Active Neoplasia & Valvular Heart Disease: Balancing Cancer and Cardiac Care

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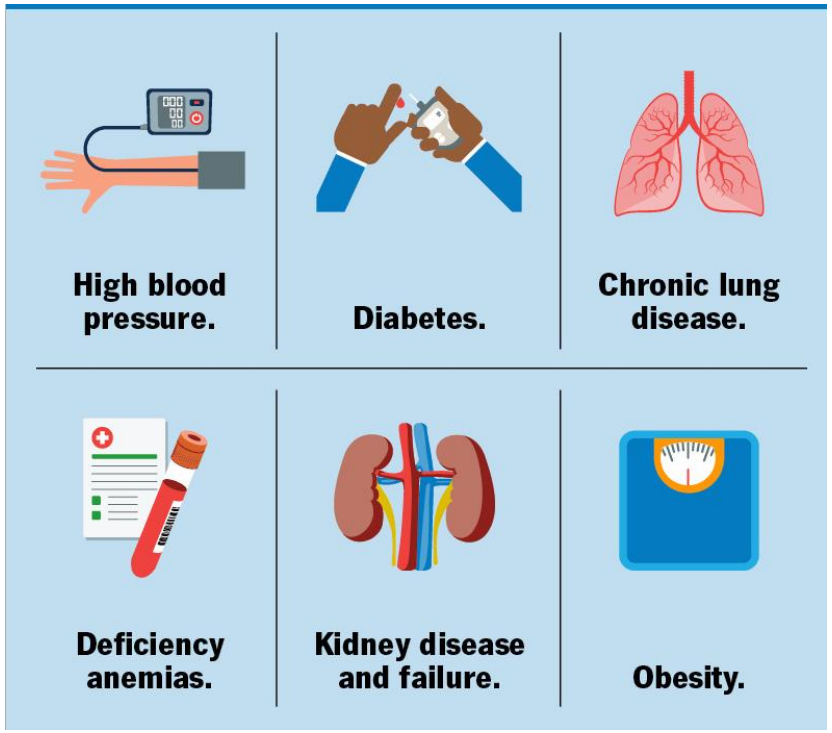
Why VHD matters in cancer patients

- The coexistence of cancer and valvular heart disease is increasingly common and clinically important due to increased survival of cancer patients, aging and share risk factors (smoking, obesity, diabetes).
- Unfortunately severe VHD can limits therapeutic options in cancer patients (increased risk of surgery, increased risk of cardiotoxicity due to antineoplastic drugs)
- On the other side cancer therapies (radio and chemo) can favor the occurrence of VHD
- Moreover cancer patients are under-referred for valve interventions (concern regarding life expectancy and comorbidities).



→ **Early identification and management of VHD can improve outcomes.**

VHD in Cancer Patients: Possible Scenarios

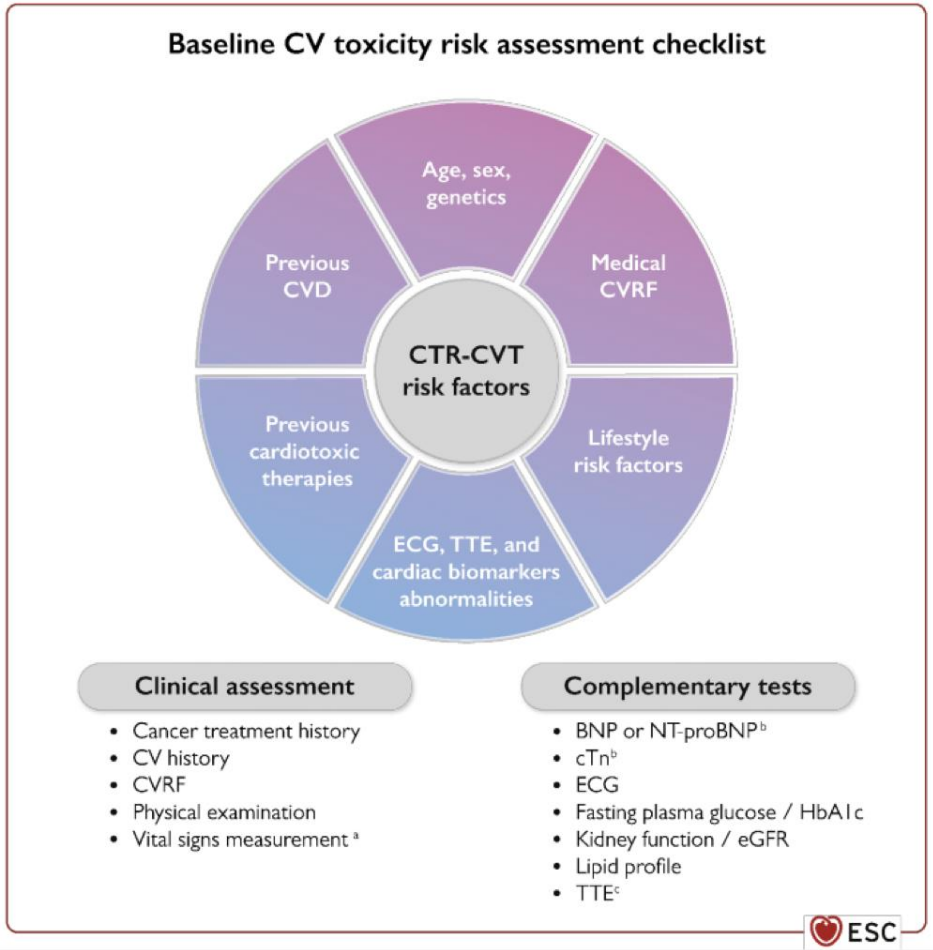
1. Patients with **pre-existing VHD** or incidentally diagnosed before cancer therapy.
2. VHD occurring or worsening **after cancer treatment** (i.e. radiotherapy) .
3. **Endocarditis** (related to immunosuppression, catheter use, or combination treatments)
4. **Nonbacterial thrombotic endocarditis** (as the first possible symptom of cancer)

1. Patients with pre-existing VHD

Pre-existing VHD increases risk from cancer therapies (surgery and chemo) and limit therapeutic options.

HFA-ICOS baseline cardiovascular toxicity risk stratification—previous CVD (1)

Baseline CV toxicity risk factors	Anthracycline chemotherapy	HER2-targeted therapies	VEGF inhibitors	BCR-ABL inhibitors	Multiple Myeloma therapies	RAF and MEK inhibitors
HF/ cardiomyopathy/ CTRCD	VH	VH	VH	H	VH	VH
Severe VHD	H	H	–	–	–	H
MI or PCI or CABG	H	H	VH	–	–	H
Stable angina	H	H	VH	–	–	H
Arterial vascular disease	–	–	VH	VH	VH	–
Abnormal ankle-brachial pressure index	–	–	–	H	–	–
PH	–	–	–	H	–	–



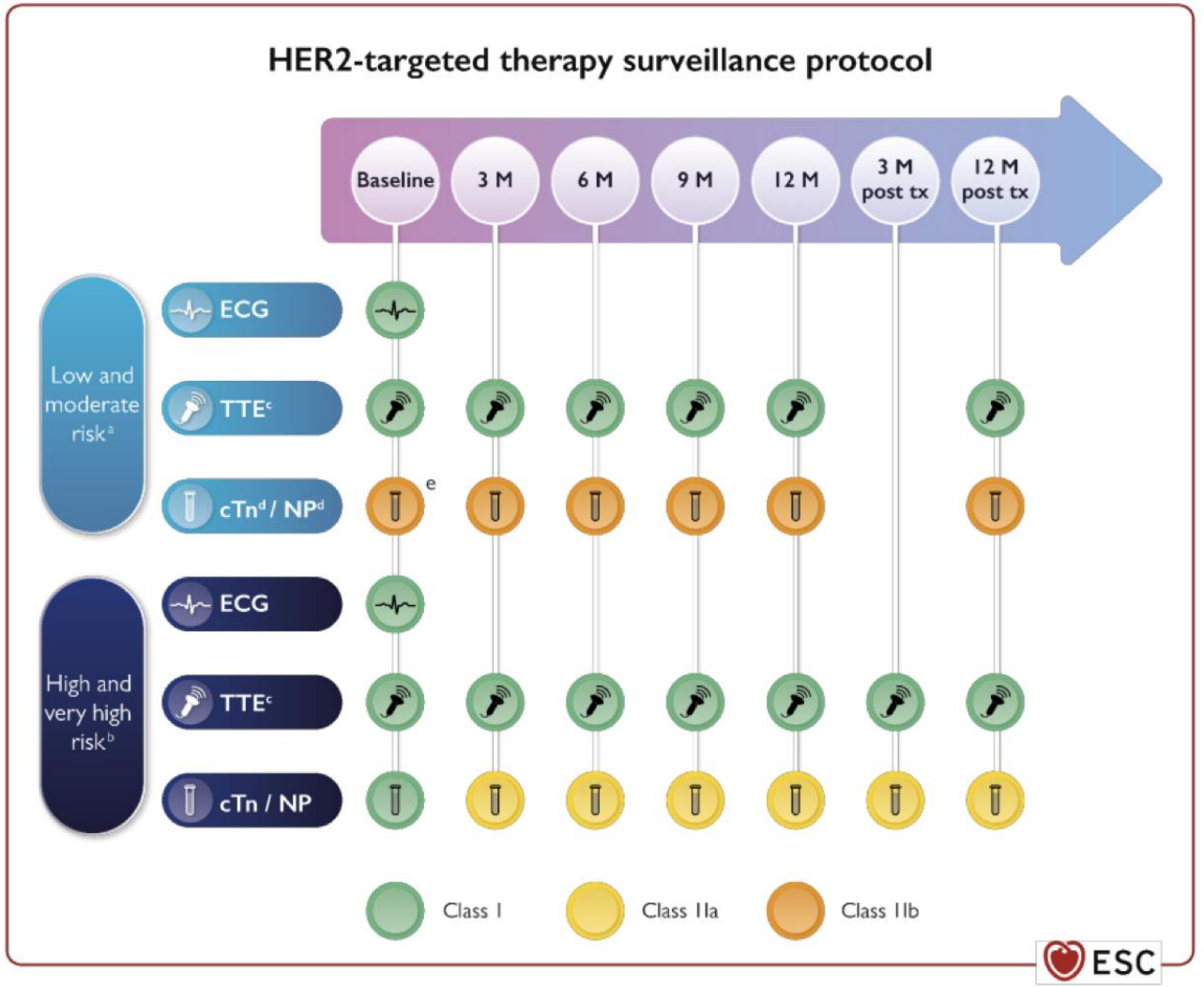
ESC Guidelines Cardio-oncology 2022

2022 ESC Guidelines on cardio-oncology
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac244)

Managing Untreated VHD During Cancer Therapy

1.Frequent CV surveillance is recommended in patients with VHD receiving cardiotoxic cancer treatment (echocardiographic evaluation, measurement of biomarkers).

2.The frequency of surveillance should be individualized guided by the patient CV toxicity risk and the type of cancer treatment.



ESC Guidelines Cardio-oncology 2022

Managing severe VHD before cancer treatment

Severe, life-threatening VHD must be addressed before cancer treatment because they may limit cancer treatment options

No specific recommendation regarding management of VHD in cancer patients

Refer to 2022 guidelines for NCS and 2025 VHD but……

<u>In the decision to treat take into consideration:</u>

- **estimated life expectancy and comorbidities**
- **Expected benefits in term of addressing cancer treatment**
- **MDT** (oncologist, cardiologist, cardiac surgeon) is crucial to decide the best treatment option

Recommendations	Class[a]	Level[b]
In patients with cancer and pre-existing severe VHD, management according to the 2021 ESC/EACTS Guidelines for the management of VHD is recommended, taking into consideration cancer prognosis and patient preferences.[507]	I	C
In patients with cancer developing new VHD during cancer therapy, management according to the 2021 ESC/EACTS Guidelines for the management of VHD[507] is recommended, taking into consideration cancer prognosis and patient	I	C

Recommendations	Class	Level
A MDT approach is recommended to discuss and define the surgical risk in CS with severe VHD.	I	C

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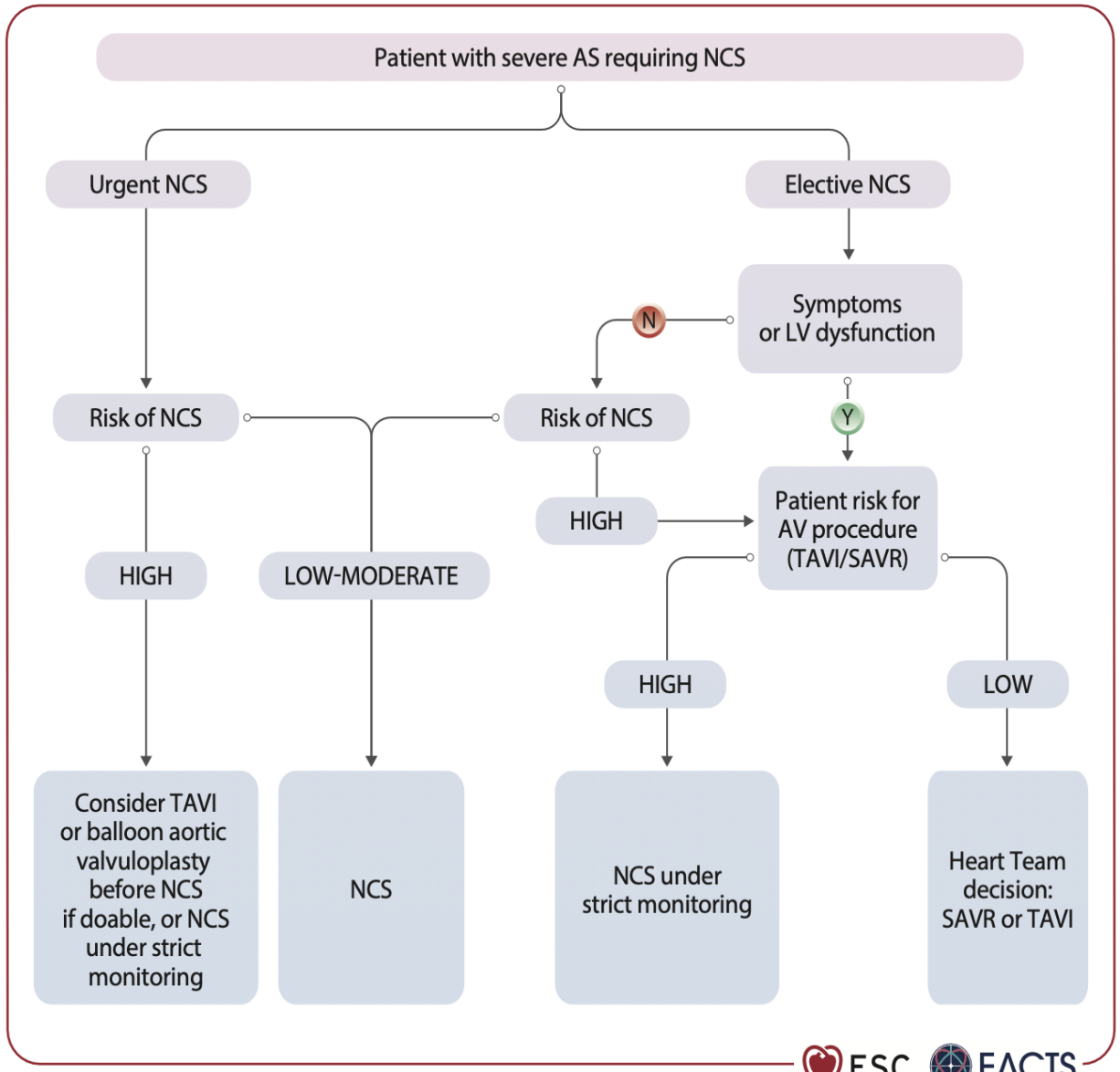
SEVERE AORTIC STENOSIS



Patient with severe symptomatic AS o with LVD if high risk NCS can be deferred should be treated after Heart Team evaluation to determine whether SAVR or TAVI is preferable.

TAVI may be preferred to SAVR in cancer patients for :
Faster recovery
Risk of infections in immuncompromised patients (leukemia pts)
Risk of bleeding

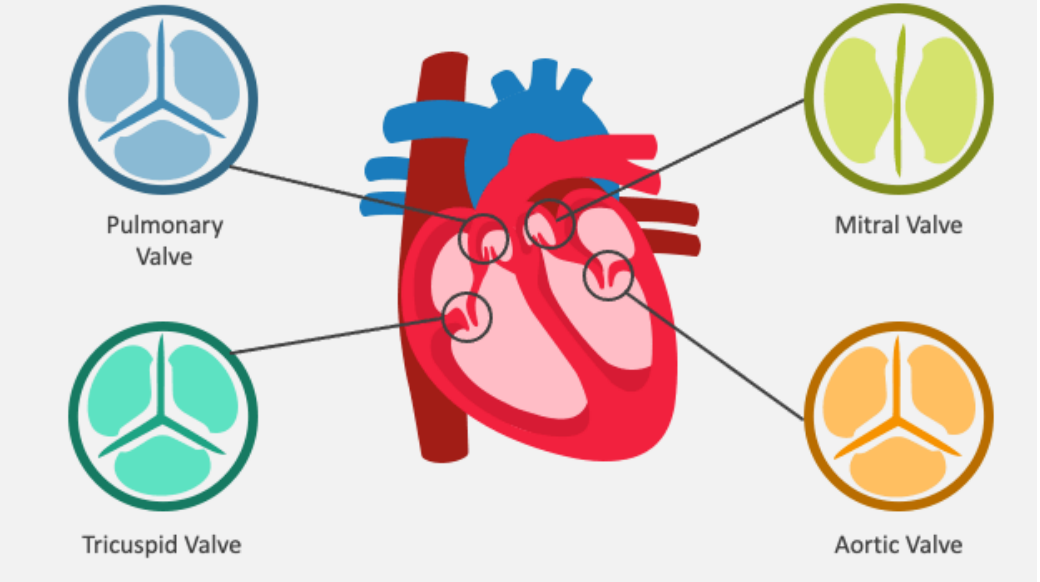
ADDITIONALLY TO BE CONSIDERED IN CANCER PATIENTS:

- **Cancer prognosis and estimated life expectancy (>12 m) and comorbidities**
- Utility to complete cancer treatment (LV's ability to cope with fluid overload needed during chemotherapy)

2. Patients with VHD After cancer treatments

2a.VHD related to Radiotherapy

2b. CTRCD-related valve disease



Treatment of is the same as functional valve disease from other causes. The mainstay of treatment is **pharmacological management of HF** (beta-blockers, sodium-glucose cotransporter 2 inhibitors, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, sacubitril/valsartan, mineralocorticoid receptor antagonists, diuretics).

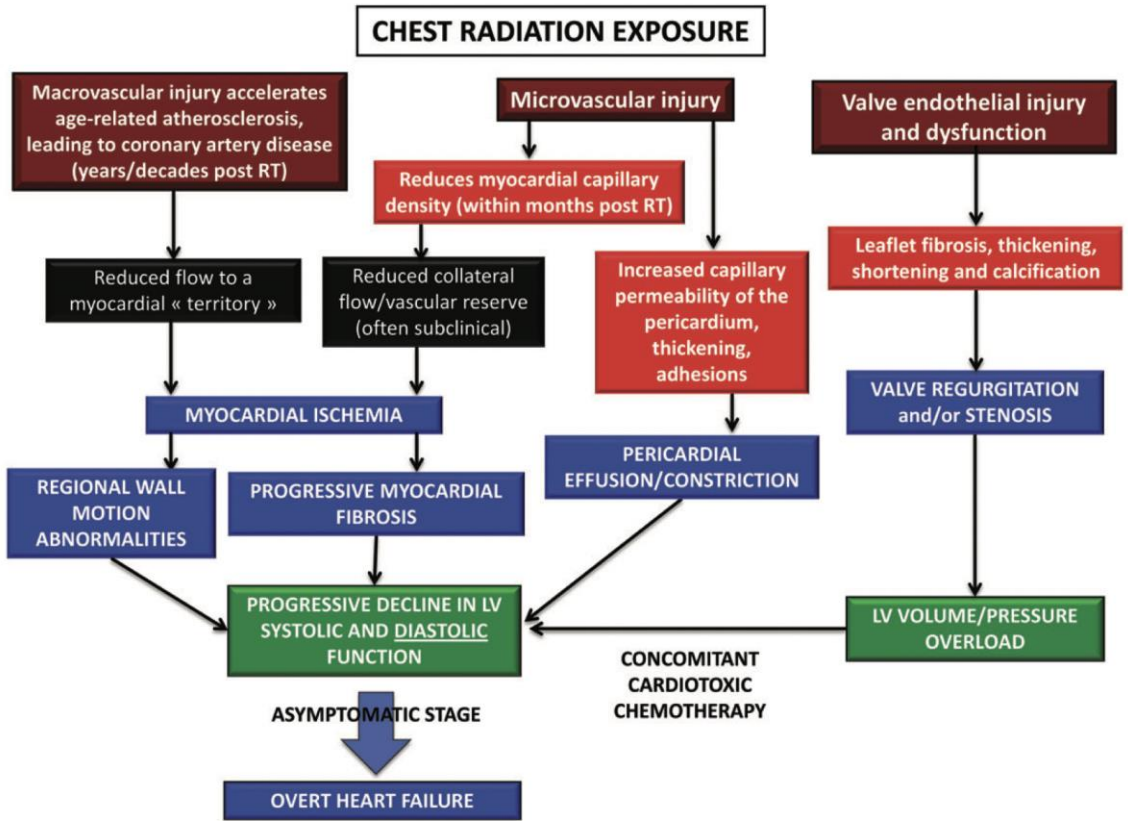
Antineoplastic drugs favoring VHD:
anthracyclines,
anti-HER-2
monoclonal antibody,
combination RAF/MEK inh.

2a.VHD After Radiotherapy

- Especially in patients receiving mediastinal radiotherapy (limphoma, lung, breast) between 1965 and 1995 before the era of modern radiotherapy planning
- Radiation causes inflammation, collagen accumulation, fibrosis, and calcification. Affects not only valvular tissues but the whole heart and vessels
- Latency can span years or decades.

Risk factors:

- Dose (total >30Gy, dose per fraction >2Gy/day)
- Concomitant administration of cardiotoxic systemic agents (i.e. anthracyclines)
- Patient-related factors: *younger age* (<50 years) and C*V risk factors* (hypertension, smoking, diabetes..etc), *Previous heart disease*



Lancellotti et al. European Heart Journal – Cardiovascular Imaging (2013) 14, 721–740

ECHOCARDIOGRAPHIC FEATURES OF RADIATION INDUCED VALVULAR HEART DISEASE

From: Edyta Płońska-Gościniak et al. Kardiologia Polska 2022

Valve disease

- Valve apparatus and leaflet thickening, fibrosis, shortening, and calcification predominant on left-sided valves (related to pressure difference between the left and right side of the heart).
- Valve regurgitation more commonly encountered than stenosis.
- Stenotic lesions more commonly involving the aortic valve.
- Reported incidence of clinically significant valve disease: 1% at 10 years; 5% at 15 years; 6% at 20 years after radiation exposure.
- Valve disease incidence increases significantly after >20 years following irradiation: mild AR up to 45%, ≥moderate AR up to 15%, AS up to 16%, mild MR up to 48%, mild PR up to 12%.

Lancellotti et al. European Heart Journal – Cardiovascular Imaging (2013) 14, 721–740

~10% have clinically significant **VHD**.

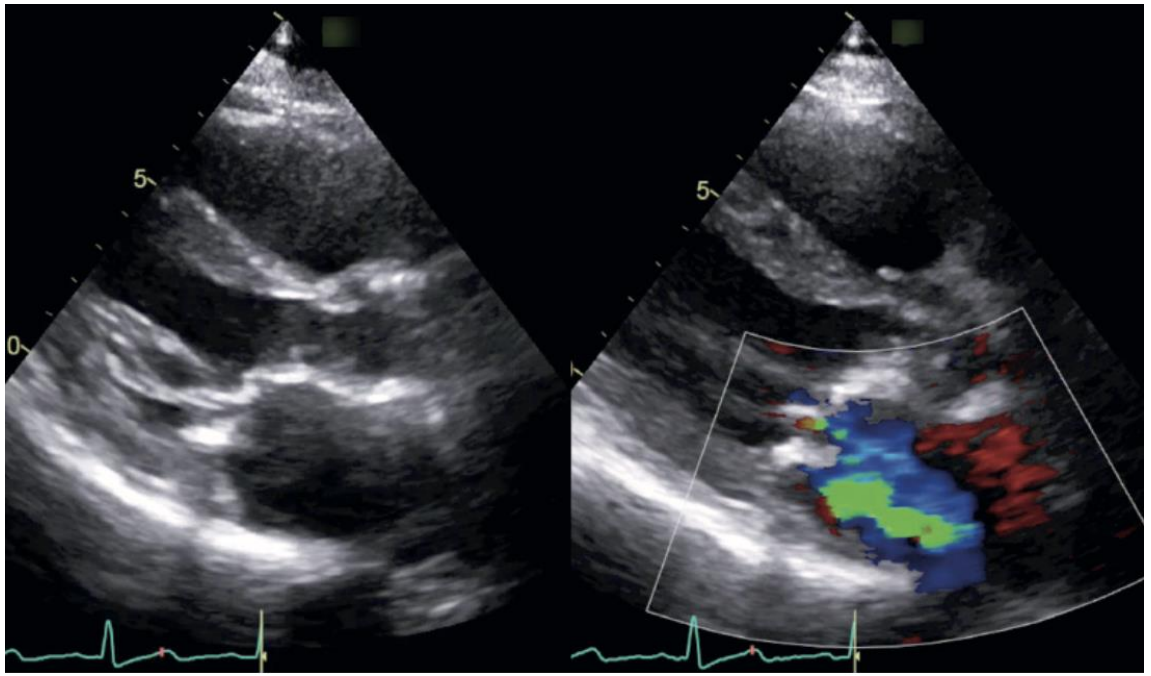


Table 3. Echocardiographic features of radiation-induced valvular heart disease

Uniform valvular thickening due to fibrosis
Uniform distribution of lesions in the aorto-mitral curtain
Porcelain aorta
More severe lesions in left-sided valves (aortic, mitral) than in right-sided valves (tricuspid, pulmonary)
Regurgitation prior to stenosis
Fibrosis and calcification mostly of the base and mid portions of the valves; preservation of mitral commissural fissures

VHD After Radiotherapy

Risk of VHD After Mediastinal RT (HL Survivors)

Cohort: 1852 HL survivors; 89 VHD cases, latency ~23 yrs

Dose-response: risk ↑ with valve dose

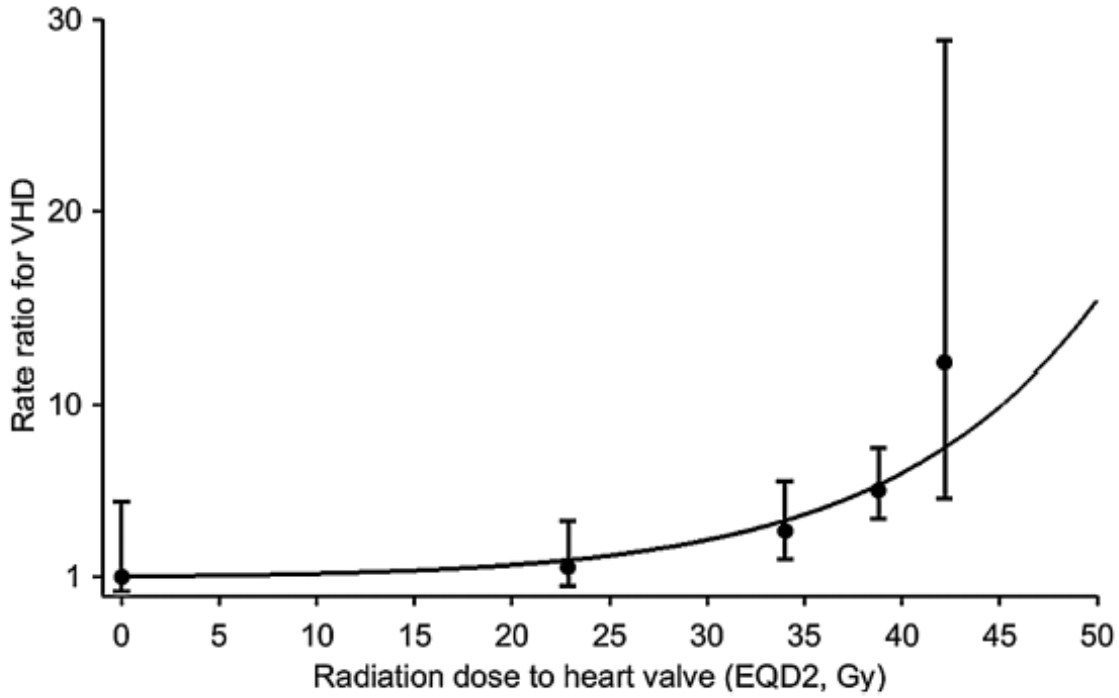
- ≤30 Gy: ~1.4×
- 31–35 Gy: 3.1×
- 36–40 Gy: 5.4×
- 40 Gy: 11.8×

30-yr cumulative risk: 1.6% (no RT) → 12.4% (>40 Gy)

Other factor increasing risks: splenectomy, obesity, hypercholesterolemia

Modern RT (20–30 Gy): ~1.4% excess 30-yr risk

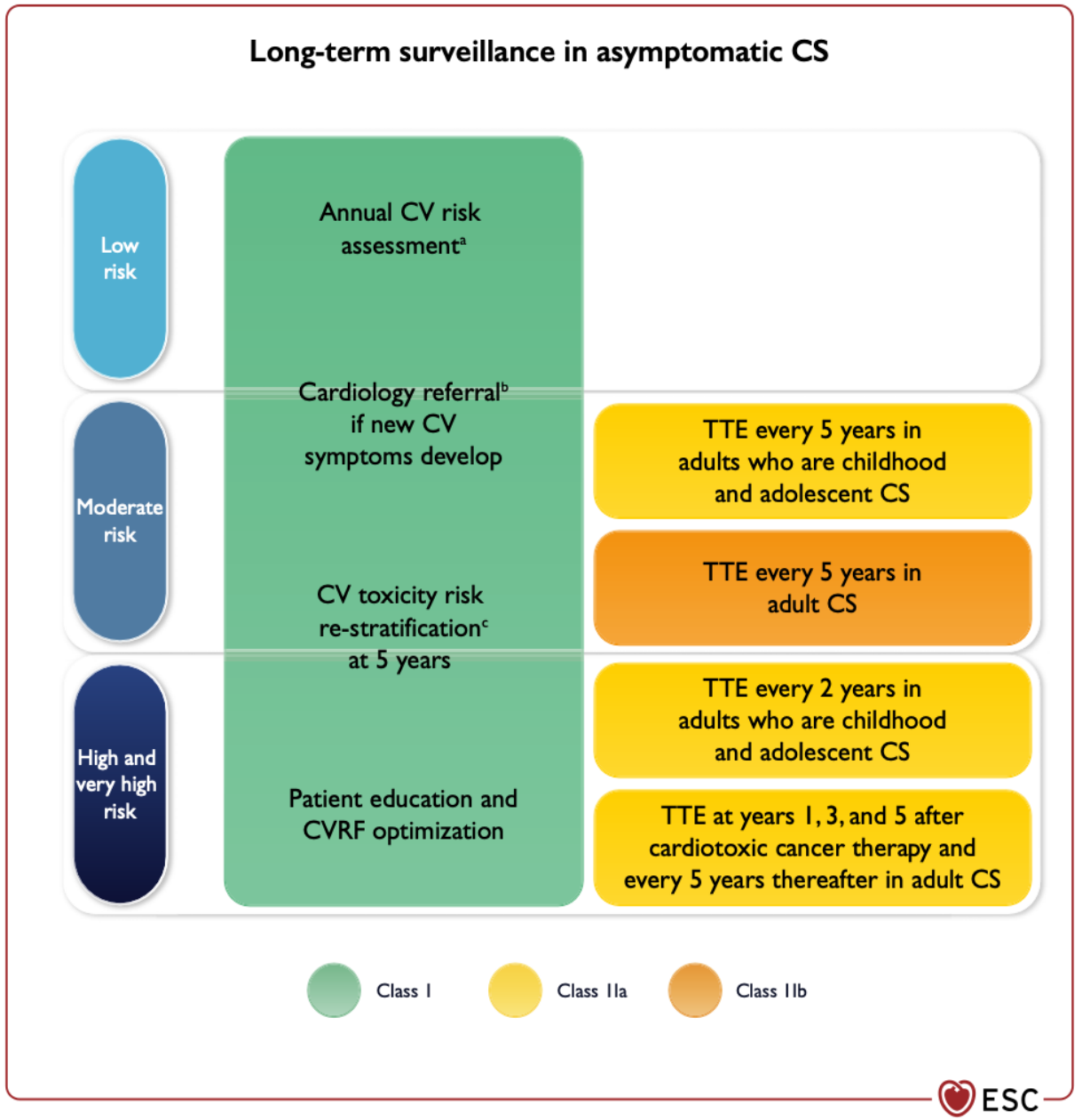
Conclusion: VHD risk is **dose-dependent**; minimized with current RT.



Cutter, D. J. et al. Risk for valvular heart disease after treatment for hodgkin lymphoma. J Natl Cancer Inst 107, (2015).

Table 12 **Risk categories for asymptomatic adult cancer survivors**

Risk category[a]	Patient characteristics
Very high risk	• Very high baseline CV toxicity risk pre-treatment • Doxorubicin[b] ≥ 400 mg/m^2 • RT > 25 Gy MHD[c] • RT > 15–25 Gy MHD[c] + doxorubicin[b] ≥100 mg/m^2
Early high risk (<5 years after therapy)	• High baseline CV toxicity risk • Symptomatic or asymptomatic moderate-to-severe CTRCD during treatment • Doxorubicin[b] 250–399 mg/m^2 • High-risk HSCT[d]
Late high risk	• RT > 15–25 Gy MHD[c] • RT 5–15 Gy MHD[e] + doxorubicin[b] ≥100 mg/m^2 • Poorly controlled CVRF
Moderate risk	• Moderate baseline CV toxicity risk • Doxorubicin[b] 100–249 mg/m^2 • RT 5–15 Gy MHD[e] • RT < 5 Gy MHD[f] + doxorubicin[b] ≥ 100 mg/m^2
Low risk	• Low baseline CV toxicity risk and normal end-of-therapy cardiac assessment • Mild CTRCD during therapy but recovered by the end of cancer therapy • RT < 5 Gy MHD[f] • Doxorubicin[b] < 100 mg/m^2



Surgical vs Minimally Invasive Valve Options

Patients with cancer could be poor candidates for classic cardiac surgery (I.e.. bleeding risk due to coagulopathy/thrombocytopenia, porcelain aorta, infectious risk due immunocompromised states)

Minimally invasive procedures without extracorporeal circulation and transcatheter heart valve interventions present some advantages:

- Minimize perioperative risk and complications associated with major surgery.
- Faster recovery and timely cancer surgery /initiation of cancer therapy

- Suitability depends on anatomy and cancer status.
- Requires careful patient selection and MDT

TAVI: Efficacy and Limitations

TOP-AS Registry (Transcatheter Aortic Valve Replacement in Oncology Patients With Severe Aortic Stenosis)

AIM: To collect data on patients who undergo TAVR while having active malignancy

222 cancer patients (40% stage IV) vs 2522 non-cancer patients from 5 centers.

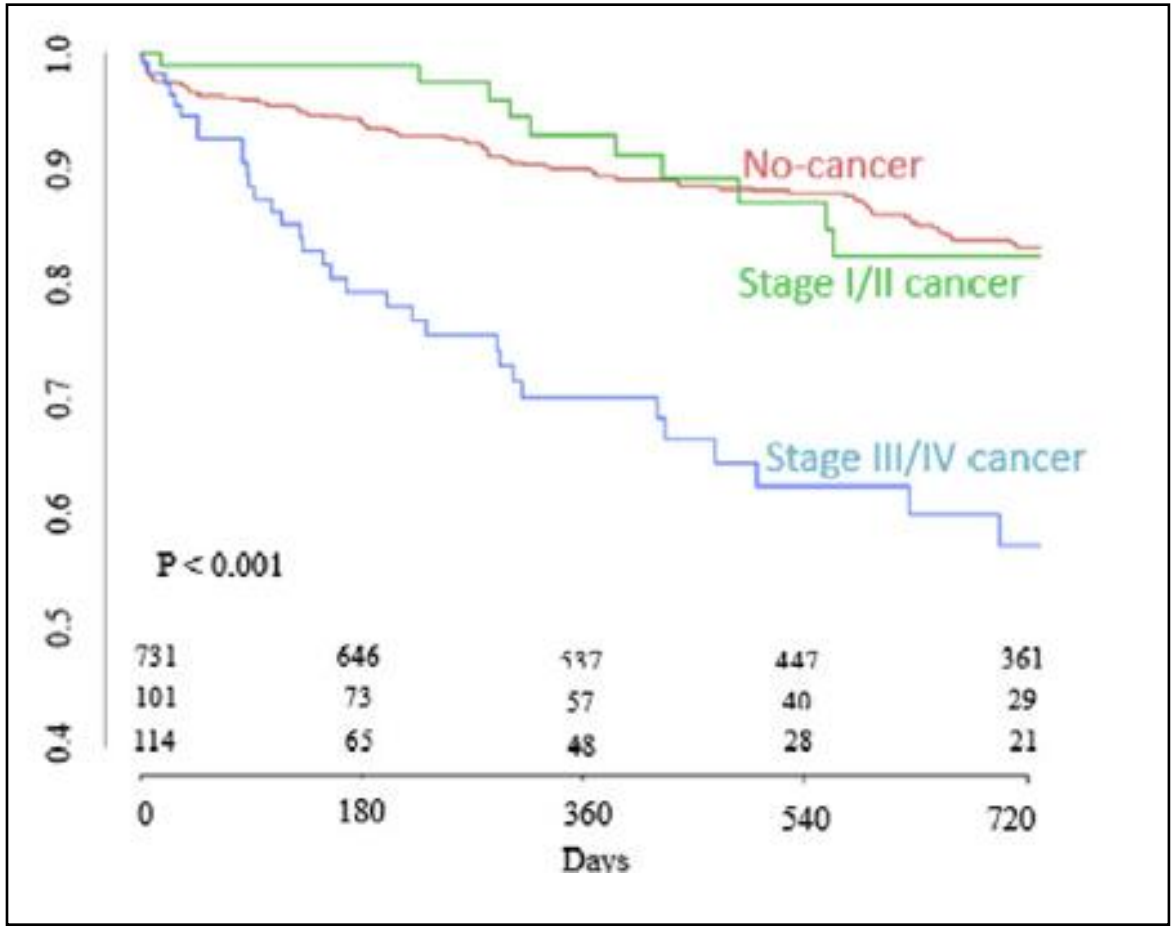
30-day mortality: comparable between groups

1-year mortality:15% in cancer (≈50% cancer-related)
9% in non-cancerp (p< 0.001)

By cancer stage:

Stage I–II → outcomes similar to non-cancer

Stage III–IV/progressive disease → significantly worse survival



Landes, U. *et al.* Transcatheter Aortic Valve Replacement in Oncology Patients With Severe Aortic Stenosis. *JACC Cardiovasc Interv* **12**, 78–86 (2019).

TAVI: Efficacy and Limitations

TAVR in Active Cancer – Role of Tumor Stage

OCEAN-TAVI (n=2336; 89 active cancer) prospective Japanese registry

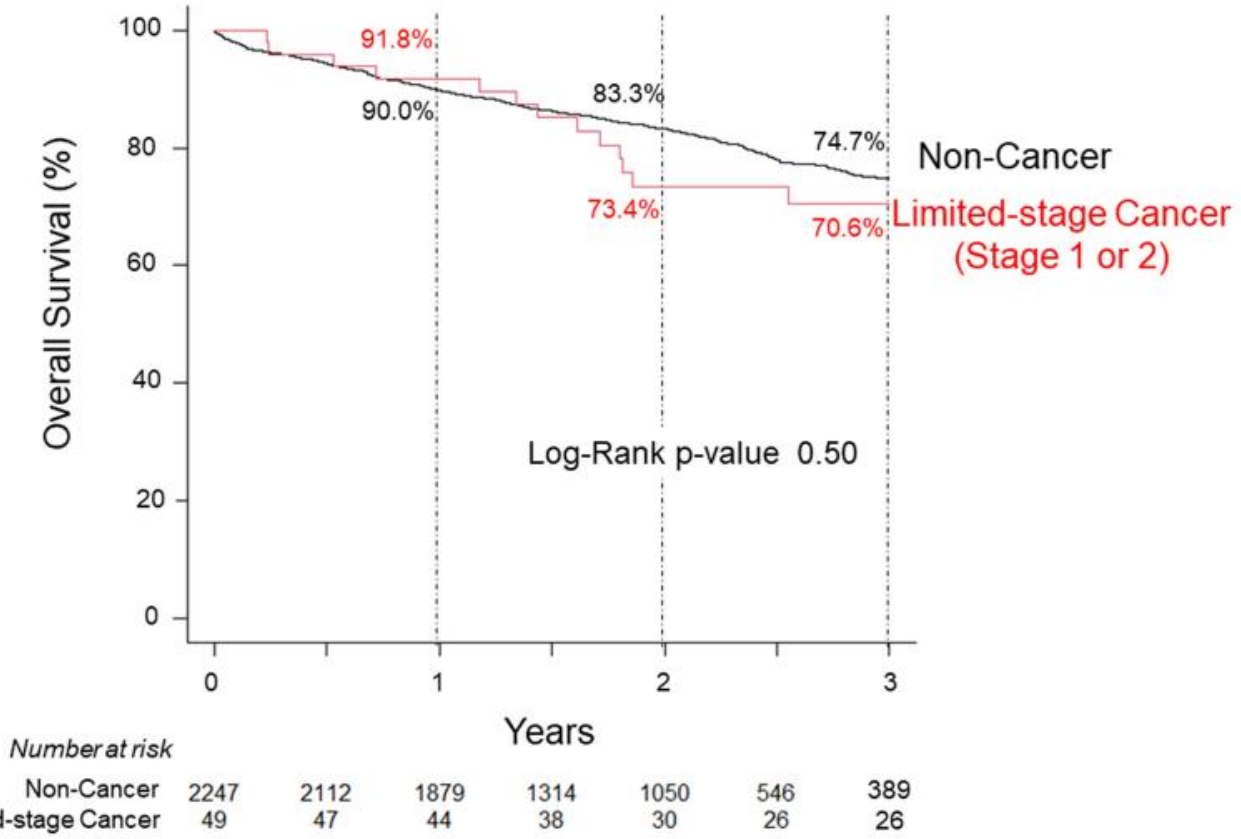
30-day mortality: similar to non-cancer

3-year survival: 64.7% active cancer
74.7% without active cancer (p=0.016).

Limited-stage (I–II): comparable to non-cancer (70.6% vs 74.7%, p=0.50)

Advanced-stage (III–IV): significantly worse, deaths mostly cancer-related

Conclusion:
TAVR is safe in active cancer, but **prognosis depends strongly on cancer stage**.



Noguchi, M. *et al.* Midterm outcomes of transcatheter aortic valve replacement in patients with active cancer. *Open Heart* **11**, (2024).

TAVI: Efficacy and Limitations

Meta-analysis: TAVR in Active Cancer Patients

9 observational studies, 133,906 patients

Population: 9,792 patients with **active cancer** vs non-cancer controls

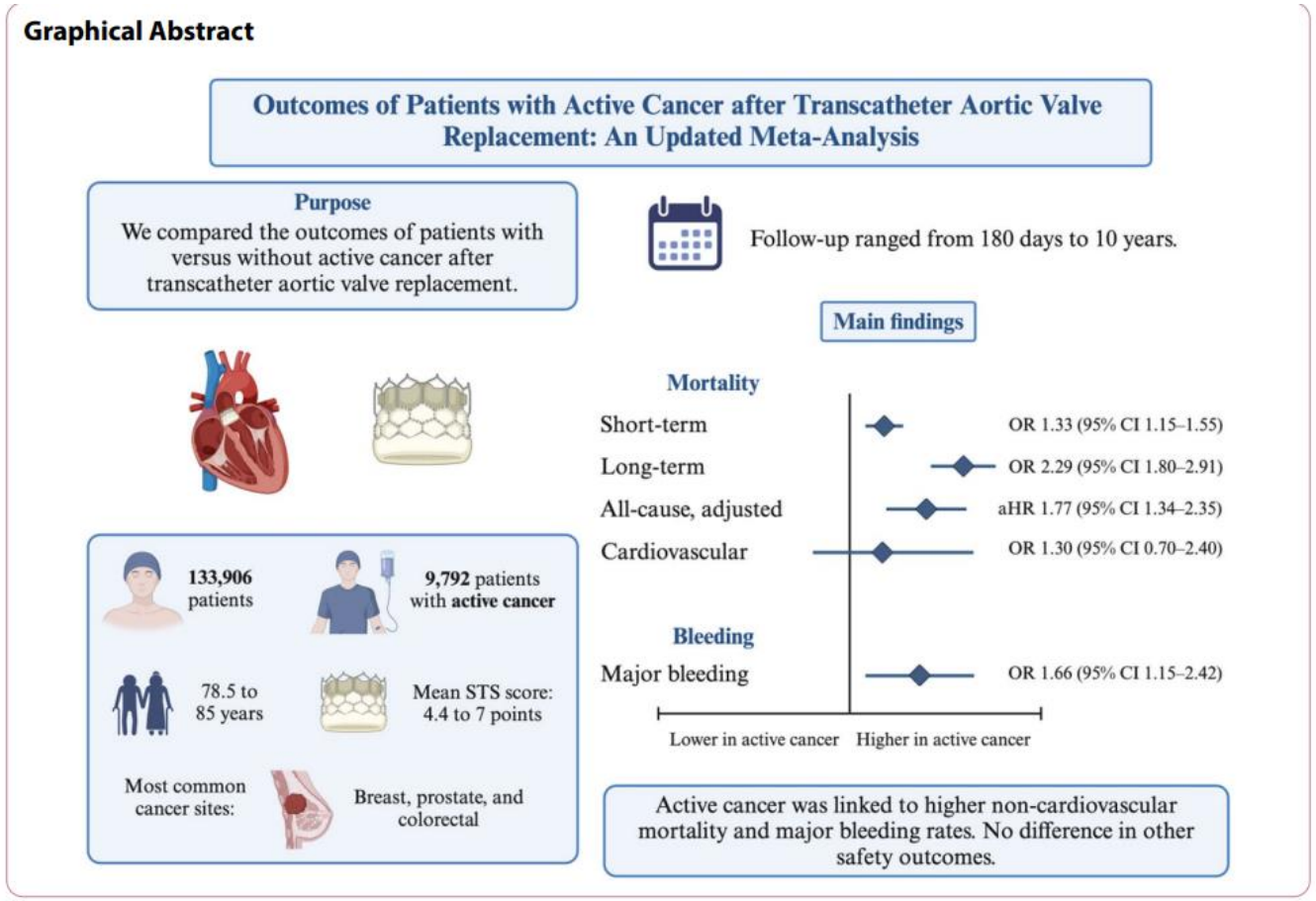
Inclusion criteria:

Severe aortic stenosis treated with **TAVR**

Active malignancy at the time of procedure

Follow-up: 180 days to 10 years

Conclusion:
TAVR in active cancer → **higher non-cardiovascular mortality and bleeding**, but **similar rates of CV mortality**. Need of careful **patient selection and optimal timing for intervention** .



Felix, N. *et al.* Outcomes of patients with active cancer after transcatheter aortic valve replacement: an updated meta-analysis. *Cardio-Oncology* **10**, (2024).

TAVI vs SAVR: The Nationwide Inpatient Sample Database

Data source: Nationwide Inpatient Sample database (2002–2018)

Population: Adults (>18 yrs) undergoing TAVI vs SAVR

Endpoints:

Primary: In-hospital mortality + stroke (MACE)

Secondary: Major bleeding, PPM implantation

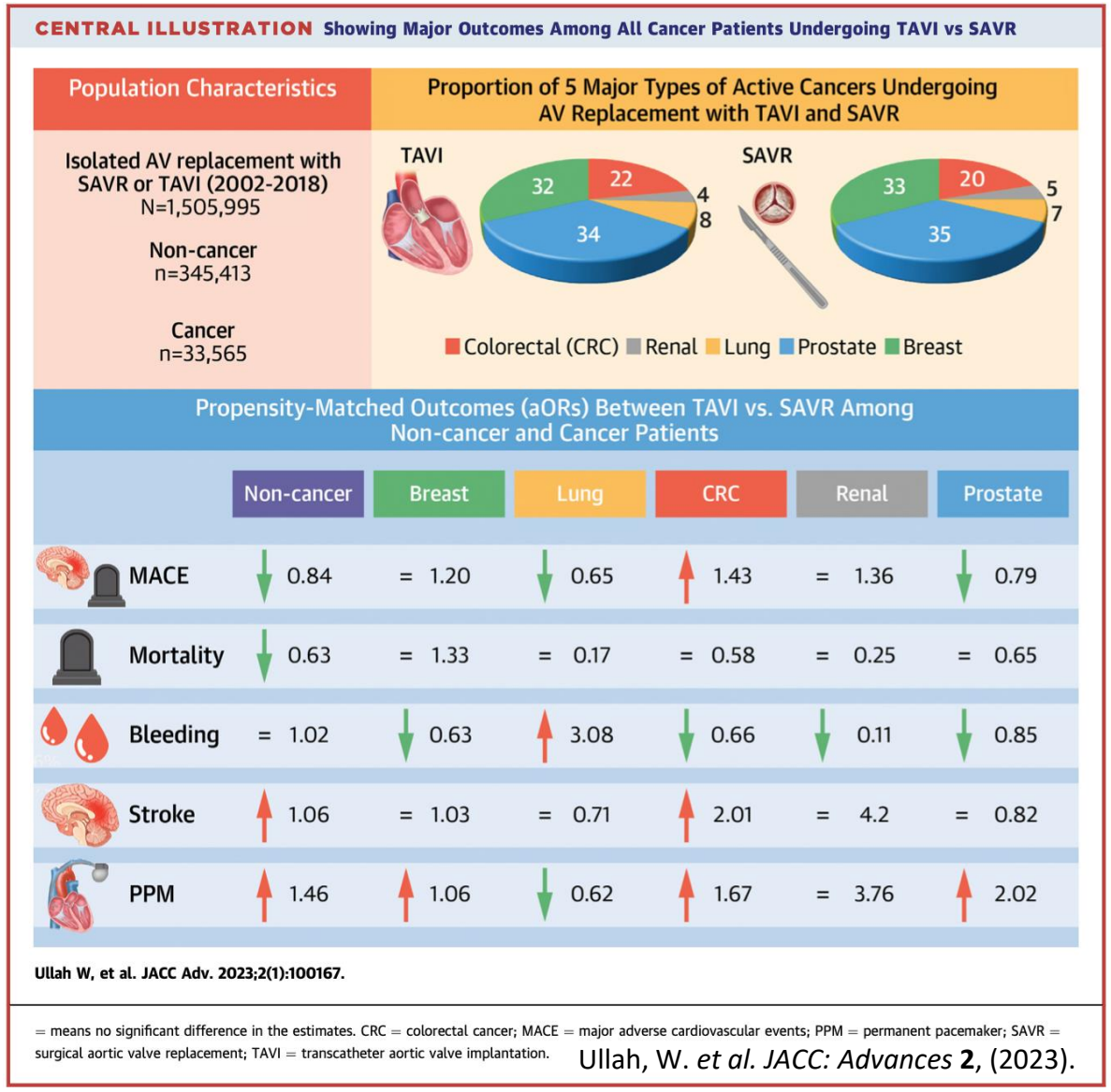
Results

Prostate & lung cancer: lower MACE with TAVI

Colorectal cancer: higher MACE and stroke risk with TAVI

Breast & renal cancer: outcomes comparable to SAVR

Major bleeding lower with TAVI (except lung); pacemaker use consistently higher



Ullah, W. *et al. JACC: Advances* **2**, (2023).

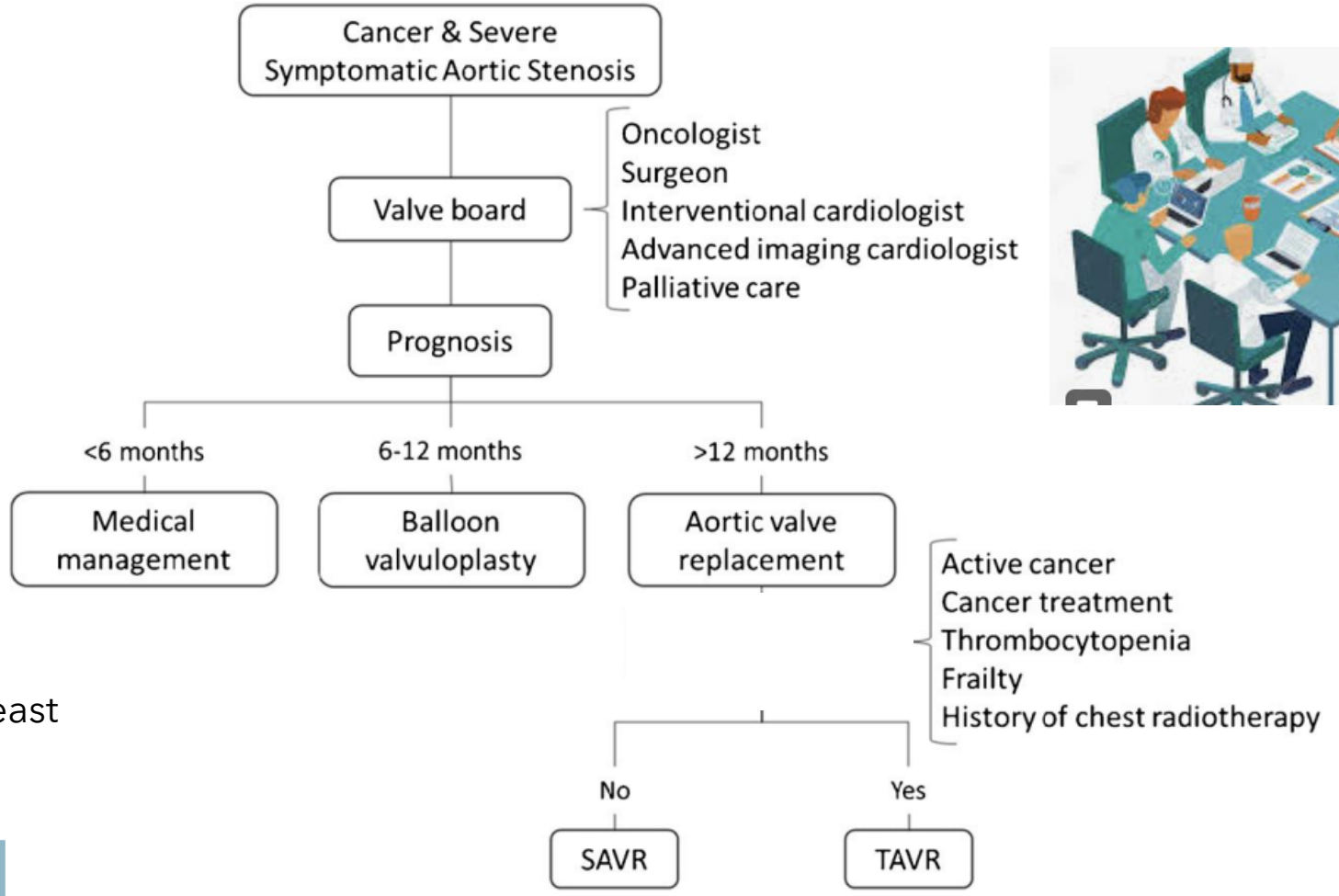
Conclusion:TAVI appears to be a safer alternative to SAVR in patients with breast, prostate, renal, and lung cancers due to a similar or lower risk of MACE and mortality. Females and patients >65 years old might have higher MACE with TAVI in colorectal cancer; however, there was no difference in mortality irrespective of age and sex.

Proposed Algorithm

Comprehensive Assessment:
Characterize the cancer (type, stage, prognosis);
evaluate valvular disease severity;
assess comorbidities;
functional status;
patient preferences.

Estimate life expectancy; estimate risks from valve intervention; expected **gains in symptoms and ability to receive or complete cancer therapy (avoid futility)**

If intervention justified: choose least invasive that achieves goals



TAVI should be considered for patients with symptomatic severe aortic stenosis caused by radiation at intermediate surgical risk.[504,506,693,694,696,697]	IIa	B

2022 ESC Guidelines on cardio-oncology

Modified from Balanescu, S. M. *et al.* The Onco-cardiologist Dilemma: to Implant, to Defer, or to Avoid Transcatheter Aortic Valve Replacement in Cancer Patients with Aortic Stenosis? *Current Cardiology Reports* vol. 21

TEER in Mitral Valve Disease in prior cancer vs non cancer patients

Mitral TEER in Patients With Prior Cancer

Design: Retrospective, multicenter study (Spanish national TEER registry, 2010–2022)

Population: 1237 TEER patients; 164 with prior cancer (breast 20%, leukemia/lymphoma 19%, colorectal 11%)

Methods: Propensity score matching → 163 pairs (cancer vs non-cancer)

Procedural success: High and similar (93% vs 96%)

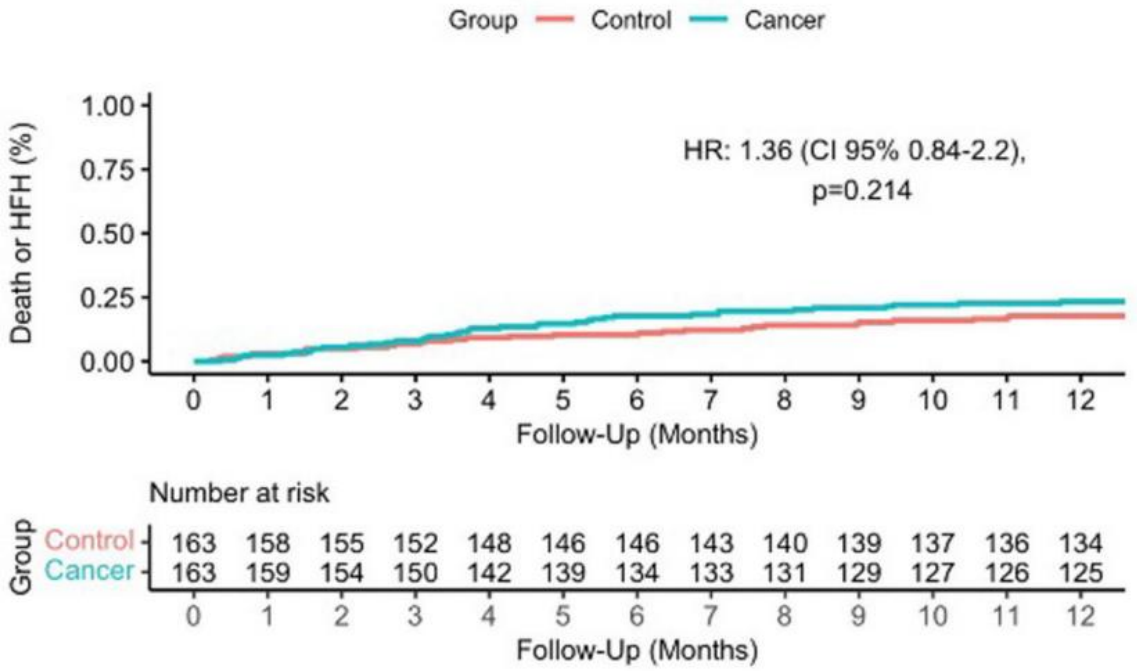
Primary endpoint (death or HF hospitalization at 1 year):

Cancer: 23% vs Non-cancer: 18%, **p=NS**

HR 1.36 (95% CI 0.84–2.20)

Conclusion:
Mitral TEER in patients with prior cancer shows similar safety and efficacy to non-cancer patients → treatment should not be withheld.

Figure 2B. Primary efficacy endpoint



Gonzalez-Manzanares, R. *et al. Transcatheter Mitral Edge-to-Edge Repair in Patients with Prior Cancer Diagnosis*. Abstract European Heart Journal (2024) 45 (Suppl 1)

TEER in Mitral Valve Disease in prior cancer vs non cancer patients

- **Safety and Efficacy of Mitral TEER in Patients With Cancer**
- **Design:** Retrospective cohort (TriNetX database, 2013–2021)
- **Population:** 2,280 TEER patients
  - 513 with history of cancer (28% hematologic, 12.5% metastatic)
  - Propensity-matched: 503 vs 503
- **Outcomes (30 days & 12 months):**
  - HF exacerbation, mortality, stroke, tamponade, bleeding → **NS**
  - 1-year mortality: 16.3% (cancer) vs 18.5% (non-cancer) → **NS**
- **Subgroup (antineoplastic therapy):** similar outcomes
- **Conclusion:**
  TEER shows **comparable safety and efficacy** in patients with and without a history of cancer. It should be **considered in selected cancer patients**.

Table 4
Outcomes at 30 days and 12 months.

Outcome	30 days			12 months		
	TEER without cancer = 503	TEER with cancer = 503	P-value	TEER without cancer = 503	TEER with cancer = 503	p-value
HF exacerbation	52 (10.3 %)	56 (11.1 %)	0.68	70 (13.9 %)	74 (14.7 %)	0.72
All-cause mortality	27 (5.4 %)	19 (3.8 %)	0.23	93 (18.5 %)	82 (16.3 %)	0.36
Blood product transfusion	10 (2.0 %)	10 (2.0 %)	1.00	13 (2.6 %)	21 (4.2 %)	0.16
Ischemic Stroke	10 (2.0 %)	10 (2.0 %)	0.86	10 (2.0 %)	16 (3.2 %)	0.16
Cardiac tamponade	10 (2.0 %)	10 (2.0 %)	1.00	10 (2.0 %)	10 (2.0 %)	1.00
All-cause hospitalization	147 (29.2 %)	152 (30.2 %)	0.73	235 (46.7 %)	265 (52.7 %)	0.06
Subgroup analysis at 12 month						
	No anti-neoplastic therapy = 107			Antineoplastic therapy = 107		p-value
HF exacerbation	24 (22.4 %)			14 (13.0 %)		0.09
All-cause mortality	15 (14.0 %)			17 (15.9 %)		0.19

Khan, S. *et al.* Safety and efficacy of transcatheter edge-to-edge repair (TEER) in patients with history of cancer. *IJC Heart and Vasculature* **44**, (2023).

Key Messages

- The coexistence of active cancer and valvular heart disease is an increasing condition (increased survival of cancer patients, aging and shared risk factors).

- Severe VHD limits treatment options in cancer patients and should be addressed

In favor to treat VHD→ if early stage cancer, good prognosis, and valve treatment represent an opportunity to treat better cancer (receive surgery or chemo)

In favor to do not treat VHD → if prognosis is poor

A multidisciplinary team evaluation and customized decision are crucial in decision making . Avoid futility.

Key Messages

What kind of valve intervention ?

Prefer → minimally invasive procedures without extracorporeal circulation and transcatheter heart valve interventions if poor candidates for classic cardiac surgery and to:

1.Obtain faster recovery and shorter delay of cancer treatment;
2.At risk of infections (immunocompromised states).
3.At risk of bleeding (i.e.. coagulopathy, thrombocytopenia)
4.After radiation therapy (porcelain aorta)

Particularly TAVI represents a safe alternative to SAVR in patients with early stage cancer based to observational data

No RCT available. Long-term outcome data are needed.

THANK YOU!!!