ΠΑΤΡΙΑΝΑΚΟΣ ΑΛΕΞΑΝΔΡΟΣ

Δ/ΝΤΗΣ ΚΑΡΔΙΟΛΟΓΙΑΣ ΕΣΥ

ΠΑ.Γ.Ν.ΗΡΑΚΛΕΙΟΥ

ΚΡΗΤΗ, ΕΛΛΑΔΑ

Καρδιογκολογία: Χρειαζόμαστε κάτι παραπάνω από ένα κλάσμα εξωθήσεως ;

Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

- **Two of them evolved over time to be very useful**
  - **endomyocardial biopsies and**
  - **monitoring of LVEF by cardiac imaging.**
- **Examination of endomyocardial biopsies proved to be the most sensitive and specific parameter for the identification of anthracycline-induced LV dysfunction and became the gold standard in the 1970s**

(J Am Soc Echocardiogr 2014;27:911-39.)

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- **Definition of Cancer Therapeutics–Related Cardiac Dysfunction (CTRCD).**
- **Different definitions of CTRCD have been used historically.**
- **It is the consensus of this committee to define CTRCD as a decrease in the LVEF of >10 %, to a value <53% (normal reference value for two-dimensional (2D) echocardiography (2DE)**

(J Am Soc Echocardiogr 2014;27:911-39.)

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

Table 1 Incidence of left ventricular dysfunction associated with chemotherapy drugs[10–21]

Chemotherapy agents	Incidence (%)
Anthracyclines (dose dependent)	
Doxorubicin (Adriamycin) 400 mg/m² 550 mg/m² 700 mg/m²	 3–5 7–26 18–48
Idarubicin (>90 mg/m²)	5–18
Epirubicin (>900 mg/m²)	0.9–11.4
Mitoxanthone >120 mg/m²	2.6
Liposomal anthracyclines (>900 mg/m²)	2
Alkylating agents	
Cyclophosphamide	7–28
Ifosfamide <10 g/m² 12.5–16 g/m²	 0.5 17
Antimetabolites	
Clofarabine	27
Antimicrotubule agents	
Docetaxel	2.3–13
Paclitaxel	<1
Monoclonal antibodies	
Trastuzumab	1.7–20.1[28a]
Bevacizumab	1.6–4[14b]
Pertuzumab	0.7–1.2
Small molecule tyrosine kinase inhibitors	
Sunitinib	2.7–19
Pazopanib	7–11
Sorafenib	4–8
Dasatinib	2–4
Imatinib mesylate	0.2–2.7
Lapatinib	0.2–1.5
Nilotinib	1
Proteasome inhibitors	
Carfilzomib	11–25
Bortezomib	2–5
Miscellaneous	
Everolimus	<1
Temsirolimus	<1

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Table 4 Baseline risk factors for cardiotoxicity

Current myocardial disease	*Demographic and other CV risk factors*
• Heart failure (with either preserved or reduced ejection fraction) • Asymptomatic LV dysfunction (LVEF <50% or high natriuretic peptide[a]) • Evidence of CAD (previous myocardial infarction, angina, PCI or CABG, myocardial ischaemia) • Moderate and severe VHD with LVH or LV impairment • Hypertensive heart disease with LV hypertrophy • Hypertrophic cardiomyopathy • Dilated cardiomyopathy • Restrictive cardiomyopathy • Cardiac sarcoidosis with myocardial involvement • Significant cardiac arrhythmias (e.g. AF, ventricular tachyarrhythmias)	• Age (paediatric population <18 years; >50 years for trastuzumab; >65 years for anthracyclines) • Family history of premature CV disease (<50 years) • Arterial hypertension • Diabetes mellitus • Hypercholesterolaemia
Previous cardiotoxic cancer treatment	***Lifestyle risk factors***
• Prior anthracycline use • Prior radiotherapy to chest or mediastinum	• Smoking • High alcohol intake • Obesity • Sedentary habit

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Table 1 Characteristics of type I and II CTRCD

	Type I	Type II
Characteristic agent	Doxorubicin	Trastuzumab
Clinical course and typical response to antiremodeling therapy (β-blockers, ACE inhibitors)	May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress	High likelihood of recovery (to or near baseline cardiac status) in 2–4 months after interruption (reversible)
Dose effects	Cumulative, dose related	Not dose related
Effect of rechallenge	High probability of recurrent dysfunction that is progressive; may result in intractable heart failure or death	Increasing evidence for the relative safety of rechallenge (additional data needed)
Ultrastructure	Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)	No apparent ultra structural abnormalities (though not thoroughly studied)

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Table 2 Recommended cardio-oncology echocardiogram protocol

Standard transthoracic echocardiography
- In accordance with ASE/EAE guidelines and IAC-Echo

2D strain imaging acquisition
- Apical three-, four-, and two-chamber views
  - Acquire ≥3 cardiac cycles
- Images obtained simultaneously maintaining the same 2D frame rate and imaging depth
  - Frame rate between 40 and 90 frames/sec or ≥40% of HR
- Aortic VTI (aortic ejection time)

2D strain imaging analysis
- Quantify segmental and global strain (GLS)
- Display the segmental strain curves from apical views in a quad format
- Display the global strain in a bull's-eye plot

2D strain imaging pitfalls
- Ectopy
- Breathing translation

3D imaging acquisition
- Apical four-chamber full volume to assess LV volumes and LVEF calculation
- Single and multiple beats optimizing spatial and temporal resolution

Reporting
- Timing of echocardiography with respect to the IV infusion (number of days before or after)
- Vital signs (BP, HR)
- 3D LVEF/2D biplane Simpson's method
- GLS (echocardiography machine, software, and version used)
- In the absence of GLS, measurement of medial and lateral s′ and MAPSE
- RV: TAPSE, s′, FAC

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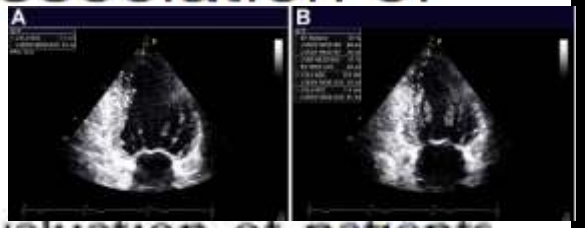

Key Points

- Echocardiography is the method of choice for the evaluation of patients before, during, and after cancer therapy. Accurate calculation of LVEF should be done with the best method available in the echocardiography laboratory (ideally 3DE).
- When using 2DE, the modified biplane Simpson's technique is the method of choice.
- LVEF should be combined with the calculation of wall motion score index.
- In the absence of global longitudinal strain (GLS) by STE, quantification of LV longitudinal function using mitral annular displacement by M-mode echocardiography and/or peak systolic velocity (s′) of the mitral annulus by pulsed-wave DTI is recommended.
- LVEF assessed by 2DE often fails to detect small changes in LV contractility.

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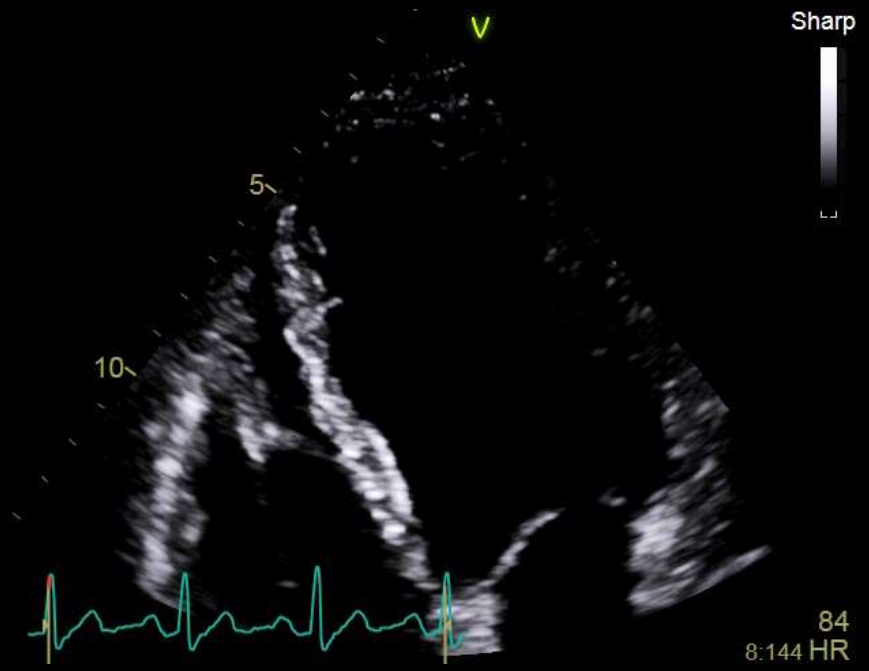
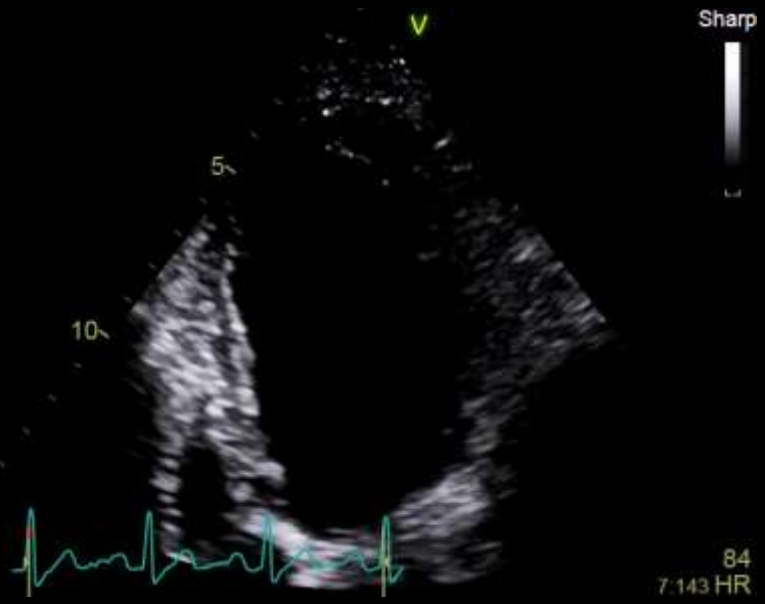
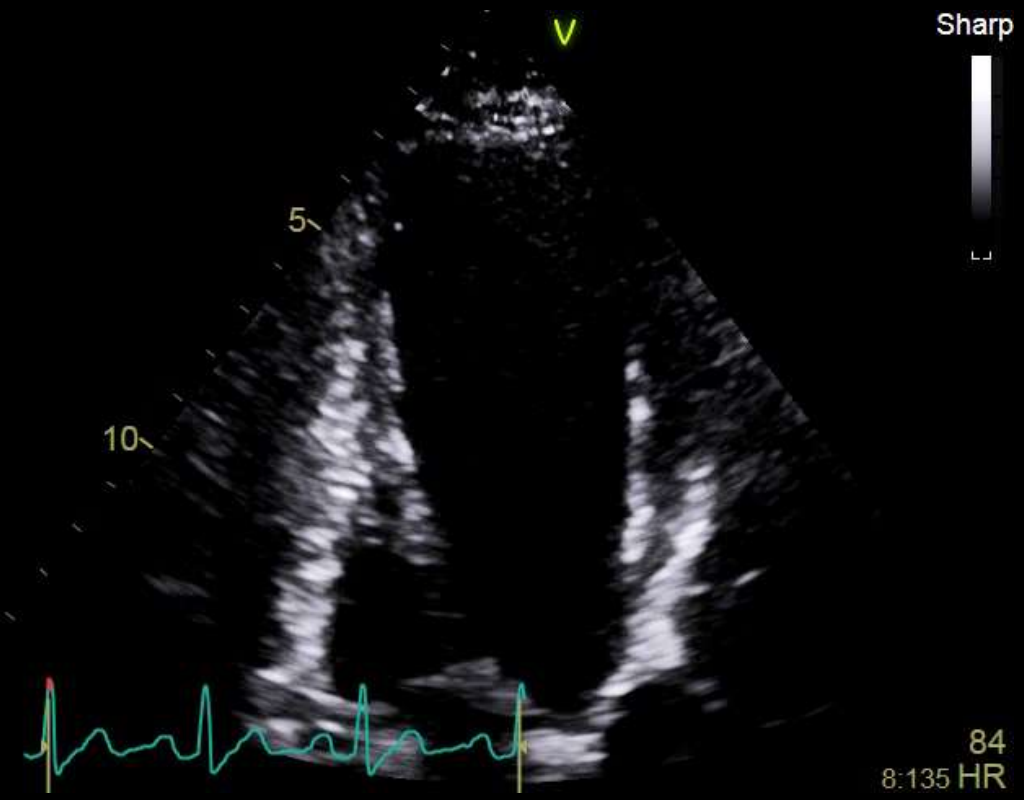
Table 6 Proposed diagnostic tools for the detection of cardiotoxicity

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Echocardiography: - 3D-based LVEF - 2D Simpson's LVEF - GLS	LLN = lower limit of normality; decrease to a value below the LLN suggests cardiotoxicity. • GLS: >15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.	• Wide availability. • Lack of radiation. • Assessment of haemodynamics and other cardiac structures.	• Inter-observer variability. • Image quality. • GLS: inter-vendor variability, technical requirements.
Nuclear cardiac imaging (MUGA)	• >10 percentage points decrease in LVEF with a value <50% identifies patients with cardiotoxicity.	• Reproducibility.	• Cumulative radiation exposure. • Limited structural and functional information on other cardiac structures.
Cardiac magnetic resonance	• Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines.	• Accuracy, reproducibility. • Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation.	• Limited availability. • Patient's adaptation (claustrophobia, breath hold, long acquisition times).
Cardiac biomarkers: - Troponin I - High-sensitivity Troponin I - BNP - NT-proBNP	• A rise identifies patients receiving anthracyclines who may benefit from ACE-Is. • Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs futher investigation.	• Accuracy, reproducibility. • Wide availability. • High-sensitivity.	• Insufficient evidence to establish the significance of subtle rises. • Variations with different assays. • Role for routine surveillance not clearly established.

Ασθενής 63 ετών με γνωστό ιστορικό DCM υπό ΧΜΘ λόγω non- Hodgkin Λεμφώματος







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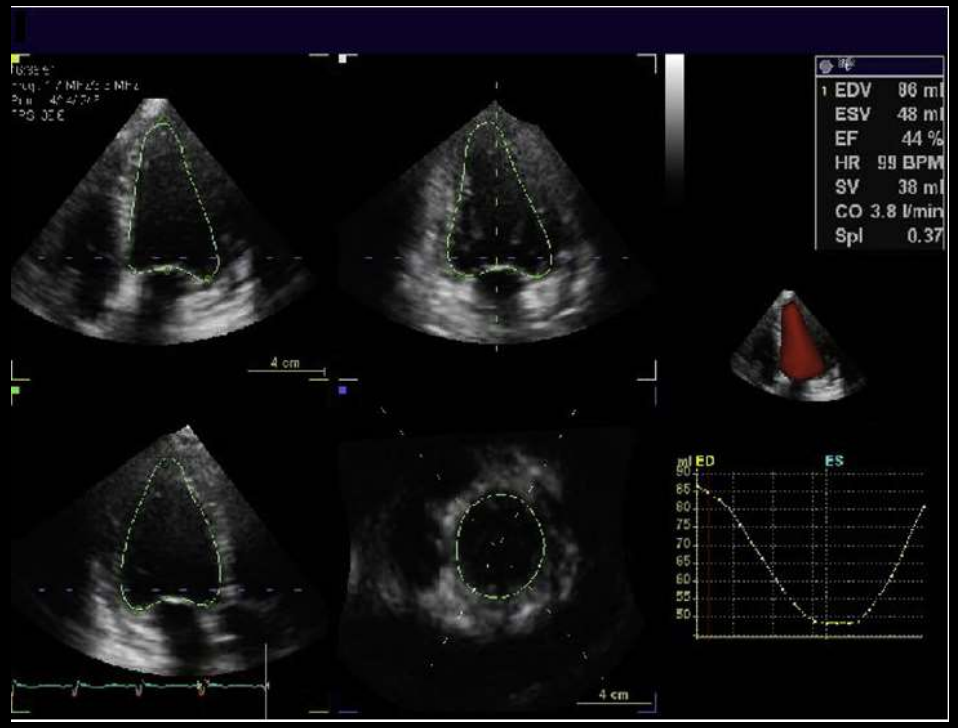

Key Points

- Three-dimensional echocardiography is the preferred technique for monitoring LV function and detecting CTRCD in patients with cancer. Advantages include better accuracy in detecting LVEF below the lower limit of normal, better reproducibility, and lower temporal variability compared with 2DE in patients with cancer treated with chemotherapy.
- Costs, availability, high reliance on image quality, and need for training of operators currently limit the wide application of 3DE in the oncologic setting.

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Key Points

- Myocardial deformation (strain) can be measured using DTI or 2D STE. The latter is favored because of a lack of angle dependency.
- GLS is the optimal parameter of deformation for the early detection of subclinical LV dysfunction.
- Ideally, the measurements during chemotherapy should be compared with the baseline value. In patients with available baseline strain measurements, a relative percentage reduction of GLS of <8% from baseline appears not to be meaningful, and those >15% from baseline are very likely to be abnormal.
- When applying STE for the longitudinal follow-up of patients with cancer, the same vendor-specific ultrasound machine should be used.

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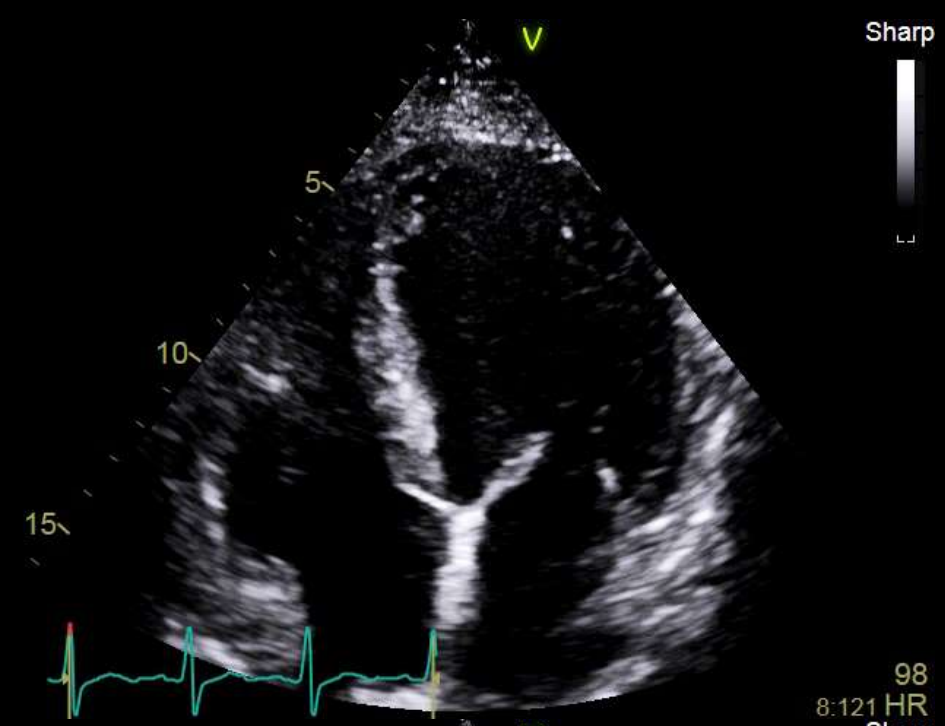

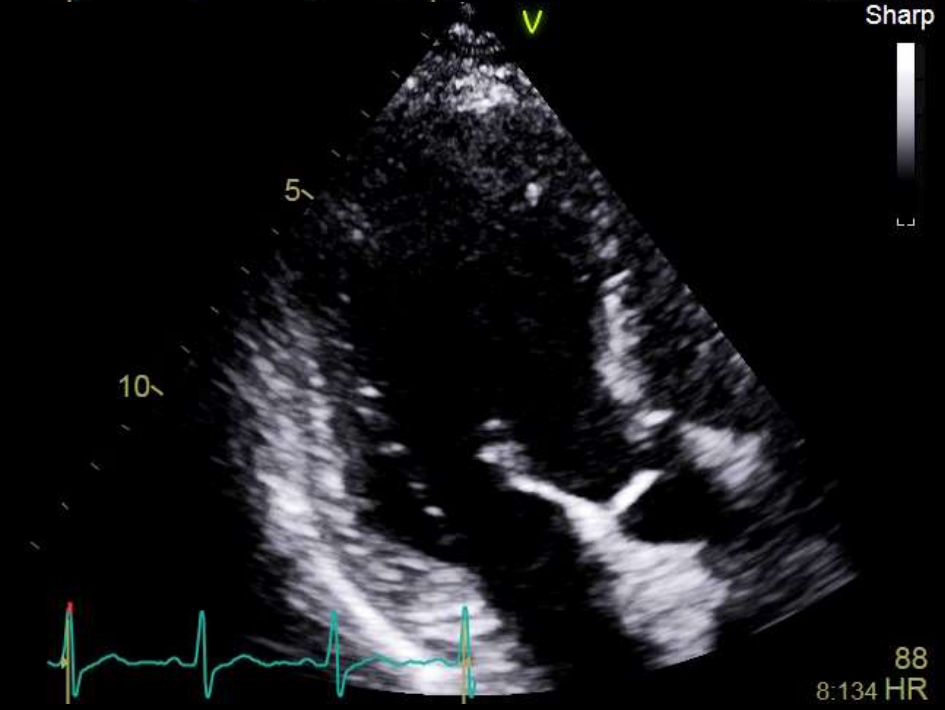

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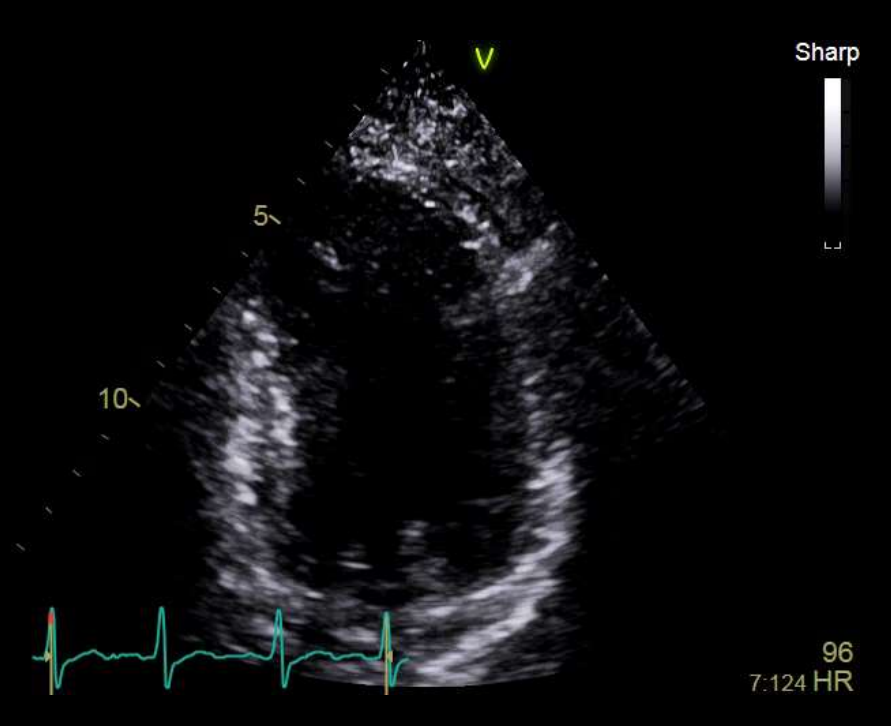

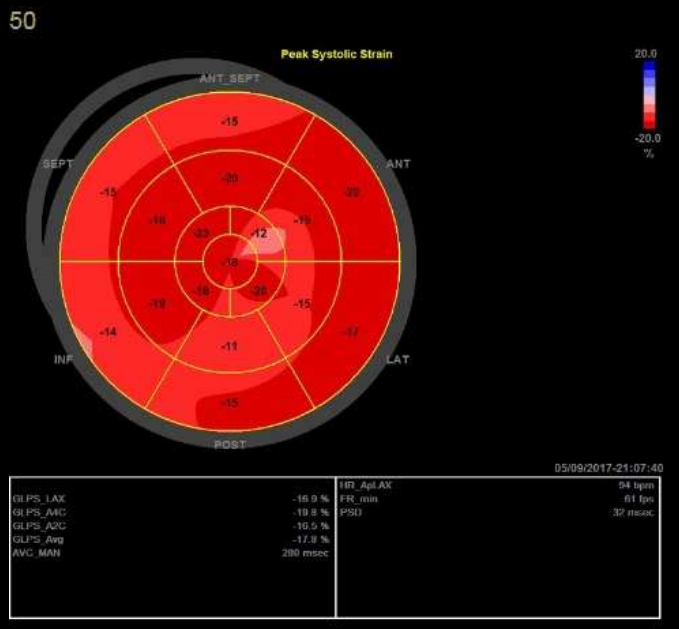

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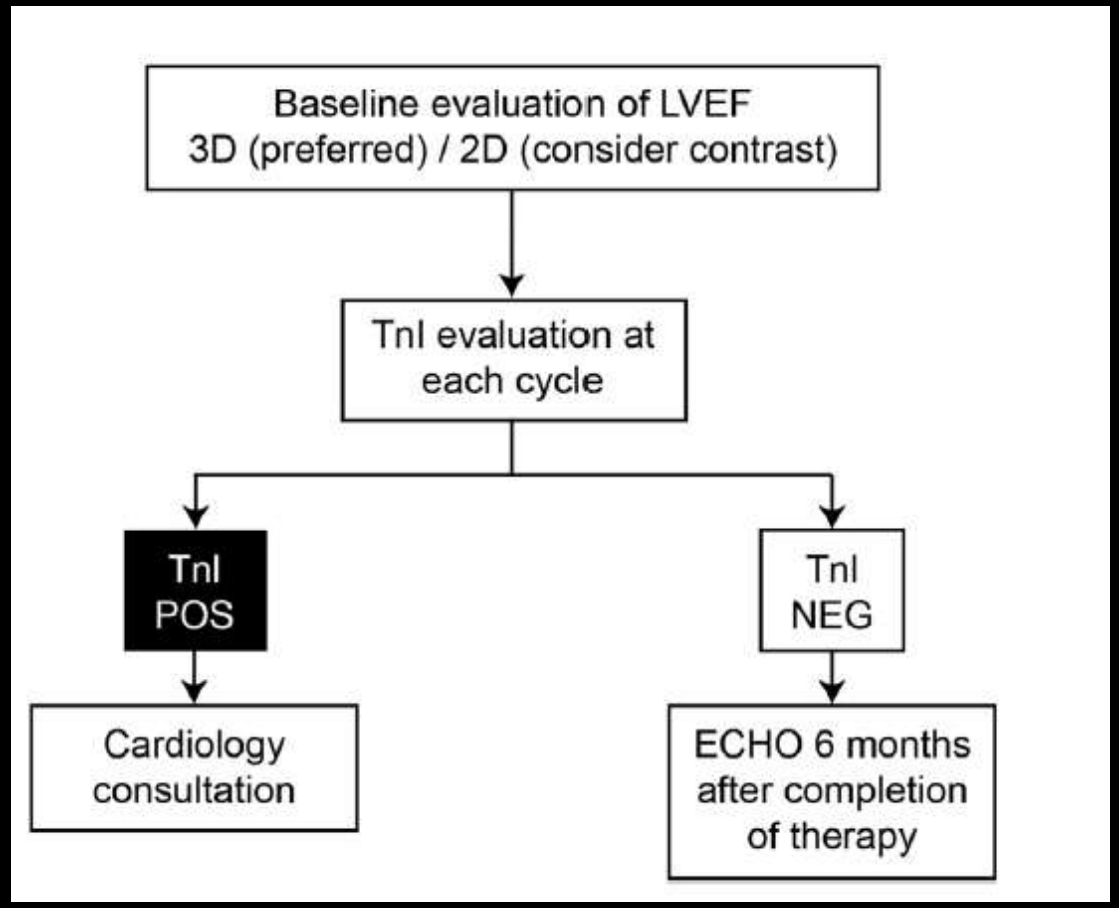

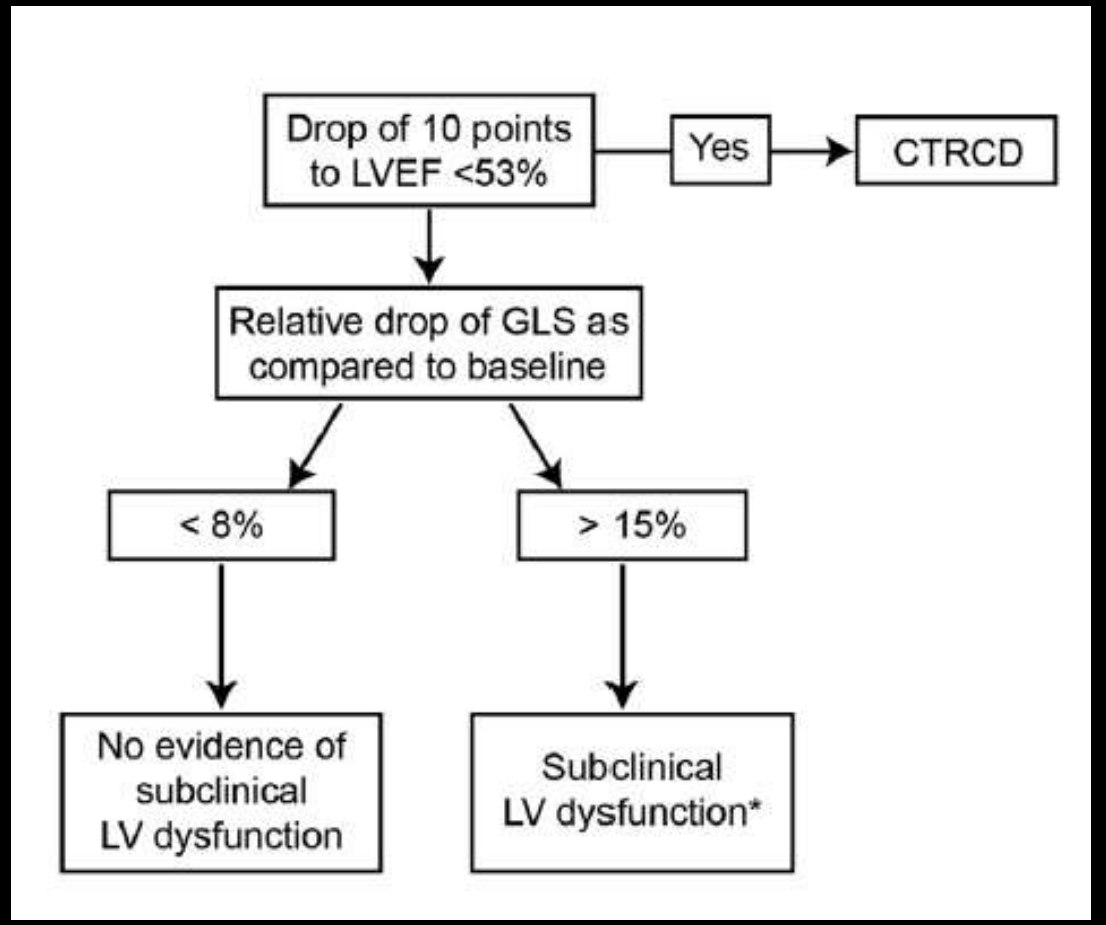

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Table 8 Cancer drug agents associated with cardiac arrhythmias

Type of arrhythmia	Causative drug
Bradycardia	Arsenic trioxide, bortezomib, capecitabine, cisplatin, cyclophosphamide, doxorubicine, epirubicine, 5-FU, ifosfamide, IL-2, methotrexate, mitoxantrone, paclitaxel, rituximab, thalidomide.
Sinus tachycardia	Anthracyclines, carmustine.
Atrioventricular block	Anthracyclines, arsenic trioxide, bortezomib, cyclophosphamide, 5-FU, mitoxantrone, rituximab, taxanes, thalidomide.
Conduction disturbances	Anthracyclines, cisplatin, 5-FU, imatinib, taxanes.
Atrial fibrillation	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan), anthracyclines, antimetabolites (capecitabine, 5-FU, gemcitabine), IL-2, interferons, rituximab, romidepsin, small molecule TKIs (ponatinib, sorafenib, sunitinib, ibrutinib), topoisomerase II inhibitors (amsacrine, etoposide), taxanes, vinca alkaloids.
Supraventricular tachycardias	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan), amsacrine, anthracyclines, antimetabolites (capecitabine, 5-FU, methotrexate), bortezomib, doxorubicin, IL-2, interferons, paclitaxel, ponatinib, romidepsin.
Ventricular tachycardia/fibrillation	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide), amsacrine, antimetabolites (capecitabine, 5-FU, gemcitabine), arsenic trioxide, doxorubicin, interferons, IL-2, methotrexate, paclitaxel, proteasome inhibitors (bortezomib, carfilzomib), rituximab, romidepsin.
Sudden cardiac death	Anthracyclines (reported as very rare), arsenic trioxide (secondary to torsade de pointes), 5-FU (probably related to ischaemia and coronary spasm), interferons, nilotinib, romidepsin.

5 FU — 5 fluorouracil; IL 2 — interleukin 2; TKI — tyrosine kinase inhibitor.

Table 7 Pathophysiological mechanisms of coronary artery disease in cancer treatment[7,60,81,99,117–123]

Agent	Pathophysiological mechanism	Risk of coronary artery disease and acute coronary syndrome
Fluoropyrimidines (5-FU, capecitabine, gemcitabine)	• Endothelial injury • Vasospasm	• Up to 18% manifest myocardial ischaemia • Up to 7–10%: silent myocardial ischaemia
Platinum compounds (cisplatin)	• Procoagulant status • Arterial thrombosis	• 20-year absolute risk of up to 8% after testicular cancer • 2% risk of arterial thrombosis
VEGF inhibitors (bevacizumab, sorafenib, sunitinib)	• Procoagulant status • Arterial thrombosis • Endothelial injury	• Risk of arterial thrombosis: bevacizumab 3.8%, sorafenib 1.7%, sunitinib 1.4%
Radiotherapy	• Endothelial injury • Plaque rupture • Thrombosis	• 2–7-fold increased relative risk of myocardial infarction • Cumulative 30-year coronary events incidence of 10% in Hogdkin lymphoma survivors • Risk proportional to irradiation dose

5 FU — 5 fluorouracil; VEGF — vascular endothelial growth factor.

Συμπέρασμα –Ερωτήματα

- Φτάνει μόνο του το ΚΕ ?
- Φτάνει το ΚΕ σε συνδυασμό με το AFI?
- Φτάνει το ΚΕ +AFI+ Troponin?
- Χρειάζονται άλλοι παράμετροι και ποιοι και σε ποιους ασθενείς ?