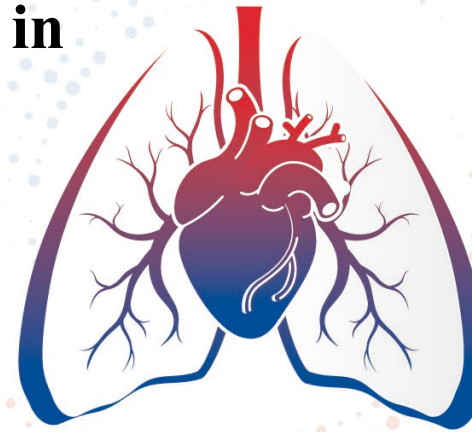


2023 대한심장혈관흉부외과학회

제55차 추계학술대회 & APELSO 2023

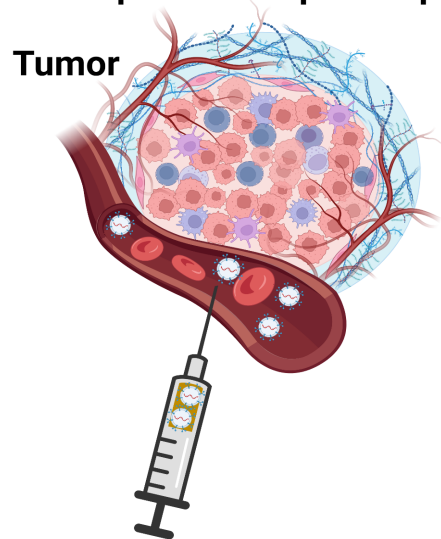
2023. 11. 02 (Thu) - 11. 04 (Sat), 그랜드 인터컨티넨탈 파르나스 서울

Prognostic Significance of Small Extracellular Vesicles-GCC2 in Pulmonary Vein for Resected Lung Adenocarcinoma

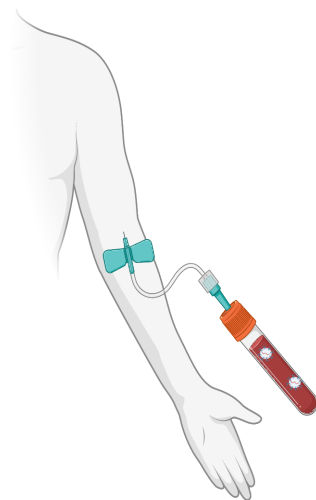


Type of liquid biopsies

Tumor proximal liquid biopsy

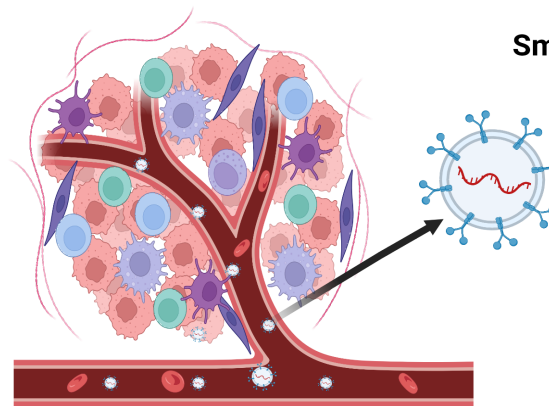


Peripheral liquid biopsy



Concentration of tumor associated molecules

sEV for liquid biopsy



Small extracellular vesicles

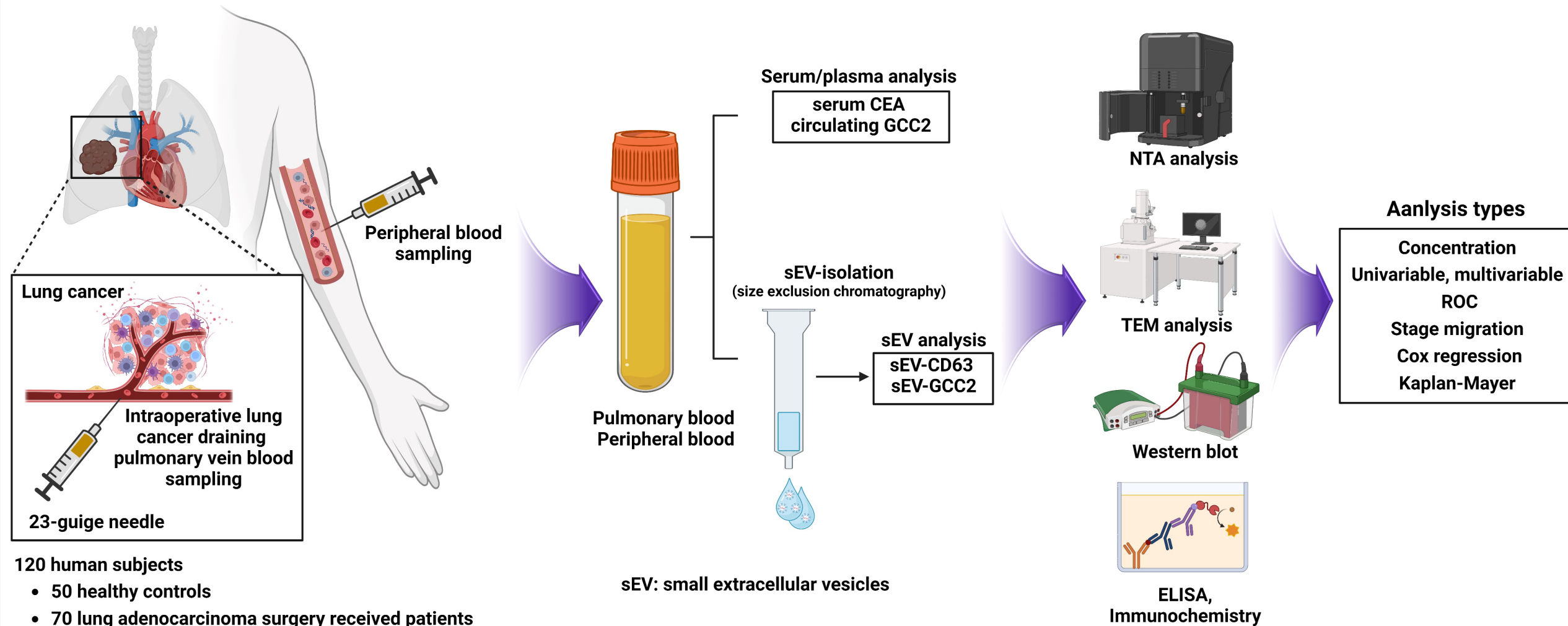
- 30 ~ 200nm vesicle
- Contains various molecules
- Cell to cell communication
- Cellular differentiation
- Metabolic regulation
- Immune response
- Tumor growth, metastasis
- Stable than CTCs or ctDNAs
- Abundant than CTCs or ctDNAs

- Tumor proximal liquid biopsy could provide more crucial information on tumor biology and be used for accurate diagnostic and prognostic tools in patients who underwent lung cancer surgery.
- sEV-GCC2 is a promising biomarker and therapeutic target for early detection of lung adenocarcinoma in pilot studies.
- The purpose of this research is that the concentration of sEV-GCC2 in tumor-draining pulmonary veins (TDPV) would be significantly increased and could provide more valuable clinical information than periphery

Human subjects

Sample types

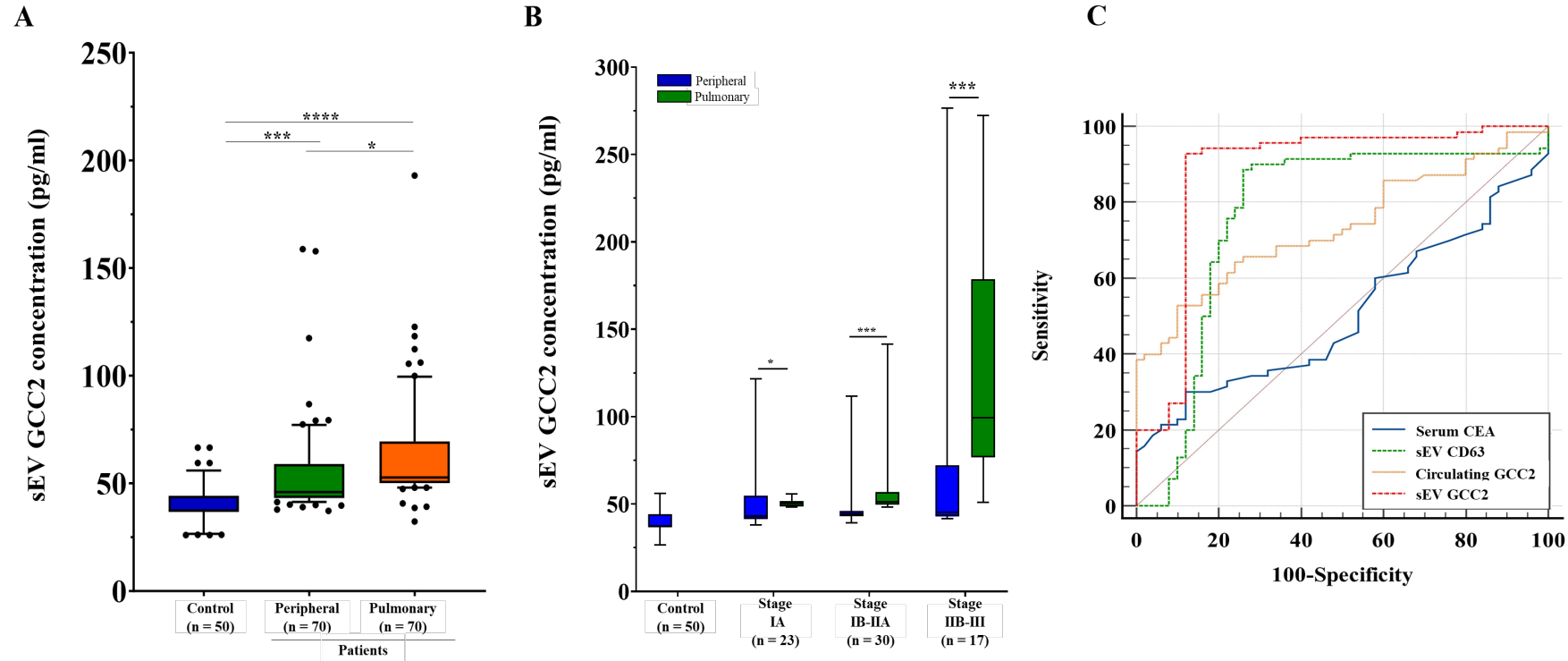
Analysis types



- 120 human subjects
- 50 healthy controls
 - 70 lung adenocarcinoma surgery received patients
- Mean follow-up duration: 33.65 ± 22.97 months
- Intraoperative blood sampling was performed at the TDPV with the periphery, and various markers (CEA, CD63, and GCC2) were analyzed.

Table 1. Patient's characteristics

		Controls (%)	Patients (%)	p-value
Sex	Male	24 (48.0)	32 (45.0)	0.88
	Female	26 (52.0)	38 (55.0)	
Age (mean ± SD)		43.2 ± 7.2	65.8 ± 9.0	< 0.0001
Smoking history	Non-smoker	31 (62.0)	45 (64.3)	0.29
	Smoker	16 (32.0)	22 (31.4)	
	Ex-smoker	3 (6.0)	3 (4.3)	
Histology	Adenocarcinoma	-	70 (100)	-
Surgery	Lobectomy	-	70 (100)	-
	Right upper lobe	-	12 (17.1)	
	Right middle lobe	-	19 (27.1)	
	Right lower lobe	-	17 (24.3)	
Site of primary tumor	Left upper lobe	-	11 (15.7)	-
	Light lower lobe	-	11 (15.7)	
	T1aN0-T1bN0-T1cN0	-	23 (32.9)	
	T2aN0	-	29 (41.4)	
	T2bN0	-	1 (1.4)	
pTNM stage	T3N0	-	1 (1.4)	-
	T4N0	-	1 (1.4)	
	T2aN1	-	5 (7.1)	
	T3N1	-	1 (1.4)	
	T4N1	-	1 (1.4)	
	T1cN2	-	1 (1.4)	
	T2aN2	-	6 (8.6)	
	T3N2	-	1 (1.4)	
	Up	-	17 (24.3)	
	Down	-	11 (15.7)	
Stage migration	Unchanged	-	42 (60.0)	-
	Lymphatic	-	8 (11.4)	
	Venous	-	9 (12.9)	
	Visceral pleural	-	7 (10.0)	
Invasion type	Lymphatic with venous	-	5 (7.1)	-
	Lymphatic with visceral pleural	-	4 (5.7)	
	None	-	37 (52.9)	
	Wild	-	49 (70.0)	
EGFR type	Mutation	-	13 (18.6)	-
	Not tested	-	8 (11.4)	
Dissected lymph node (Mean ± SD, mm)	-	-	21.8 ± 8.5	-
Tumor size (Mean ± SD, mm)	-	-	24.7 ± 1.8	-
Mean follow up duration (month)	-	-	33.65 ± 22.97	-



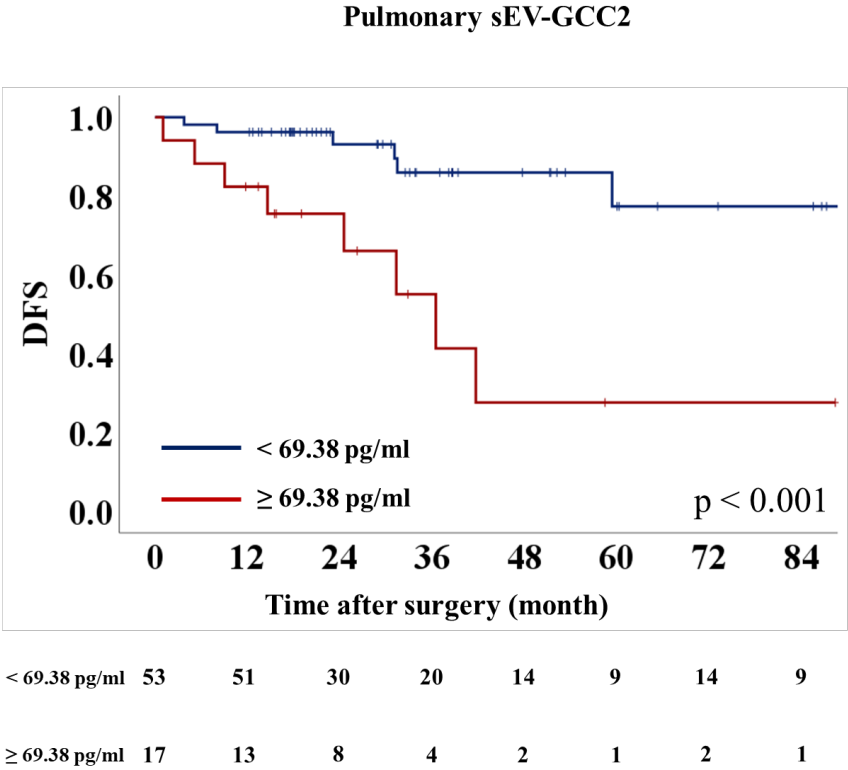
- Concentration of sEV-GCC2 in TDPV was significantly increased according to the pathological stages than periphery.
- Diagnostic accuracy of sEV-GCC2 was higher than CEA, sEV-CD63, and circulating-GCC2.
- AUC value of sEV-GCC2: 0.899, sEV-CD63: 0.765, circulating GCC2: 0.735, and CEA: 0.505 in TDPV.

Table2. Univariable and multivariable analysis of sEV-GCC2 according to blood sampling sites.

Variable	Univariable				Multivariable			
	Peripheral sEV-GCC2		Pulmonary sEV-GCC2		Peripheral sEV-GCC2		Pulmonary sEV-GCC2	
	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value
SEX	3.740	0.492	7.228	0.232				
AGE	-0.624	0.062	0.413	0.273				
Smoking history	-2.181	0.823	0.962	0.929				
Tumor site	4.321	0.442	3.117	0.620				
cTNM stage	15.139	0.04	24.818	0.0021	2.986	0.754	-0.548	0.9534
pTNM stage	17.577	0.004	25.300	0.0001	14.226	0.027	4.682	0.7343
Lymph node metastasis	17.652	0.005	20.598	0.0034	15.600	0.218	14.445	0.0193
Lymphatics invasion	6.366	0.265	10.546	0.097				
Visceral pleura invasion	3.580	0.511	3.924	0.519				
Venous invasion	-7.172	0.356	-6.138	0.479				
EGFR mutation	-2.063	0.711	-5.663	0.360				
Pathological tumor size	0.321	0.018	0.682	<0.0001	0.252	0.057	0.617	<0.001

- Increased concentration of sEV-GCC2 in TDPV was associated with pathological tumor size, lymph node metastasis.
- Higher level of sEV-GCC2 from TDPV were associated with poor DFS (80.13 vs. 42.73 months; $p < 0.001$) and poor OS (91.24 vs 70.09 months; $p = 0.016$) than lower sEV-GCC2.
- Cox-regression analysis showed that DFS was statistically significantly associated with sEV-GCC2 from TDPV and lymphatic invasion.

Figure 2. Disease free survival analysis of primary lung tumor derived sEV-GCC2.



- Characterization of disease specific sEV and better understanding of the physio-pathologic roles of these proteins in their respective disease has significant implications for the development of future clinical applications using this information for improved prognosis or therapeutics.
- Analysis of sEV-GCC2 derived from TDPV in lung cancer patients who underwent surgery is a prognostic tool that could be reflected in cancer statuses such as pathological tumor size, lymph node metastasis, pathological up-migration, poor DFS and OS.
- Although our exosome isolation protocol using size exclusion chromatography is an efficient isolation method, it is not considered a standard method for exosome isolation. And, the study population consisted of only lung adenocarcinoma cases, and it is unknown whether these findings can be directly extrapolated to other lung cancer subtypes.