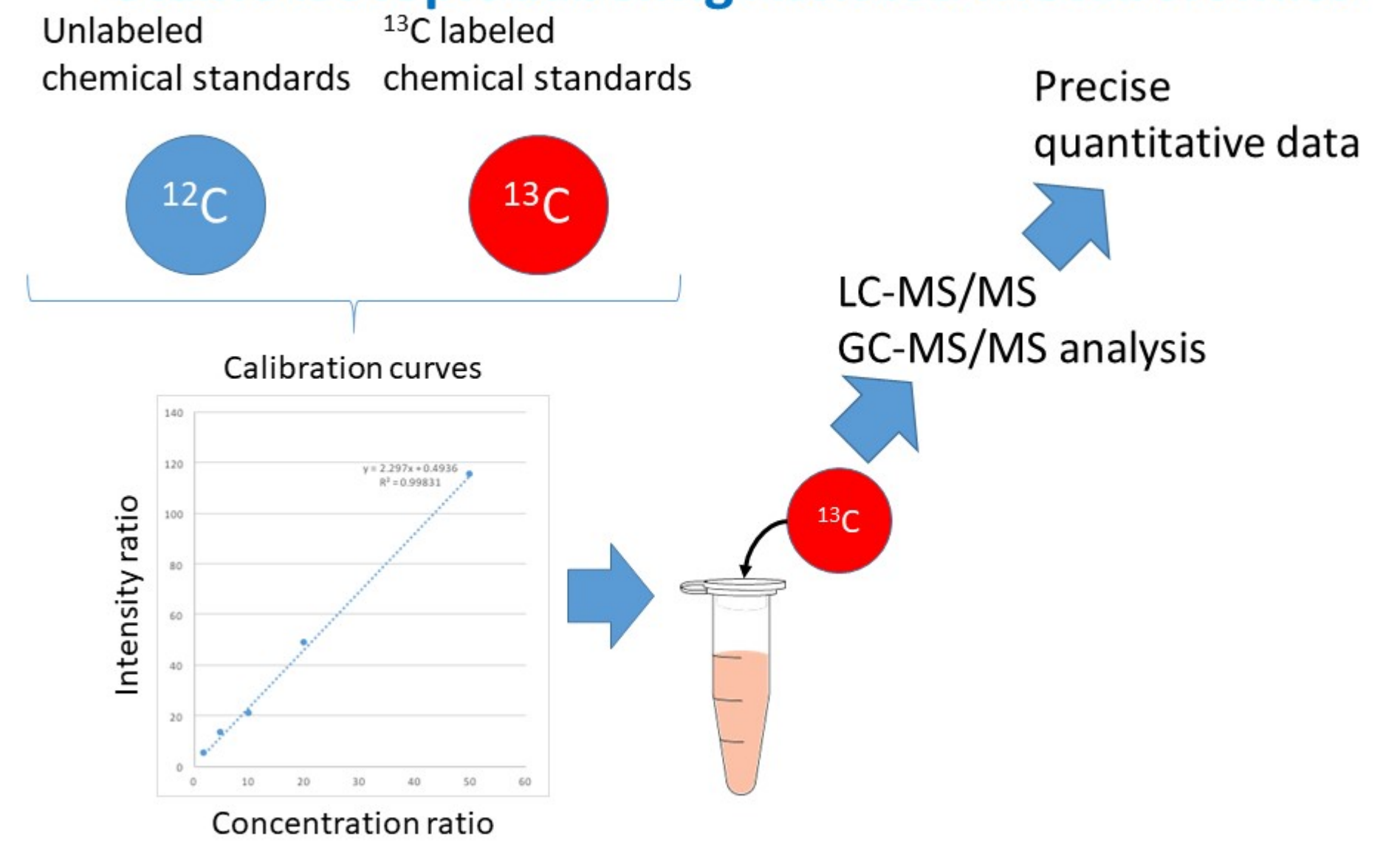
Pooled estimates for all-cause mortality for the trials that compared neoadjuvant chemoradiotherapy followed by surgery with surgery alone



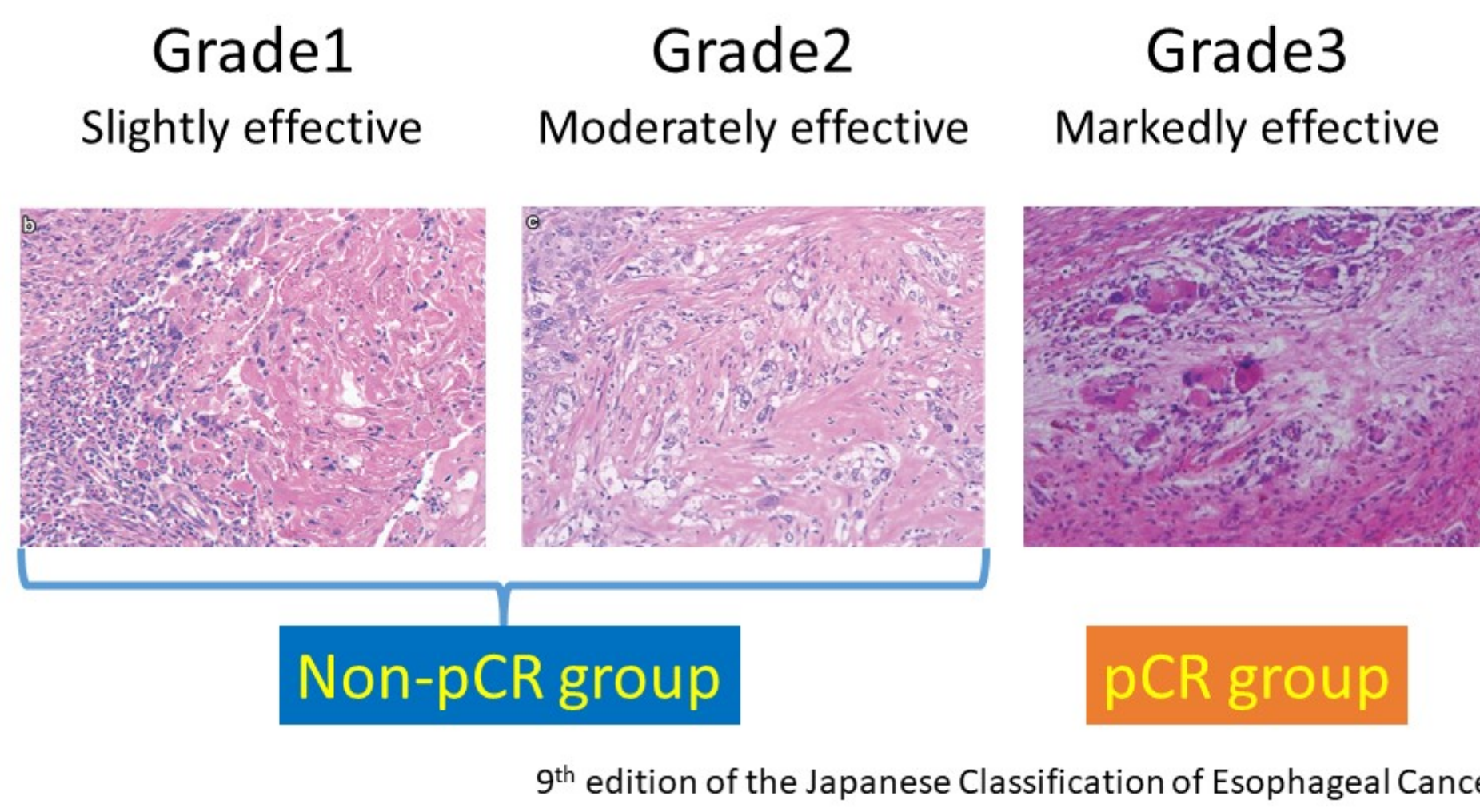
Feasibility Study of Neoadjuvant Chemoradiotherapy with Cisplatin plus 5-fluorouracil and Elective Nodal Irradiation for Stage II / III Esophageal Squamous Cell Carcinoma



Stable Isotopic Labeling Assisted Metabolomics



Pathological Examination (Histological Response)

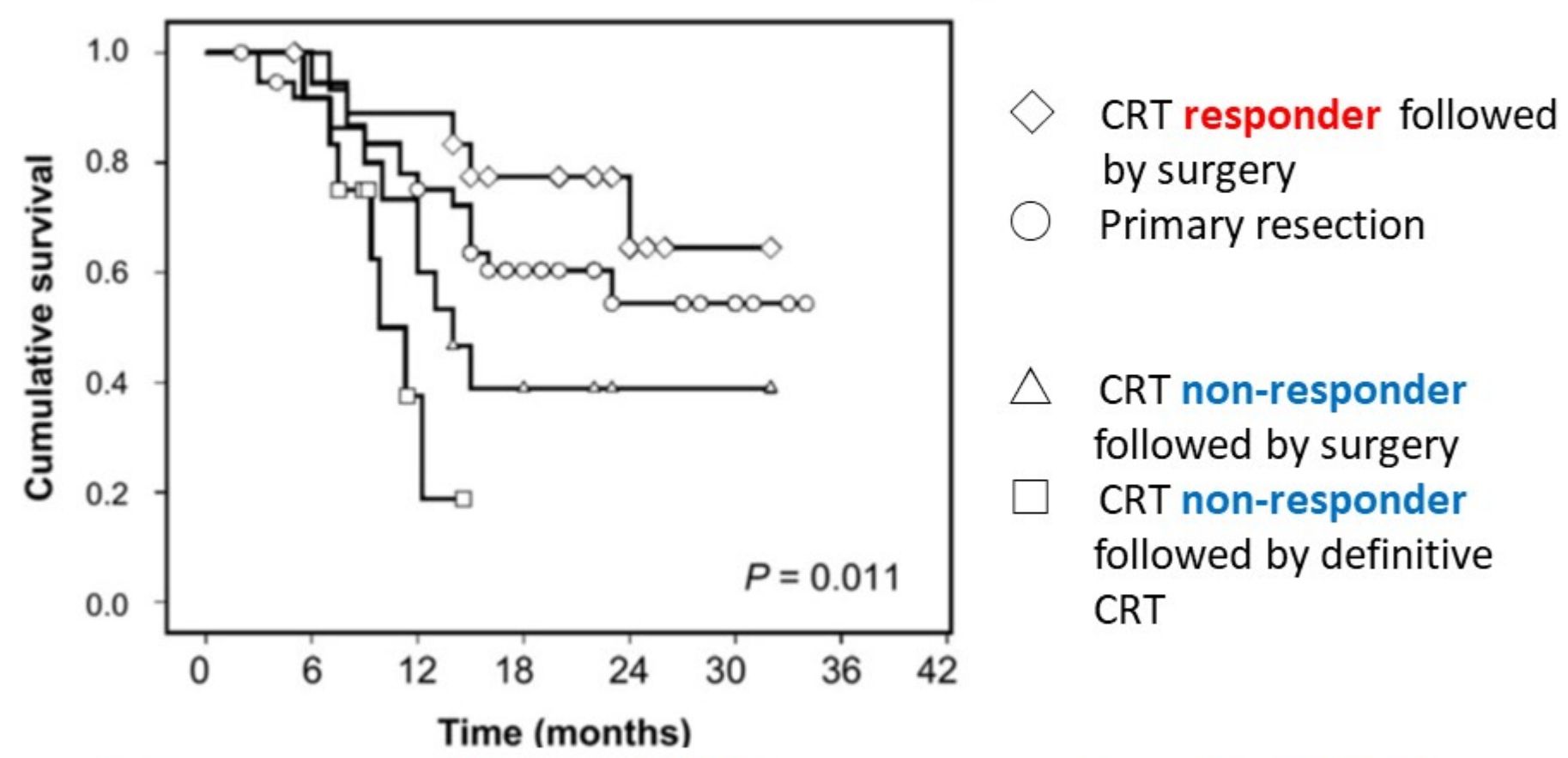


Quantitative Measurement

Metabolites	Non-pCR (n=13) Mean (µM)	pCR (n=13) Mean (µM)	Fold change	p-value
Arabitol	13.298	3.723	0.28	0.0086
Betaine	62.015	45.902	0.74	0.0613
Glycine	360.556	270.941	0.75	0.0345
L-Aspartate	42.571	34.047	0.8	0.0734
L-Serine	133.991	96.960	0.72	0.0106
L-Arginine	139.611	108.265	0.78	0.0373

Comparison of Neoadjuvant Chemoradiotherapy Responders and Non-responders

P-K. Hsu et al. / *Interact Cardiovasc Thorac Surg.* 2013;17:460-6



Primary resection vs CRT non-responder, $P = 0.036$

Characteristics of the Subjects

Variable	Histological response		p-value (Fisher's exact t-test)
	Non-pCR (n=13)	pCR (n=13)	
Age			0.411
< 65 years	10	7	
≥ 65 years	3	6	
Gender			0.22
Male	10	13	
Female	3	0	
Tumor location			0.428
Lt	4	7	
Mt	8	6	
Ut	1	0	
Clinical stage			0.529
II A	1	0	
II B	2	5	
III A	6	4	
III B	4	4	

Prediction Accuracy of pCR

Metabolites	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Cut-off value (µM)
Arabitol	0.799 (0.616-0.981)	100	61.5	5.384
Betaine	0.675 (0.437-0.912)	92.3	61.5	55.364
Glycine	0.722 (0.517-0.927)	84.6	61.5	336.315
L-Aspartate	0.692 (0.48-0.905)	84.6	61.5	39.582
L-Serine	0.781 (0.57-0.992)	92.3	76.9	110.601
L-Arginine	0.71 (0.504-0.917)	92.3	46.2	138.768

Aim

To avoid unfavorable outcomes unnecessary adverse events, reliable methods for predicting the response of esophageal cancer to chemoradiotherapy are desired.

Serum Metabolites Associated with the Chemoradiosensitivity

Metabolites	Subclass	Non-pCR (n=13) Mean	pCR (n=13) Mean	Fold change*	p-value
Arabitol	Sugar alcohols	0.047	0.011	0.230	0.0066
3-Aminoglutaric acid	Amino acids	0.561	0.396	0.705	0.0313
Uracil	Pyrimidines	0.0012	0.0009	0.726	0.0378
Betaine	Amino acids	1.645	1.135	0.690	0.0103
Glycine	Amino acids	1.231	0.99	0.804	0.0103
L-Aspartate	Amino acids	1.249	0.958	0.767	0.021
L-Serine	Amino acids	4.43	3.509	0.792	0.024
L-Arginine	Amino acids	5.386	4.147	0.770	0.0313
2-Hydroxyglutaric acid	Organic acids	0.023	0.016	0.726	0.0402

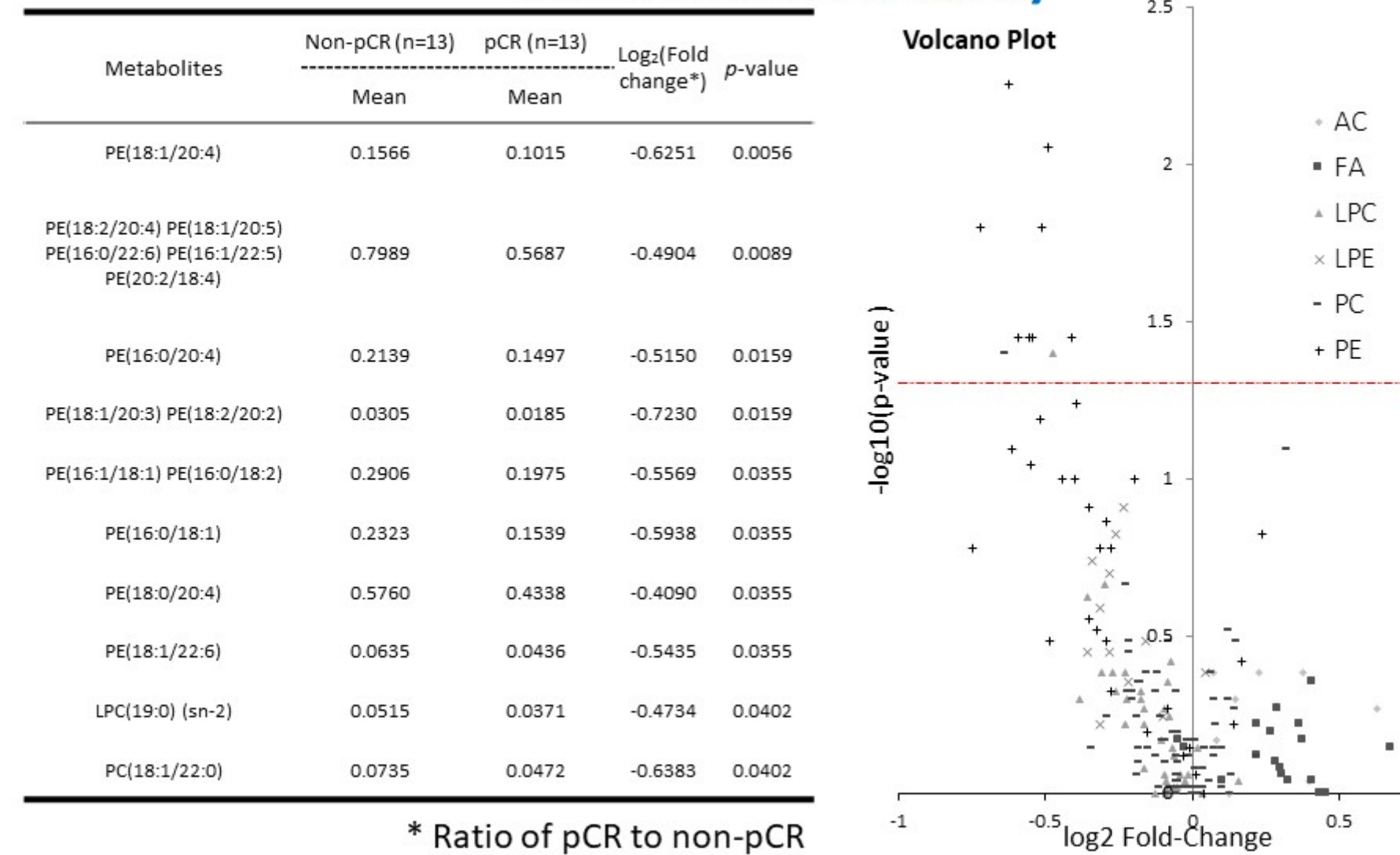
* Ratio of pCR to non-pCR

Association of High Serum L-Serine with Shorter Time to Progression (TTP)

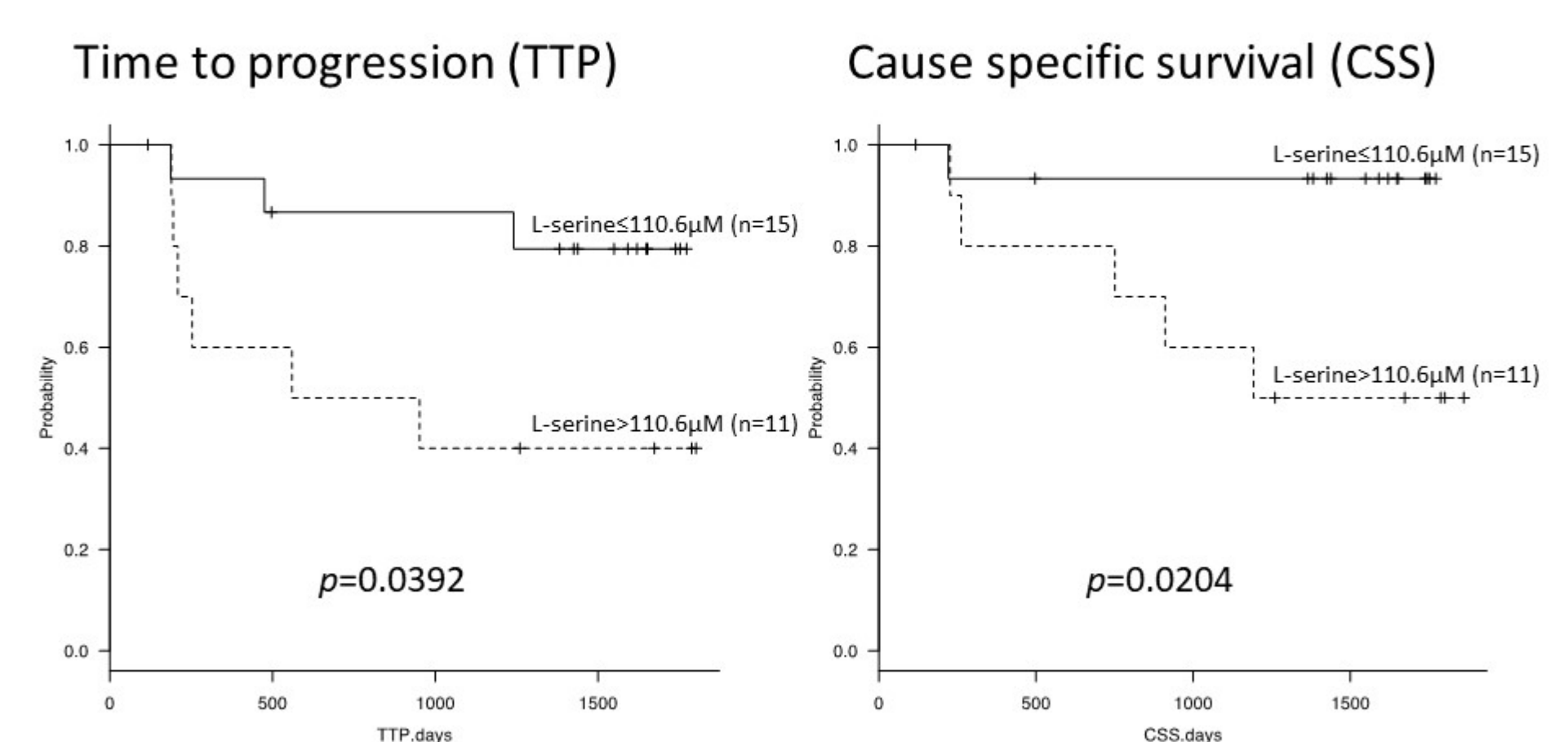
Cox regression model analysis of prognostic significance

Variable	Univariate analysis		
	HR	95% CI	p-value
Age			
≥65 years/<65 years	0.46	0.096-2.24	0.339
Clinical stage			
III A and III B / II A and II B	5.33	0.97-99.3	0.0551
Serum Arabitol			
>5.384 µM/≤5.384 µM	3.08	0.81-12.5	0.097
Serum Glycine			
>336.3 µM/≤336.3 µM	2.34	0.62-9.52	0.2056
Serum L-Serine			
>110.6 µM/≤110.6 µM	3.91	1.02-18.7	0.0463
Serum L-Arginine			
>138.8 µM/≤138.8 µM	2.77	0.68-10.5	0.1463

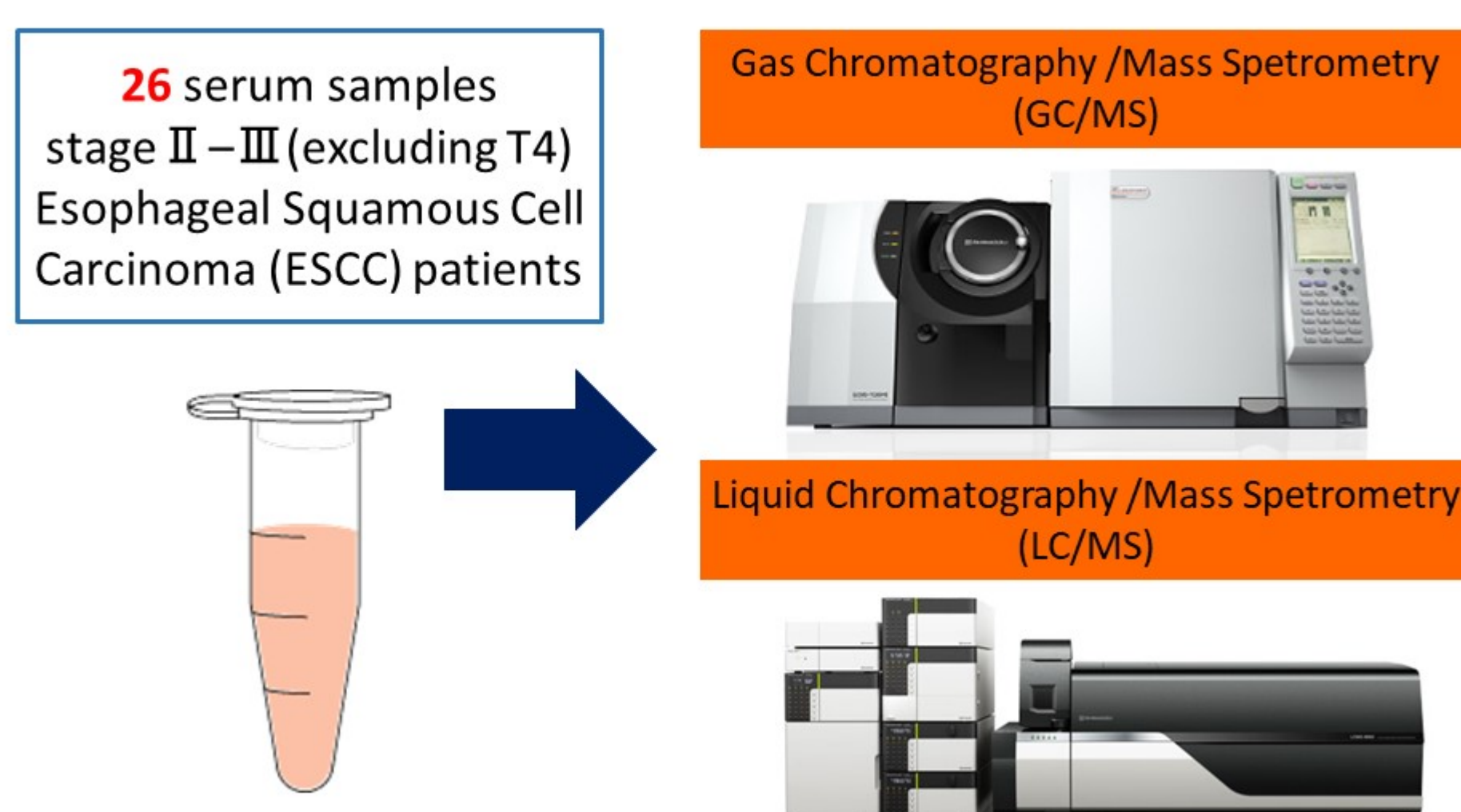
Serum Metabolites Associated with the Chemoradiosensitivity



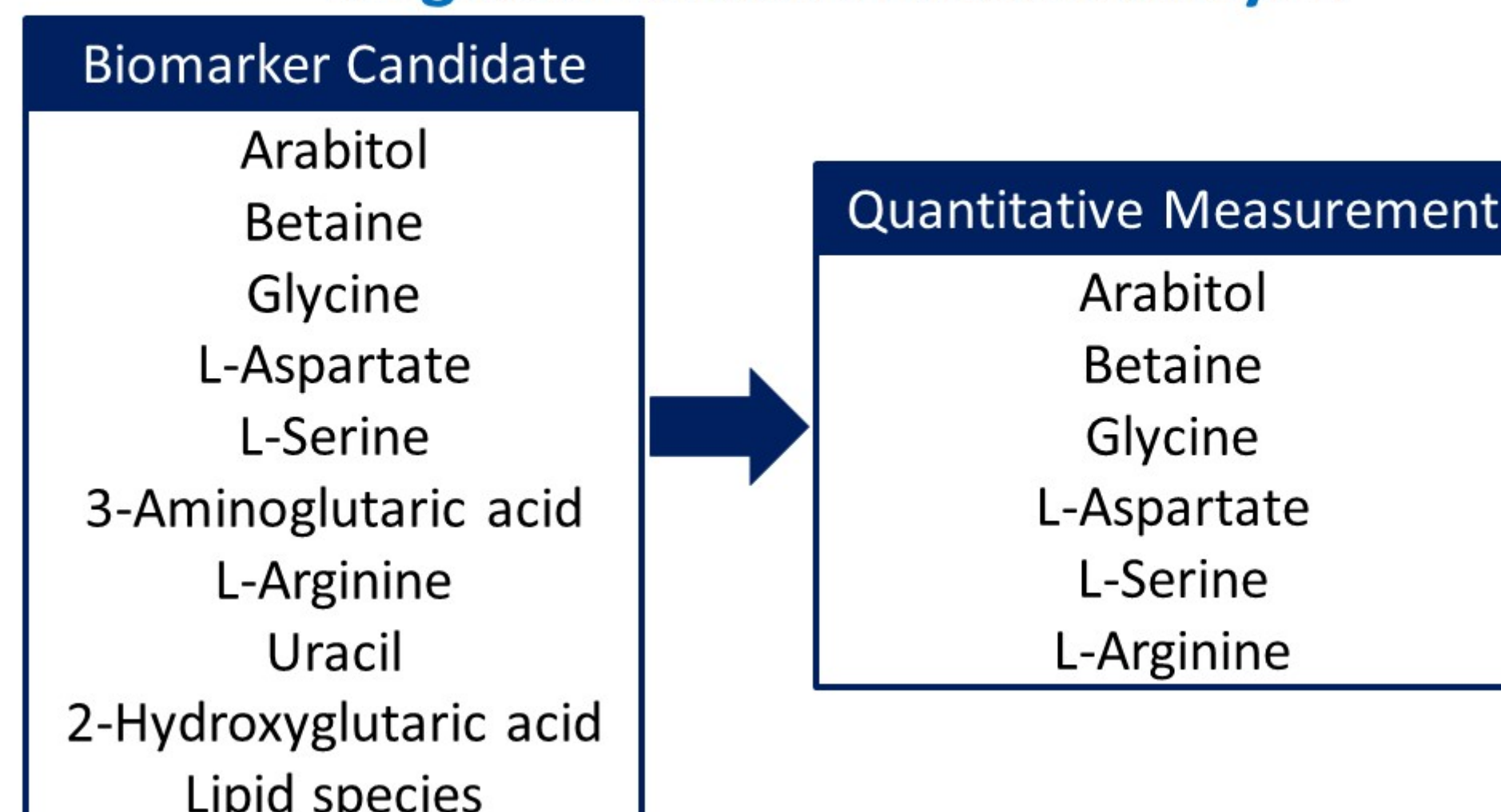
Serum L-Serine was Significantly Correlated with Long-term Prognosis (Time to Progression and Cause Specific Survival)



Multiplexed Metabolomics Approach



Targeted Metabolomics Analysis



Conclusion

- In the comprehensive metabolomics analysis, it was confirmed that the serum metabolite profiles of the pCR group were different from those of the non-pCR group.
- The pCR group exhibited significantly lower serum concentrations of serine, glycine, arginine, and arabitol than the non-pCR group.
- The serum concentration of serine could be used to predict the prognosis of ESCC patients who received neoadjuvant chemoradiotherapy.