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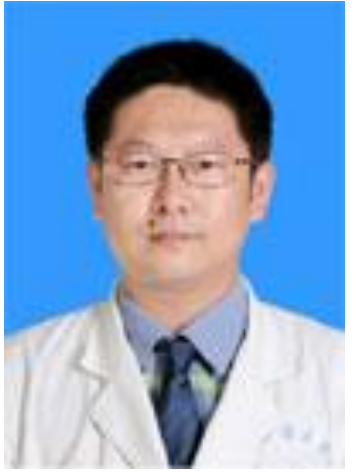
SNP in CD133 Predict Recurrence and Metastasis in NSCLC With Radiotherapy

Affiliated Cancer Hospital of Zhengzhou University, China
Henan Cancer Hospitaly, China
The University of Texas M.D. Anderson Cancer Center, USA
Qiming Wang

I have no COI with regard to our presentation.



- Postdoctoral Fellow, , The University of Texas MD Anderson Cancer Center, Houston, TX, USA

- Professor, Oncology, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, Henan, P.R.C.

Lung Cancer

- local recurrence, distant metastasis and treatment resistance are the main reasons leading to failure of treatment

Cancer Stem Cell (CSC)

- ★ initiate tumor formation
- ★ differentiate along multipotent pathways
- ★ resistant to conventional chemotherapy and radiotherapy
- ★ formed metastasis as a “seed”

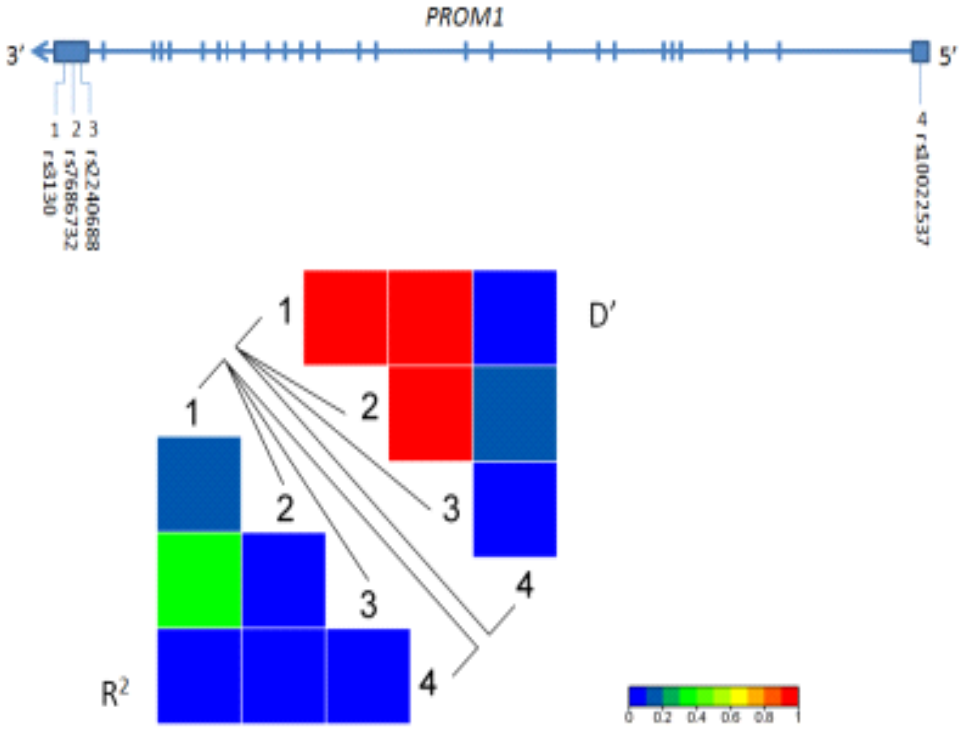
Characteristics of Cancer Stem Cell

- ★ in vivo: tumourigenicity
- ★ in vitro: spheroid colony formation
- ★ self-renewal (by symmetric and asymmetric division)
- ★ differentiation into the heterogeneous non-tumorigenic cancer cell types
- ★ resistant to conventional chemotherapy and radiotherapy
- ★ expression of specific surface markers（CD133, CD44, ALDH, SOX-2、、Bmi-l、survivin、ABCG-2）

CD133

- ★ *PROM1，4p15*
- ★ *thought to serve as a marker of asymmetric division, lineage plasticity, tumor cell dormancy, and inherent embryonic gene expression*
- ★ *most common surface markers of stem cell and CSC*

Functional SNP of CD133



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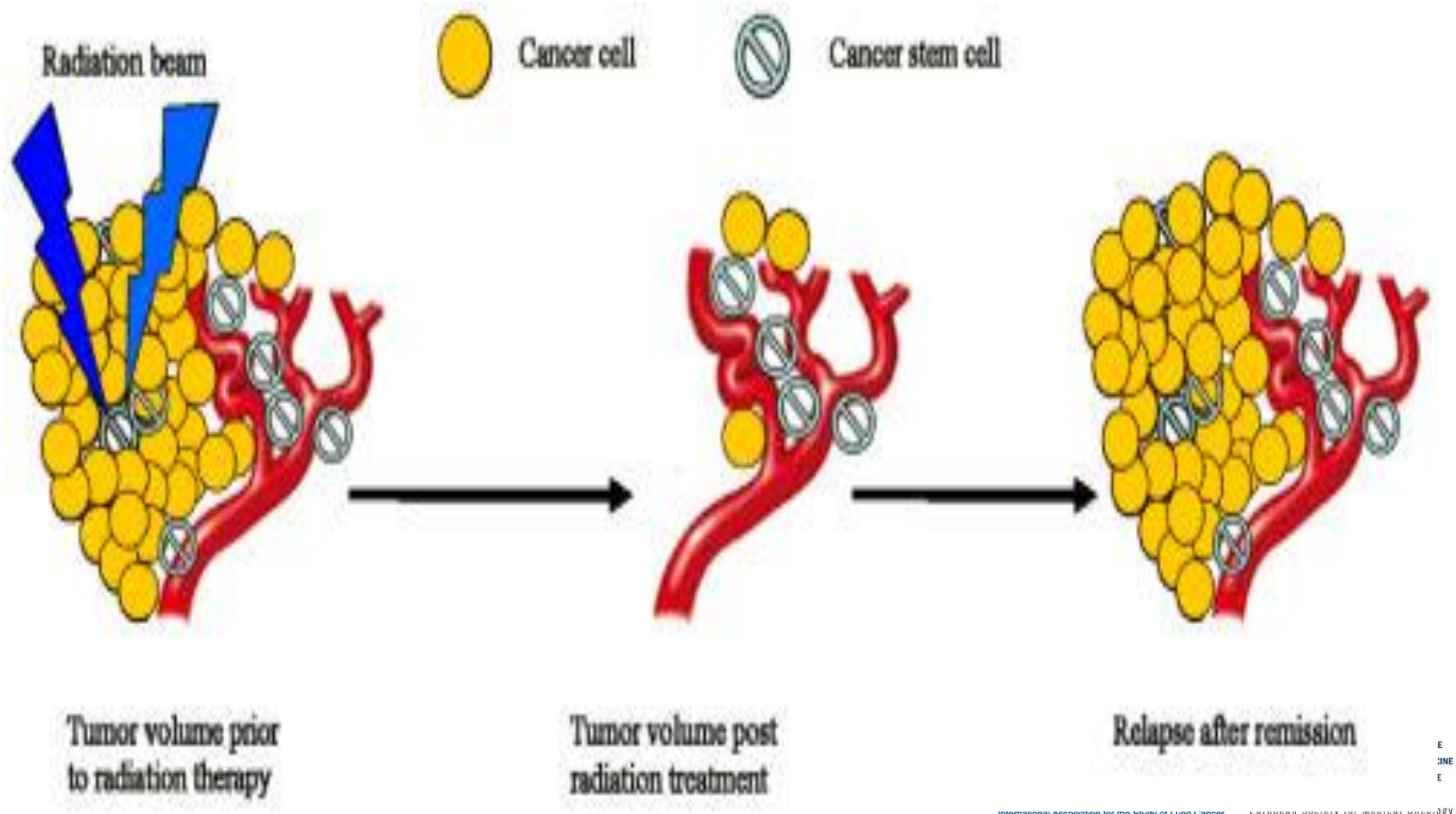
Lung cancer stem cell and Radiotherapy



Hypothesis

- functional SNPs in CD133 may induce resistance to chemotherapy or radiation and impact prognosis of lung cancer patients

Study Design

- we genotyped four selected potential functional SNPs in PROM1 in 393 NSCLC patients received definitive radiotherapy
- SNP: rs2240688A>C, rs7686732C>G, rs10022537T>A, and rs3130C>T
- estimated their associations with LRFS, DMFS, and OS by Cox proportional hazards model.

		LRFS		DMFS		OS	
	N	Event	P*	Event	P*	Event	P*
Age <65	202	162 (80)		164 (81)		153 (76)	
Age ≥65	191	162 (85)	0.206	163 (85)	0.92	157 (82)	0.147
Male	216	180 (83)		181 (84)		175 (81)	
Female	177	144 (81)	0.309	146 (82)	0.792	135 (76)	0.263
KPS≥ 80	317	258 (81)		260 (82)		244 (77)	
KPS< 80	76	66 (87)	0.079	67 (88)	0.136	66 (87)	***0.023***
White	328	267 (81)		269 (82)		254 (77)	
Black	65	57 (88)	0.399	58 (89)	0.413	56 (86)	0.408
Stage I, II	55	40 (73)		40 (73)		40 (73)	
Stage III, IV	336	282 (84)	***0.015***	285 (85)	***0.002***	268 (80)	***0.039***
Squamous	138	118 (86)		120 (87)		116 (84)	
Adeno	145	116 (80)	0.035	117 (81)	0.533	106 (73)	***0.017***
Other	110	90 (82)	0.261	90 (82)	0.826	88 (80)	0.391
Ever Smoking	359	295 (82)		297 (83)		285 (79)	
Never Smoking	34	29 (85)	0.613	30 (88)	0.33	25 (74)	0.821

		LRFS		DMFS		OS	
Chemotherapy	N	Event	P*	Event	P*	Event	P*
No	35	28 (80)		28 (80)		28 (80)	
Yes	358	296 (83)	0.957	299 (84)	0.788	282 (79)	0.929
MLD < 19.0	181	140 (77)		140 (77)		132 (73)	
MLD ≥ 19.0	181	155 (86)	***0.005***	158 (87)	***0.006***	149 (82)	***0.002***
dose < 66Gy	185	158 (85)		156 (84)			
dose ≥ 66Gy	208	166 (80)	0.06	171 (82)	0.174	0.237	0.111
IMRT	167	131 (78)		131 (78)		120 (72)	
3D CRT	177	155 (88)	0.88	157 (89)	0.237	153 (86)	0.216
Other	49	38 (78)	0.944	39 (80)	0.842	37 (76)	0.923
GTV <108	173	130 (75)		130 (75)		120 (69)	
GTV ≥108	174	152 (87)	***<0.0001***	155 (89)	***<0.0001***	149 (86)	***<0.0001***

Results

- Only rs2240688 SNPs were associated with LRFS and DMFS .
- Specifically, patients with the rs2240688C variant genotypes (AC/CC) had longer LRFS (adjusted P=0.023) and DMFS (adjusted P=0.032) than did patients with the AA genotypes.
- In stratification analysis, associations of the AC/CC variant genotypes with LRFS, DMFS, and OS were strongest among patients with stage III-IV disease, or those who received <66 Gy .

rs2240688 could Predict LRFS and DMFS

Fig 1A LRFS and rs2240688 genotypes

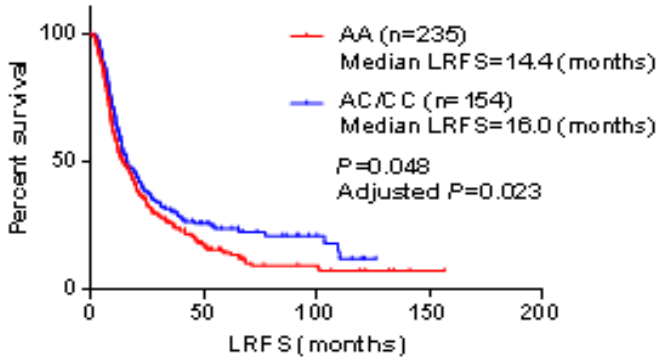


Fig 1B DMFS and rs2240688 genotypes

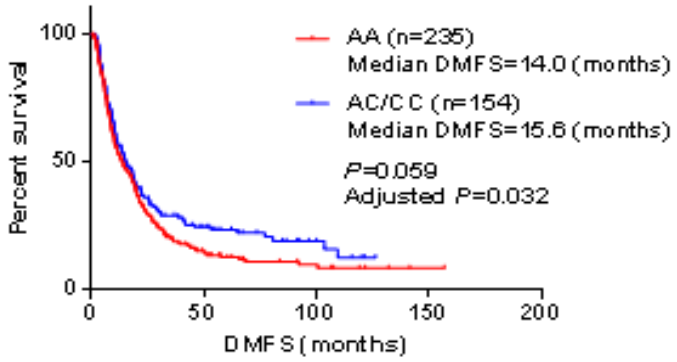
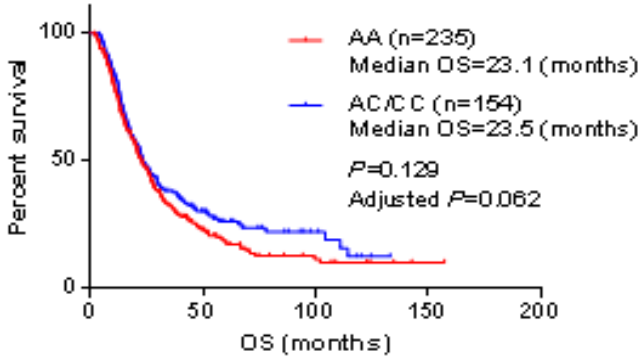


Fig 1C OS and rs2240688 genotypes



stratification analysis: among patients with stage III-IV disease

Fig 2A. Patients with stage III-IV

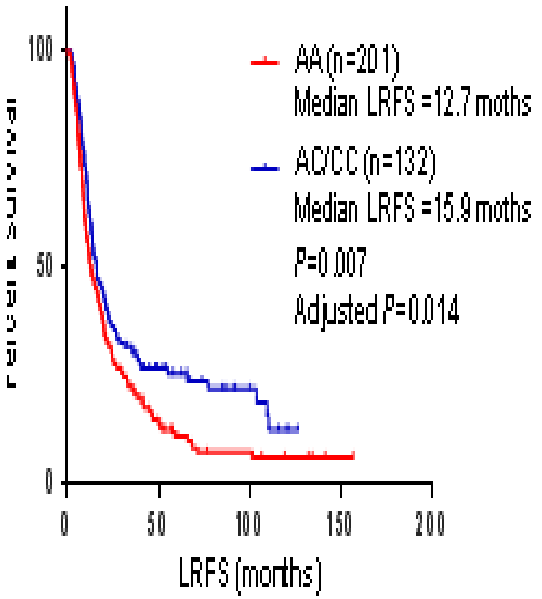


Fig 2B. Patients with stage III-IV

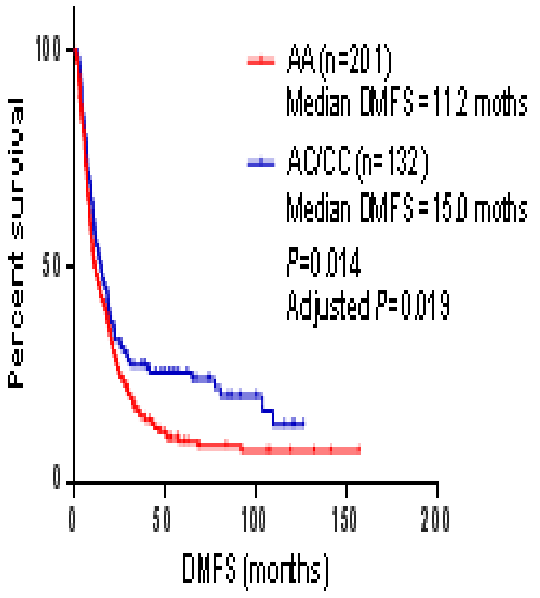
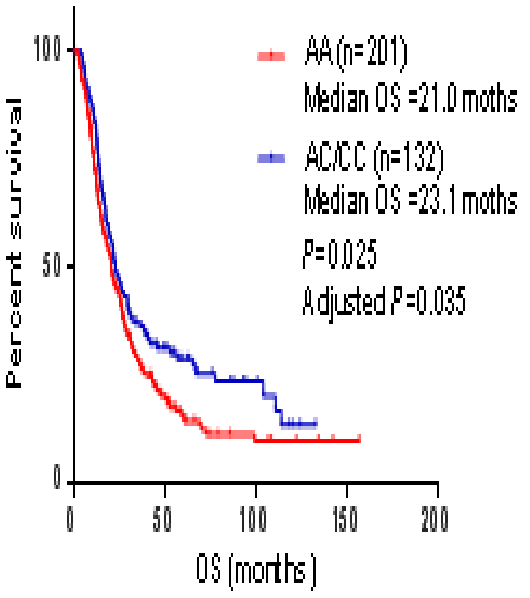


Fig 2C. Patients with stage III-IV



stratification analysis: among patients received <66 Gy

Fig 2D. Patients with radiation dose<66Gy

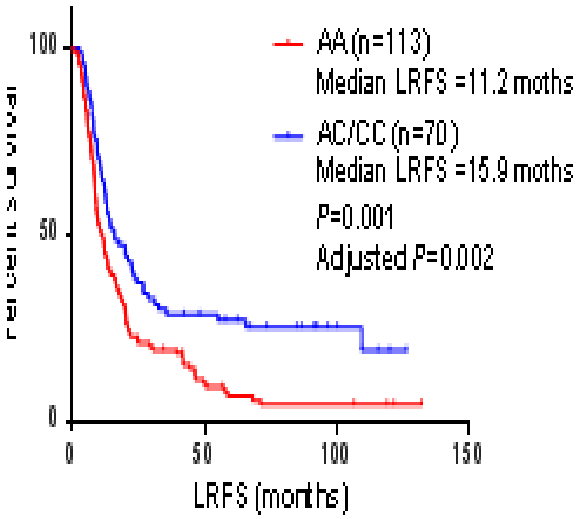


Fig 2E. Patients with radiation dose<66Gy

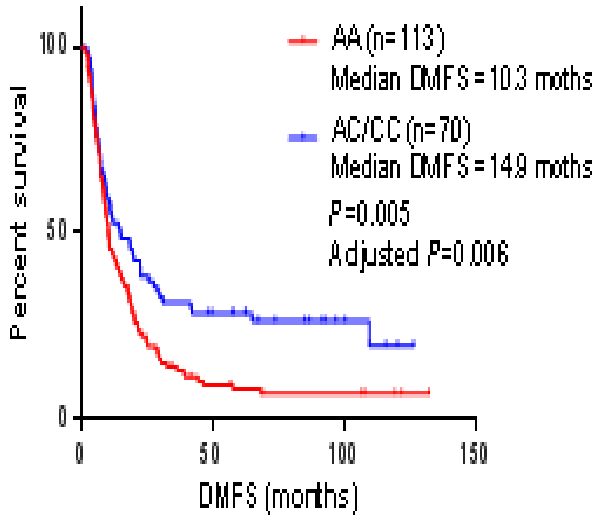
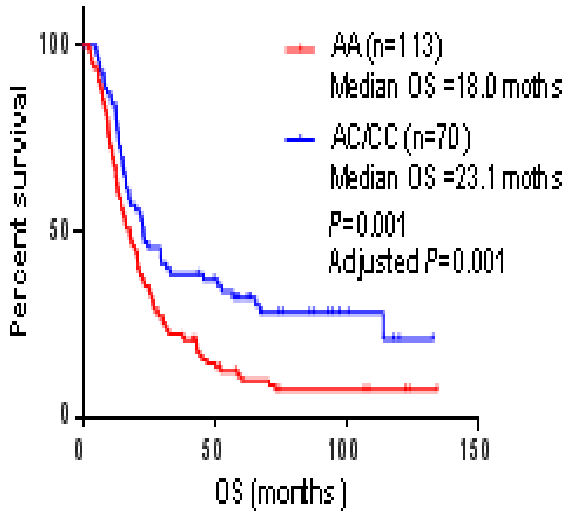


Fig 2F. Patients with radiation dose<66Gy



stratification analysis: among patients with squamous carcinoma or with chmotherapy

Fig 2I. Patients with chemotherapy

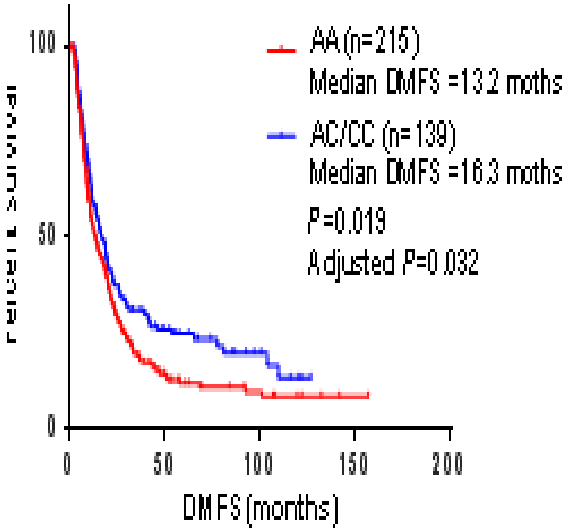


Fig 2G. Patients with squamous cell carcinoma

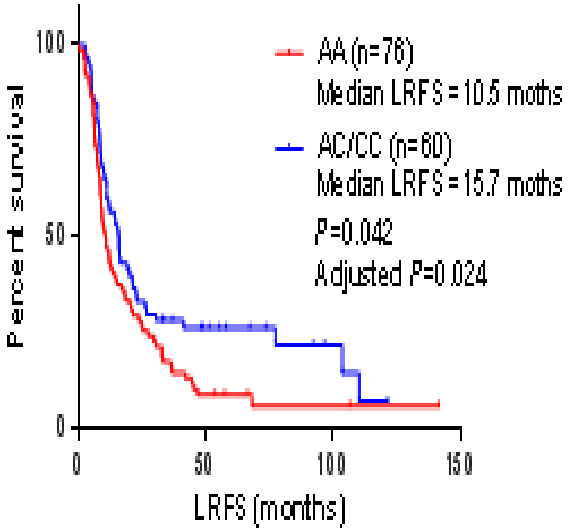
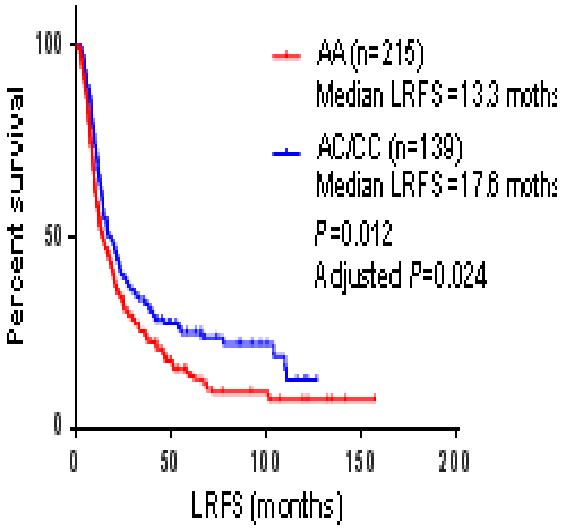


Fig 2H. Patients with chemotherapy



Discussion

- radiation resistant and cisplatin resistant subpopulations of NSCLC cells had putative stem cell-like signatures including CD133 both in vitro and in vivo
- the rs2240688 A-to-C transition gained a new binding site of the microRNA hsa-miR-135a/b and decreased the CD133 expression
- TT in rs3130 showed a significantly increased PFS in patients with metastatic colorectal cancer treated with bevacizumab-based chemotherapy
- A microRNA-135a/b binding polymorphism in CD133 confers decreased risk and favorable prognosis of lung cancer in Chinese by reducing CD133 expression.Cheng M, Yang L, Yang R,et al.Carcinogenesis. 2013 May 28.

Conclusion

- functional SNPs rs2240688 in cancer stem cell marker gene CD133 could predict radiotherapy and chemotherapy resistance among NSCLC patients, might be a promising biomarker of CSCs to predict prognosis and optimize treatment strategies.
- suggesting CD133 as a putative lung cancer stem cell marker.
- but require further validation by larger studies

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Thank you for your attention