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Induction of CD44 variant 9-expressing cancer stem cells attenuates the efficacy of chemoradioselection and worsens the prognosis of patients with advanced head and neck cancer

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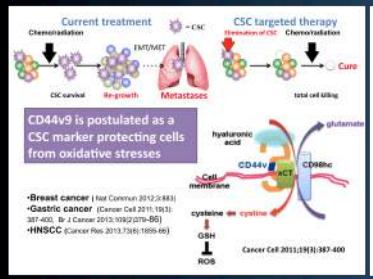
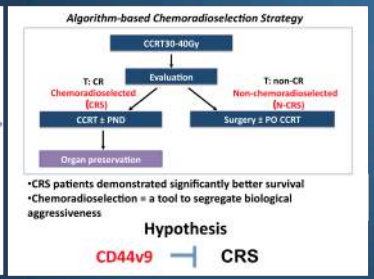
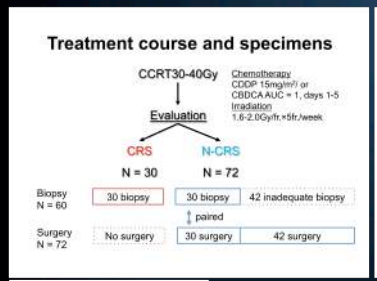
Background

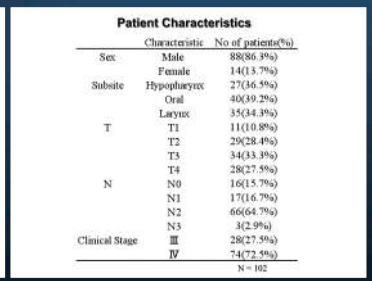




Is a novel cancer stem cell (CSC) marker, CD44v9, therapeutic hurdle for chemoradioselection ?

Patients & Immunostainings

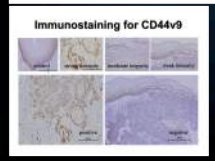




Patient Characteristics

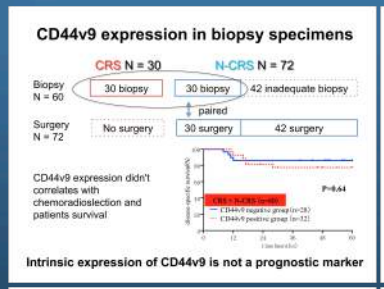
Characteristic		No of patients(%)
Sex	Male	88(86.3%)
	Female	14(13.7%)
Subsite	Hypopharynx	27(36.5%)
	Oral	40(39.2%)
	Larynx	35(34.3%)
T	T1	11(10.8%)
	T2	29(28.4%)
	T3	34(33.3%)
	T4	28(27.5%)
N	N0	16(15.7%)
	N1	17(16.7%)
	N2	66(64.7%)
	N3	3(2.9%)
Clinical Stage	III	28(27.5%)
	IV	74(72.5%)

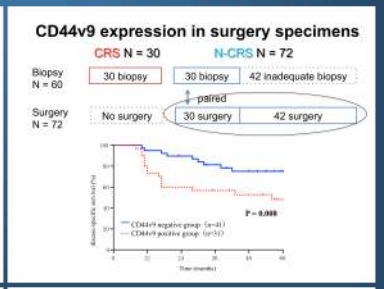
N = 102

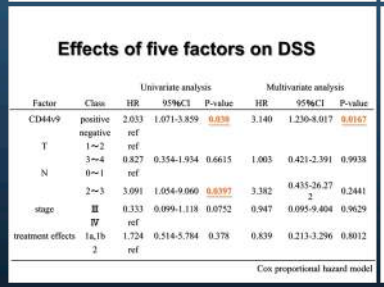


One hundred two patients (1997 to 2008) with advanced HNSCC were enrolled. According to the algorithm, 30 patients were CRC, while 72 patients were N-CRS. Using the conventional immunohistochemical technique, 60 biopsy specimens (30 from CRC and 30 from N-CRS) obtained prior to the treatment, and 72 surgically removed tumor specimens obtained form the N-CRS patients were immuno-stained with the anti-CD44v9 specific antibody (generated by Prof. Saya). According to the staining score ranging from -1 to 5, the samples were defined as CD44v9-negative (score, -1~1) and CD44v9-positive (score, 2–5).

Results & Conclusions



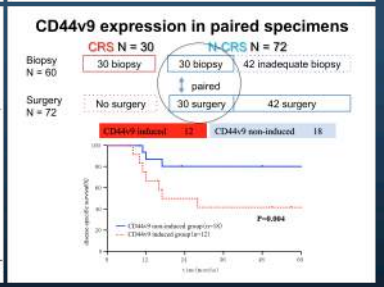




Effects of five factors on DSS

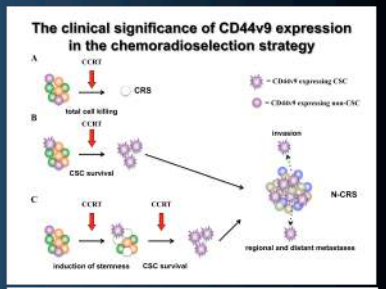
Factor	Class	Univariate analysis HR	95%CI	P-value	Multivariate analysis HR	95%CI	P-value
CD44v9	positive	2.033	1.071-3.859	0.030	3.140	1.230-8.017	0.0167
	negative	ref					
T	1~2	ref					
	3~4	0.827	0.354-1.934	0.6615	1.003	0.421-2.391	0.9938
N	0~1	ref					
	2~3	3.091	1.054-9.060	0.0397	3.382	0.435-26.272	0.2441
stage	III	0.333	0.099-1.118	0.0752	0.947	0.095-9.404	0.9629
	IV	ref					
treatment effects	1a,1b	1.724	0.514-5.784	0.378	0.839	0.213-3.296	0.8012
	2	ref					

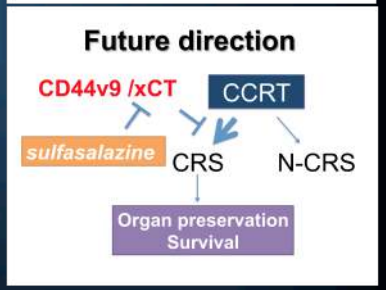
Cox proportional hazard model



The expression levels of CD44v9 in the biopsy specimens (n=60) didn't correlates with the chemoradioselection and patients' survival. However, among the N-CRS patients, CD44v9-positive group (n=31) demonstrated significantly (p=0.008) worse prognosis compared to CD44v9-negative group (n=41). Multivariate analyses demonstrated that among 5 candidate factors CD44v9 positivity alone was significantly correlated with the prognosis (HR: 3.140, 95% CI: 1.230-8.017, p=0.0167). We further compared the CD44v9 expression levels in the 30 paired biopsy and surgically removed specimens obtained from the identical patient in the N-CRS group. The CD44v9-induced group (N=12) demonstrated significantly (p=0.04) worse overall survival than that of CD44v9-non-induced group (n=18). These results strongly indicate that not the intrinsic but the CCRT-induced CD44v9 expression is a therapeutic hurdle to chemoradioselection.

Discussion & Future direction





CD44v9-expressing cancer cells are likely to be composed of CSCs and non-CSCs, as depicted in the above panel. In the biopsy specimens the CD44v9 expression does not correctly reflect cancer stemness, whereas in the surgically removed specimense CD44v9-expressing cells are highly enriched by CSCs, leading to the poor prognosis. The addition of xCT inhibitor (e.g., sulfasalazine) to chemoradioselection might open up a new avenue for clinically feasible CSC targeted therapy in HNSCC.