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ASSESSMENT OF 2-YEAR TREATMENT-RELATED CARDIOVASCULAR TOXICITY RISKS IN NON-SMALL CELL LUNG CANCER PATIENTS UTILIZING ELECTRONIC HEALTH RECORDS

Thi-Ngoc Tran MPH[1], Sanghee Lee PhD[1], Youngjoo Lee MD PhD[2], Hak Jin Kim MD PhD[3], Jin-Ho Choi MD[4], Jae Won Song MD[5], Hyunsoon Cho PhD[6,7]

First author: Thi-Ngoc Tran (ttngoc@ncc.re.kr)

Corresponding author: Hyunsoon Cho (hscho@ncc.re.kr)

[1]Departnt of Cancer Control and Population Health, National Cancer Center Graduate School of Cancer Science and Policy, Goyang, Republic of Korea

[2]Division of Hematology and Oncology, Department of Internal Medicine, National Cancer Center, Goyang, Republic of Korea

[3]Department of Cardiology, Gumdan Top General Hospital, Incheon, Republic of Korea

[4]Department of Thoracic Surgery, Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea

[5]Center for Lung cancer, Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea

[6]Department of Cancer AI and Digital Health, National Cancer Center Graduate School of Cancer Science and Policy, National Cancer Center, Goyang, Republic of Korea

[7]Integrated Biostatistics Branch, Division of Cancer Data Science, Research Institute, National Cancer Center, Goyang, Republic of Korea

1. Background and objectives

- **Cancer treatment-related cardiovascular disease, or cardiovascular (CV) toxicity** caused by diversified cancer treatments, was discovered decades ago and has become more popular in recent studies.
- **Cardio-oncology or onco-cardiology** was developed as the interdisciplinary field of oncologists and cardiologists to prevent, monitor, and manage CV toxicity based on real-world evidence to improve cancer care and cancer survivorship.

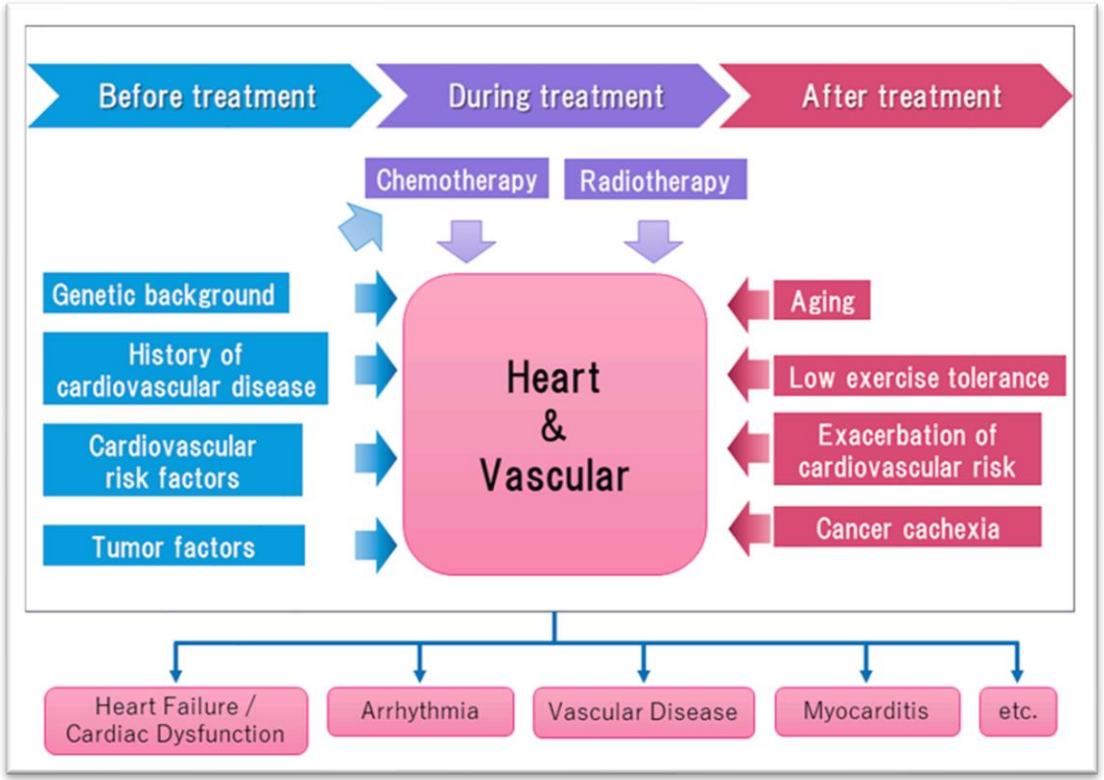


Figure. The multiple factors involved in the development of cancer treatment-related CV diseases before, during, and after cancer treatment [1].

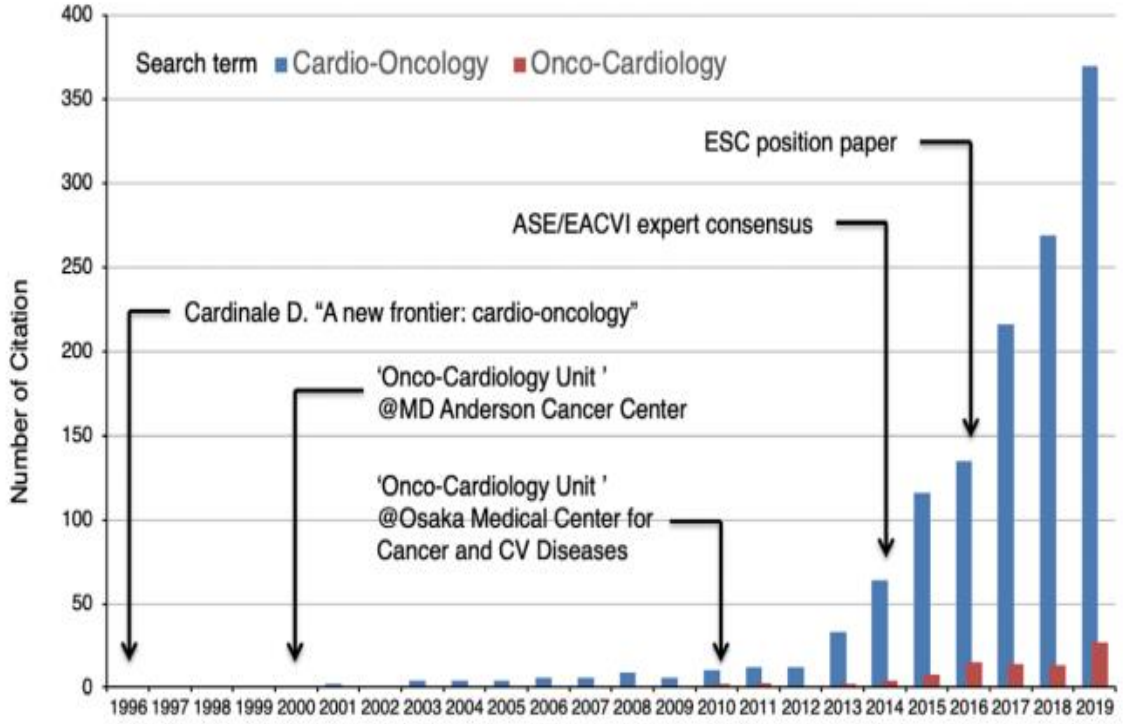


Figure. Number of PubMed citations since 1996 for the terms "Cardio-Oncology" and "Onco-Cardiology" by year [2].

1. Background and objectives

Studies about CV disease risks in cancer survivors

- **Study in UK** [3]: there was increased mortality related to CV diseases, such as pericarditis, venous thromboembolic disease, arrhythmias, and ischemic heart disease in patients with LC

-> comparing general CV disease risk between cancer patients and the general non-cancer population

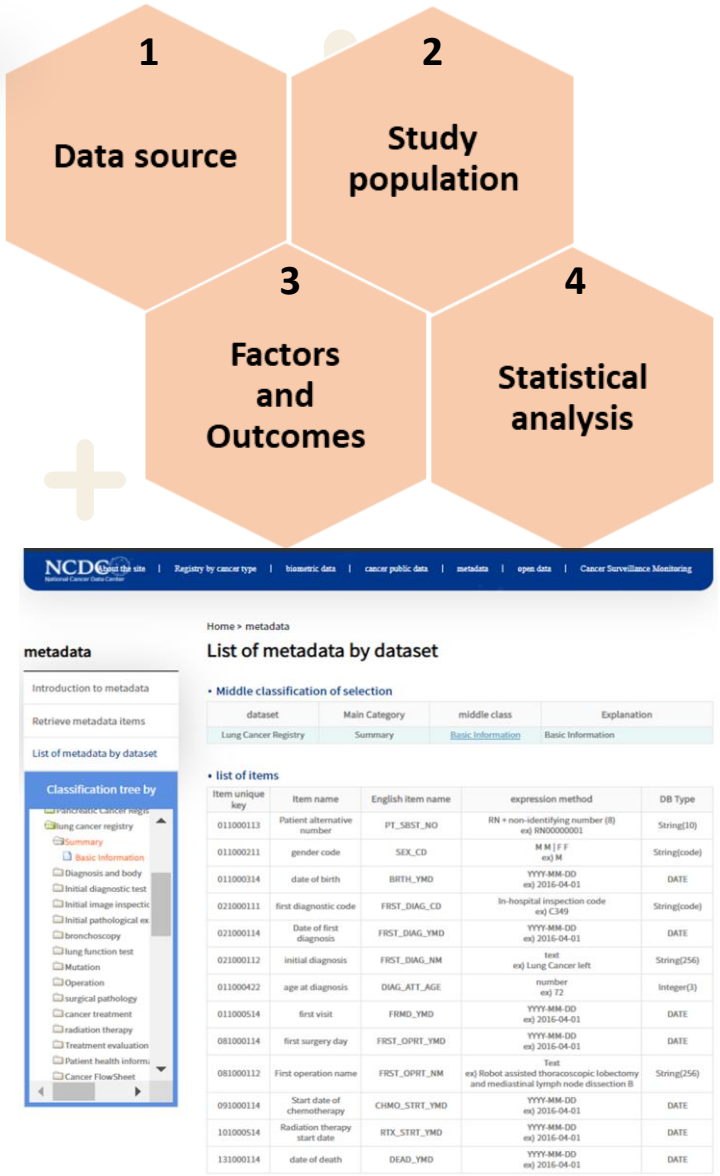
- **Study in Korea** [4]: risks of coronary heart disease, myocardial infarction, and stroke among surgery LC patients were higher than in the non-cancer population.

Diverse effects of the treatment received on the occurrence of CV toxicities in LC patients haven't been discovered.

Objectives

To assess the **cumulative incidence** of various CV toxicity types and associated **risks** in non-small cell lung cancer (NSCLC) patients **by treatment therapy**.

2. Method



https://www.cancerdata.kr/main.do

1. **Clinical Research Data Warehouse,** a database of **electronic medical records** created at the **National Cancer Center** (NCC), **Korea** in **2021.**

2. **7,868** patients aged 40+, newly diagnosed with NSCLC only between January 2007 and December 2018 had cancer treatment at the NCC within four months after their cancer diagnosis.

3. **Outcomes**: The **nine different CV toxicities:** secondary hypertension, atrial fibrillation and flutter, cerebrovascular disease, ischemic heart disease, venous thromboembolism, etc. **Variables**: demographic, SEER stage, ECOG performance status, Treatment therapy.

4. **The 2-year cumulative incidence** of CV toxicity and **Fine-Gray sub-distribution hazard models** by treatment was estimated **with death as competing event**.

3. Results - *Characteristics of CV toxicities*

Table 1. The proportion of cardiovascular toxicity types by treatment group.

CV toxicity type	Total n=7,868 n (col %)	Treatment				p-value
		Surgery only n=1,699 n (col %)	Chemotherapy only n=2,497 n (col %)	Radiotherapy only n=393 n (col %)	Combined treatment n=3,279 n (col %)	
AF (atrial fibrillation and flutter)	209 (3)	**92 (5.4)**	**66 (2.6)**	6 (1.5)	45 (1.4)	**<.001**
VTE (venous thromboembolism)	156 (2)	**44 (2.6)**	**60 (2.4)**	4 (1.0)	48 (1.5)	**0.008**
CeVD (cerebrovascular disease)	115 (1)	11 (0.7)	**66 (2.6)**	6 (1.5)	32 (1.0)	**<.001**
IHD (ischemic heart disease)	78 (1)	10 (0.6)	**39 (1.6)**	4 (1.0)	25 (0.8)	**0.005**
Cardial (pericardial effusion, cardiac tamponade)	54 (1)	7 (0.4)	**28 (1.1)**	2 (0.5)	17 (0.5)	**0.016**
CMP, HF (cardiomyopathy due to chemotherapeutic agents and heart failure)	22 (0)	5 (0.3)	8 (0.3)	1 (0.3)	8 (0.2)	0.956
Secondary HTN	16 (0)	0 (0.0)	**11 (0.4)**	0 (0.0)	5 (0.2)	**0.009**
ATE (arterial embolism and thrombosis)	8 (0)	2 (0.1)	3 (0.1)	0 (0.0)	3 (0.1)	0.905
Others	24 (0)	**15 (0.9)**	6 (0.2)	0 (0.0)	3 (0.1)	**<.001**
All CV toxicity	**611 (8)**	**162 (9.5)**	**257 (10.3)**	21 (5.3)	171 (5.2)	**<.001**

- About **8%** developed CV toxicities 2 years after cancer diagnosis.
- The most common types: **AF (3%), VTE (2%), CeVD (1%) and IHD (1%).**

3. Results - *Cumulative incidence of CV toxicities*

- The overall CV toxicity was **the highest in the chemotherapy population** (2-year cumulative incidence of 10.6%).
- The **surgery** population showed the highest **AF** (5.7%).

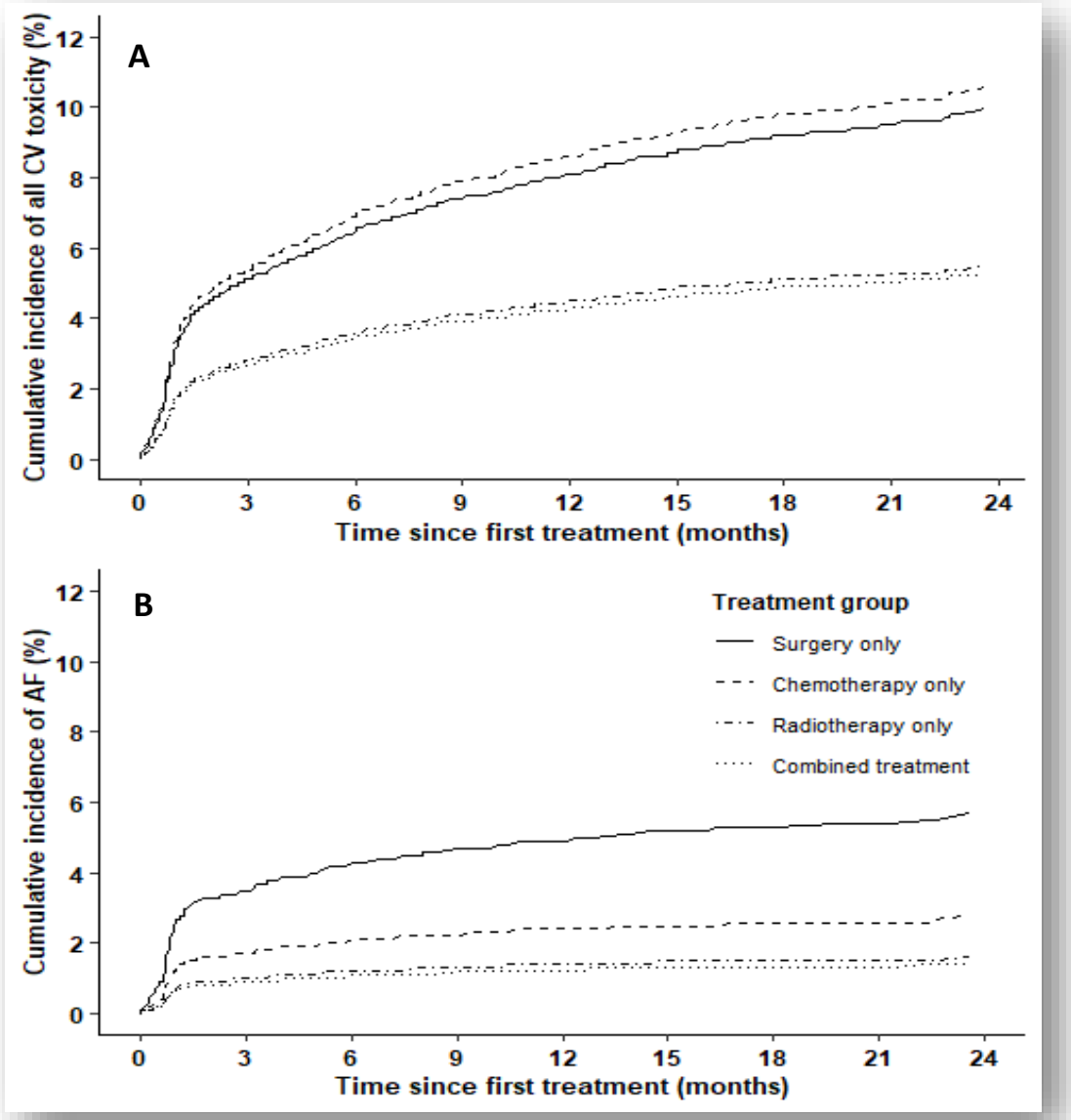


Figure 1. Cumulative incidence of all CV toxicity, AF by treatment groups.
(A) All CV toxicities; (B) Atrial fibrillation and flutter

3. Results - *Risks of CV toxicities*

- Individuals with **chemotherapy** were significantly related to **CeVD** (sHR 4.12, 95% CI 1.66-10.23).
- Risk of **AF** was significantly lower among patients with chemotherapy (sHR 0.58), radiotherapy (sHR 0.29) and combined treatment (sHR 0.20) than those with surgery.

A. All CV toxicity (no. event=611)

Variable	All CV toxicity	SHR (95% CI)
Age (Ref. Age 40-54)		
Age 55-64		**1.33 (1.02-1.73)**
Age 65-74		1.31 (0.99-1.73)
Age 75+		1.03 (0.73-1.44)
Gender (Ref. Female)		1.29 (1.00-1.67)
Smoking (Ref. No)		1.16 (0.86-1.57)
Drinking (Ref. No)		0.97 (0.80-1.18)
HTN (Ref. No)		**1.20 (1.00-1.42)**
Diabetes (Ref. No)		1.02 (0.83-1.25)
ECOG group (Ref. ECOG 0)		
ECOG 1		**1.38 (1.09-1.73)**
ECOG 2		1.18 (0.89-1.56)
LC type (Ref. Adenocarcinoma)		
Squamous cell carcinoma		**1.26 (1.03-1.55)**
Others		1.04 (0.82-1.31)
SEER stage (Ref. Localized)		
Regional		**1.80 (1.33-2.44)**
Distant		**1.61 (1.12-2.31)**
Treatment (Ref. Surgery)		
Chemotherapy only		1.13 (0.82-1.56)
Radiotherapy only		**0.58 (0.35-0.98)**
Combined treatment		**0.41 (0.31-0.55)**

0 1 2 3

SHR (95% CI)

B. Atrial fibrillation and flutter(no. event =209)

Variable	AF	SHR (95% CI)
Age (Ref. Age 40-54)		
Age 55-64		**1.83 (1.04-3.21)**
Age 65-74		**1.88 (1.06-3.34)**
Age 75+		1.18 (0.61-2.31)
Gender (Ref. Female)		**1.73 (1.05-2.83)**
Smoking (Ref. No)		1.30 (0.72-2.33)
Drinking (Ref. No)		0.83 (0.59-1.15)
HTN (Ref. No)		1.28 (0.96-1.72)
Diabetes (Ref. No)		0.87 (0.61-1.24)
ECOG group (Ref. ECOG 0)		
ECOG 1		**2.12 (1.39-3.22)**
ECOG 2		1.59 (0.92-2.74)
LC type (Ref. Adenocarcinoma)		
Squamous cell carcinoma		**1.76 (1.25-2.48)**
Others		1.43 (0.96-2.14)
SEER stage (Ref. Localized)		
Regional		**1.81 (1.19-2.78)**
Distant		1.51 (0.84-2.71)
Treatment (Ref. Surgery)		
Chemotherapy only		**0.58 (0.34-0.98)**
Radiotherapy only		**0.29 (0.12-0.70)**
Combined treatment		**0.20 (0.13-0.31)**

0 1 2 3 4

SHR (95% CI)

C. Cerebrovascular disease (no. event =115)

Variable	CeVD	SHR (95% CI)
Age (Ref. Age 40-54)		
Age 55-64		1.22 (0.64-2.33)
Age 65-74		1.15 (0.60-2.23)
Age 75+		1.01 (0.46-2.21)
Gender (Ref. Female)		1.57 (0.86-2.87)
Smoking (Ref. No)		0.87 (0.44-1.72)
Drinking (Ref. No)		1.23 (0.78-1.94)
HTN (Ref. No)		1.46 (0.96-2.20)
Diabetes (Ref. No)		1.17 (0.73-1.88)
ECOG group (Ref. ECOG 0)		
ECOG 1		1.13 (0.66-1.91)
ECOG 2		0.90 (0.49-1.65)
LC type (Ref. Adenocarcinoma)		
Squamous cell carcinoma		0.70 (0.42-1.15)
Others		0.83 (0.49-1.41)
SEER stage (Ref. Localized)		
Regional		2.44 (0.90-6.61)
Distant		1.56 (0.53-4.61)
Treatment (Ref. Surgery)		
Chemotherapy only		**4.12 (1.66-10.23)**
Radiotherapy only		2.33 (0.68-8.03)
Combined treatment		1.20 (0.51-2.80)

0 4 8 12

SHR (95% CI)

Figure 2. Forest plot for risks of all CV toxicities, IHD, AF, CeVD, VTE in total NSCLC population (n=7,868)*

Notes: In 'sHR (95% CI)' column, cell with p-value ≤.05 were bold.
The full model included: Age, gender, working status, education, smoking, drinking, hypertension, diabetes, BMI, ECOG, LC types, SEER stage, treatment.

4. Conclusions

- ✓ Diverse risks of treatment-related CV toxicities in clinical practice
- ✓ Oncologists and cardiologists should be aware of the risks of AF in surgery and CeVD in chemotherapy to achieve a better prognosis and quality of life for NSCLC patients.

Acknowledgements

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