Echokardiografie v hematologii
KARDIOTOXICITA

Lubomír Elbl

XXVI. Výroční sjezd ČKS, Brno 2018

Cancer Facts & Figures 2014

American Cancer Society. *Cancer Facts & Figures 2014*. Atlanta: American Cancer Society; 2014

Figure 2. Trends in Pediatric Cancer Incidence Rates by Site, Ages 0-19, 1975-2010

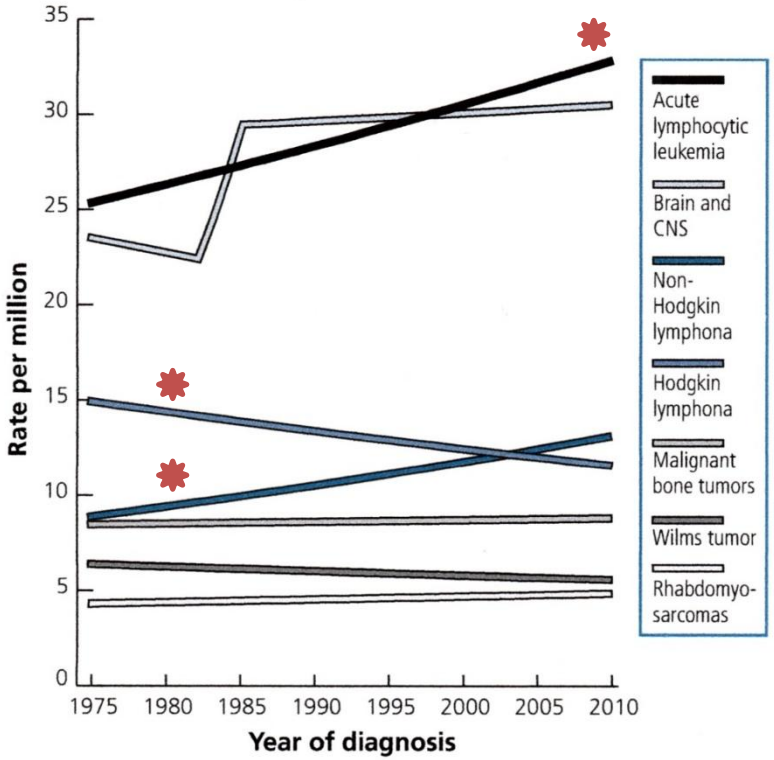
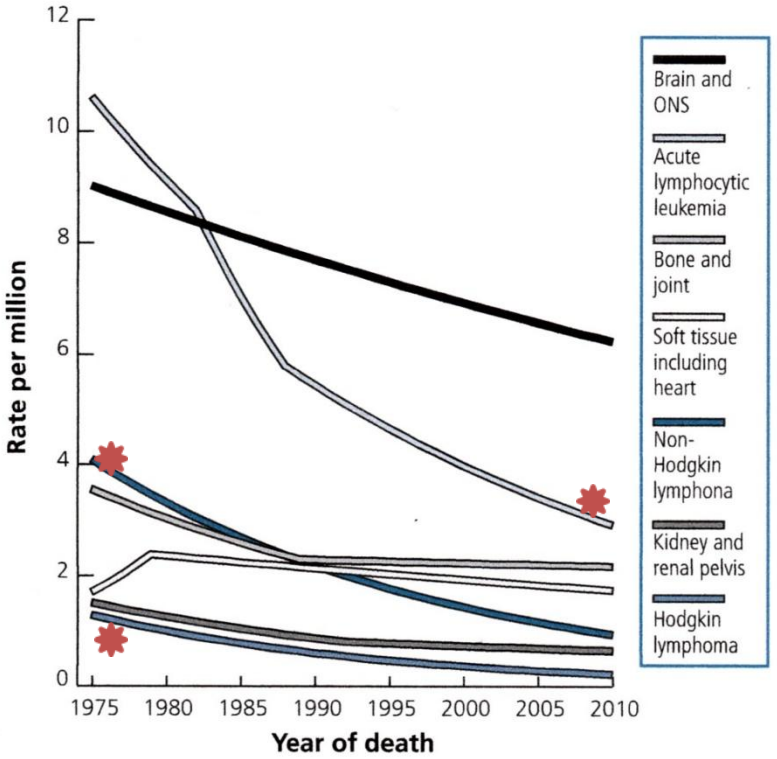


Figure 3. Trends in Pediatric Cancer Mortality Rates by Site, Ages 0-19, 1975-2010



Cancer Facts & Figures 2014

American Cancer Society. *Cancer Facts & Figures 2014*. Atlanta: American Cancer Society; 2014

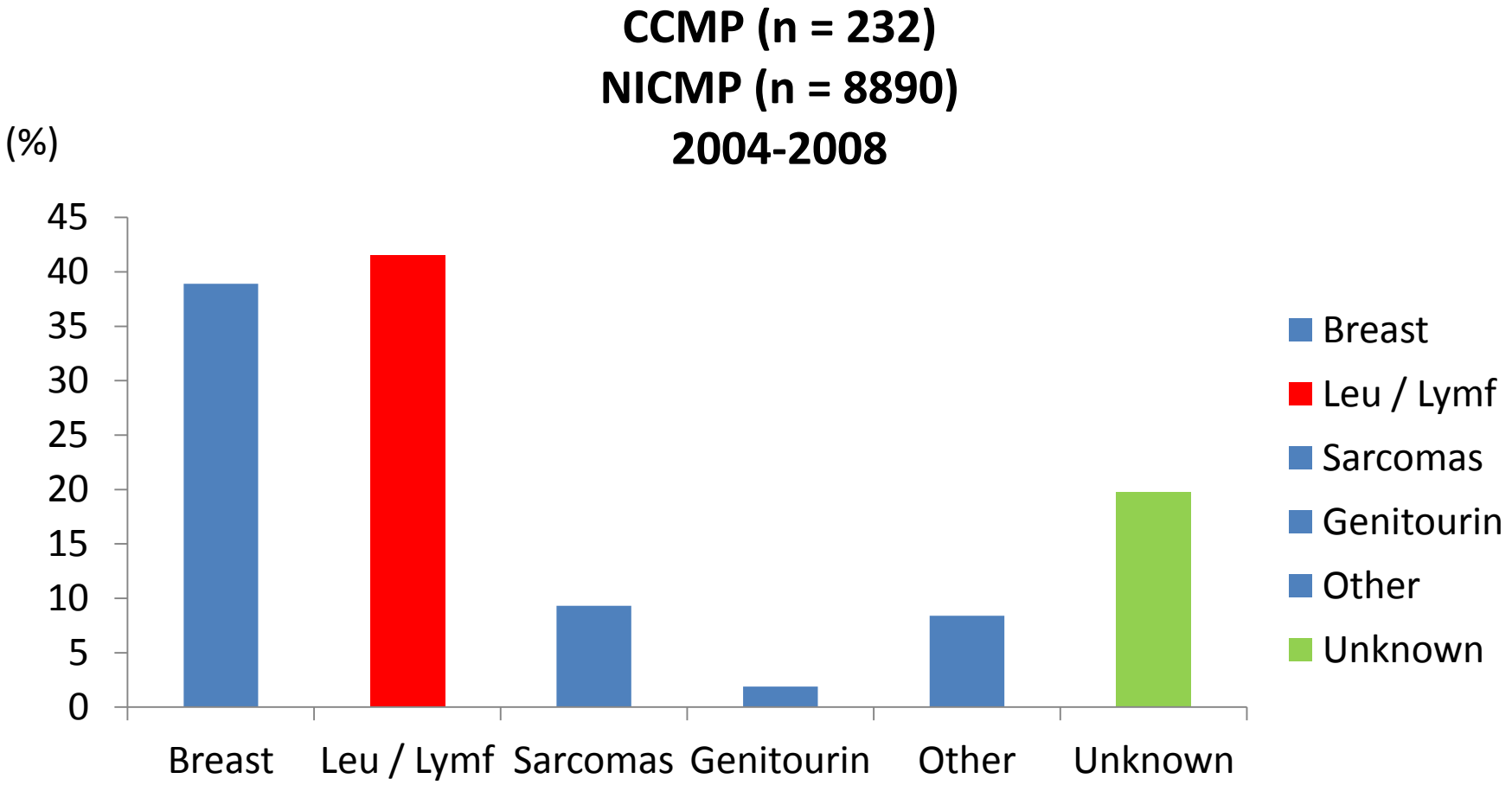
Table 1. Highest incidence invasive cancers, survivorship over time and associated cardiotoxic agents.

Cancer subtype†	Estimated new cases 2014 (n)	5-year survival 1975–1979 (%)	5-year survival 2006–2010 (%)	Cardiotoxic anticancer agents
Prostate	233,000	68.7	99.6	Doxorubicin, mitoxantrone
Breast (female)	232,670	74.6	90.6	5-fluorouracil, capecitabine, cisplatin, cyclophosphamide, doxorubicin, epirubicin, lapatinib, pertuzumab, trastuzumab
Lung and bronchus	224,210	12.5	17.5	Bevacizumab, cisplatin, doxorubicin, vincristine
Colon and rectum	136,830	50.4	65.9	5-fluorouracil, aflibercet, bevacizumab, capecitabine
Melanoma	76,100	82.0	92.8	Cisplatin, IFN-α-2b
Bladder	74,690	73.0	80.6	5-fluorouracil, cisplatin, cyclophosphamide, doxorubicin, mitomycin
Non-Hodgkin lymphoma	70,800	46.8	70.3	Doxorubicin, ifosfamide, vincristine
Kidney and renal pelvis	63,920	50.9	73.5	Bevacizumab, doxorubicin, IFN-α-2b, pazopanib, sunitinib, sorafenib,
Uterine corpus	52,630	85.8	84.7	Cisplatin, doxorubicin
Leukemia	52,380	34.6	60.8	Alemtuzumab, all-transretinoic acid, busulfan, clofarabine, cyclophosphamide, cytarabine, dasatinib, doxorubicin, idarubicin, imatinib mesylate, mitoxantrone, pentostatin, vincristine
Pancreas	46,420	2.5	7.3	5-fluorouracil, capecitabine, mitomycin, sunitinib

Estimated new cases in 2014 reported from the American Cancer Society: Cancer Facts and Figures 2014 [6].
5-year survival data for invasive disease was reported by the SEER cancer statistics [1].
†Estimated new cases from the American Cancer Society exclude basal cell and squamous cell skin carcinoma, and statistics for bladder cancer include invasive and *in situ*.

Characteristics and survival of patients with chemotherapy-induced cardiomyopathy undergoing heart transplantation

Oliveira GH et al. J Heart Lung Transplant 2012;31:805-810



Výskyt poruchy funkce LK v důsledku onkologické léčby

Protinádorová látka	Incidence LK dysfunkce (%)
ANTRACYKLINY	1-48
ALKYLAČNÍ LÁTKY - cyklofoslamid - ifosfamid	7-28
ANTIMETABOLITY - clofarabin	27
MONOKLONÁLNÍ PROTILÁTKY - trastuzumab	1-20
TYROZINKINÁZOVÉ INHIBITORY - sunitinib	3-19
INHIBITORY PROTEASOMU - bortezomib - carfilzomib	2-25

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Onkologická léčba / akutní koronární syndrom

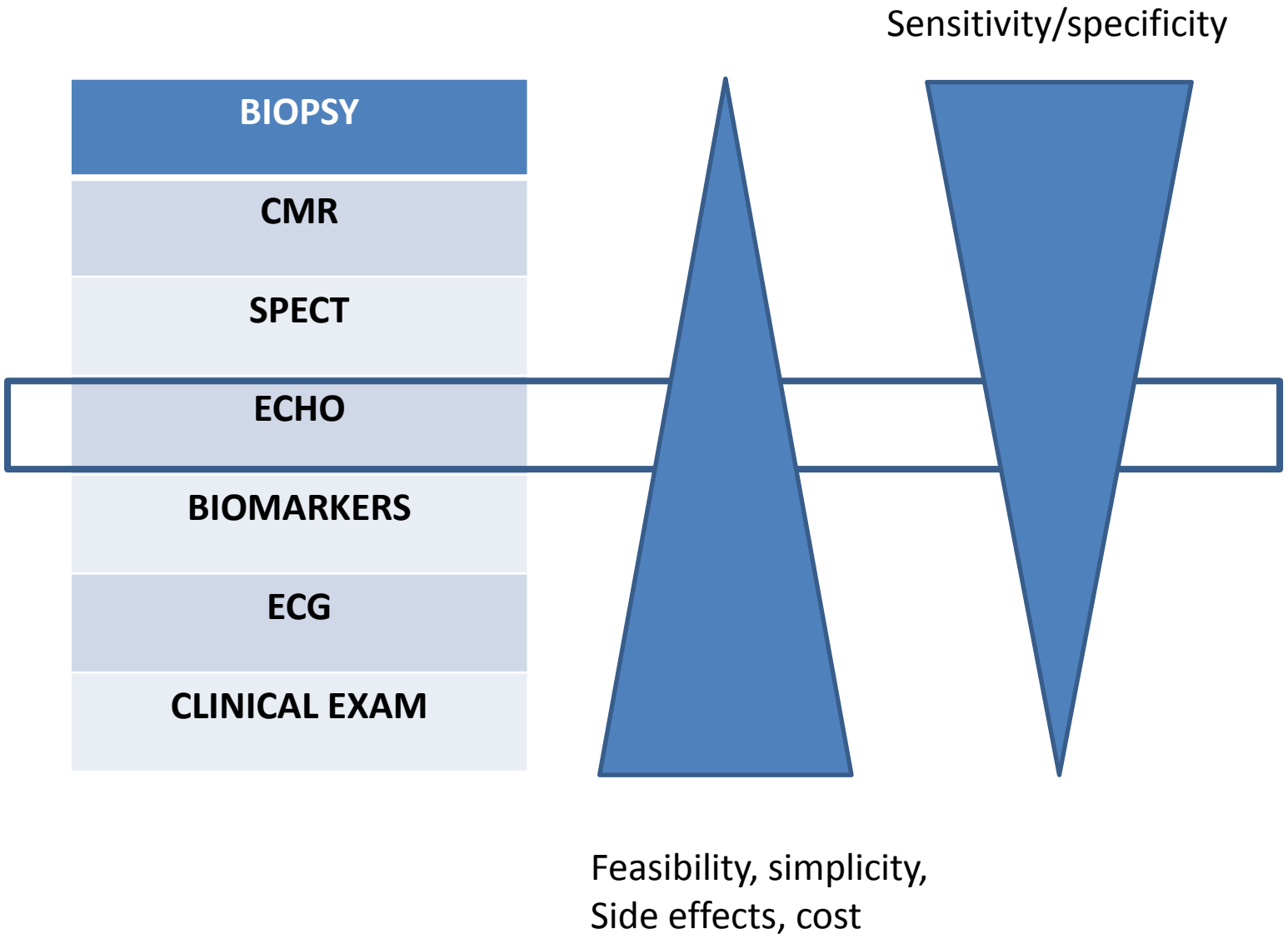
Chang HM et al. JACC 2017;70:2536-51

LÁTKA	FREKVENCE UŽITÍ	INCIDENCE (%)	TIMING
ANTIMETABOLITY Capecitabin 5 - FU	 ++++ ++++	 3 – 9 1 – 68	Během aplikace
MONOKLONÁLNÍ PROTILÁTKY Bevacizumab	+++	0,6 – 8,5	20 M follow-up
INHIBITORY THYROZINKINÁZY Nilotinib Ponatinib	 ++++ +	 5,0 – 9,4 12	Během léčby
INHIBITORY ANGIOGENEZY Lenalidomid	+++	0 – 19	Během léčby
ANTIMIKROTUBULÁRNÍ LÁTKY Paklitaxel	++++	< 15	2 T po podání

Možnosti diagnostiky kardiotoxicity

Salvatici M, Sandri MT. Future Oncol 2015;11:2077-2091

METODA	DG KRITÉRIA	VÝHODY	OMEZENÍ
ECHO 2/3D	EF, objemy LK	Neinvazivní metoda Dostupnost Absence iradiace Cena Kompletní vyšetření srdce	Nízká reproducibilita Kvalita záznamu
ECHO Strain	GLS	Neinvazivní metoda Dostupnost ???	Dostupnost ??? Časová náročnost ??? Inter-observer variabilita Závislost na typu přístroje
MUGA	EF, objemy LK	Neinvazivní metoda Reproducibilita Dostupnost ??? Nízká inter-observer variabilita	Radiace Cena ??? Dostupnost ??? Nekompletní vyšetření srdce
MRI	EF, objemy LK Struktura myokardu	Neinvazivní, absence radiace, vysoká reproducibilita a nízká inter-obserever variabilita	Horší dostupnost Náklady, časová náročnost ???
Biomarkery	Poškození myocytu Srdeční selhání	Dostupnost, cena Vysoká senzitivita Neinvazivní Přesnost, reproducibilita	Rozdílná variabilita esejí Hraniční nálezy bez klinické aplikace



Zito C et al. J Cardiovasc Med 2016;17:e35-e44

European Heart Journal – Cardiovascular Imaging (2014) **15**, 1063–1093
doi:10.1093/ehjci/jeu192

POSITION PAPER

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

1. Pokles EFLK > 10% pod hodnotu **EF 53%**
2. Potvrzení tohoto poklesu opakovaným měřením v odstupu 2-3 týdnů
3. Pokles EFLK musí být dále kategorizován:
   - **REVERSIBILNÍ:** změna je < 5% ve srovnání se vstupní hodnotou EF před léčbou
   - **ČÁSTEČNĚ REVERSIBILNÍ:** zlepší se ≥ 10% oproti maximálnímu poklesu, ale zůstává > 5% pod vstupní hodnotou EF
   - **IREVERSIBILNÍ:** EF zlepšena < 10% ale zůstává > 5% pod vstupní hodnotou EF před zahájení terapie
   - **NEDETERMINOVANÝ:** není možné provést opakovaná měření

European Heart Journal – Cardiovascular Imaging (2014) **15**, 1063–1093
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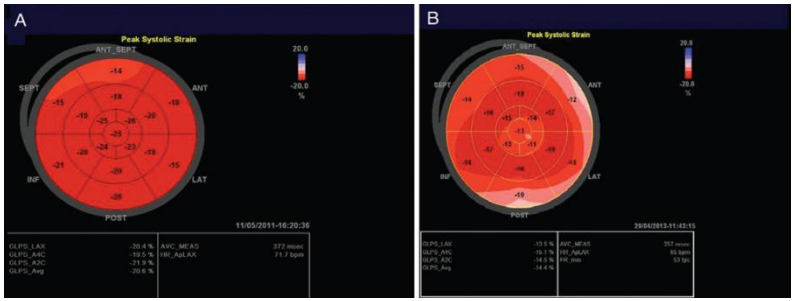
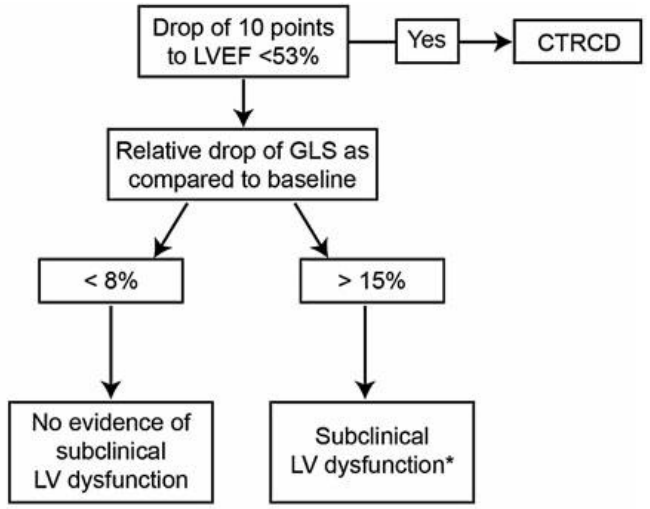




* The data supporting the initiation of cardioprotection for the treatment of subclinical LV dysfunction is limited.

SUBCLINICAL CARDIOTOXICITY

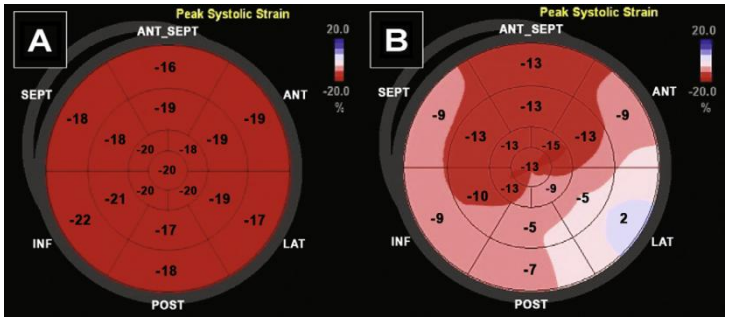
Key points

† Myocardial deformation (strain) can be measured using DTI or 2D STE. The latter is favoured because of a lack of angle dependency.

† GLS is the optimal parameter of deformation for the early detection of sub-clinical 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.



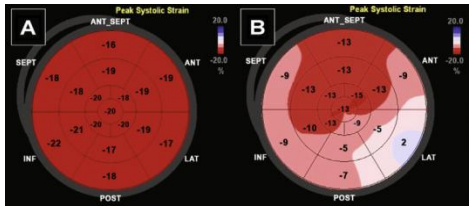
Redukce GLS > 10% během 3M monitorování

Redukce EF > 10% během dalších 6M monitorování

SENS 78 - 79% SPEC 79 – 82%

Fallah-Rad N,Walker JR,Wassef A, Lytwyn M, Bohonis S, Fang T, et al. J AmColl Cardiol 2011; 57:2263-70

Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Cohen V, et al. Am J Cardiol 2011;107:1375-80.

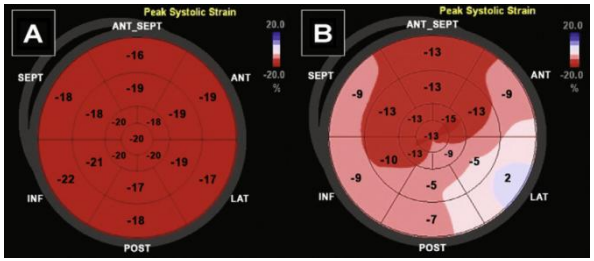


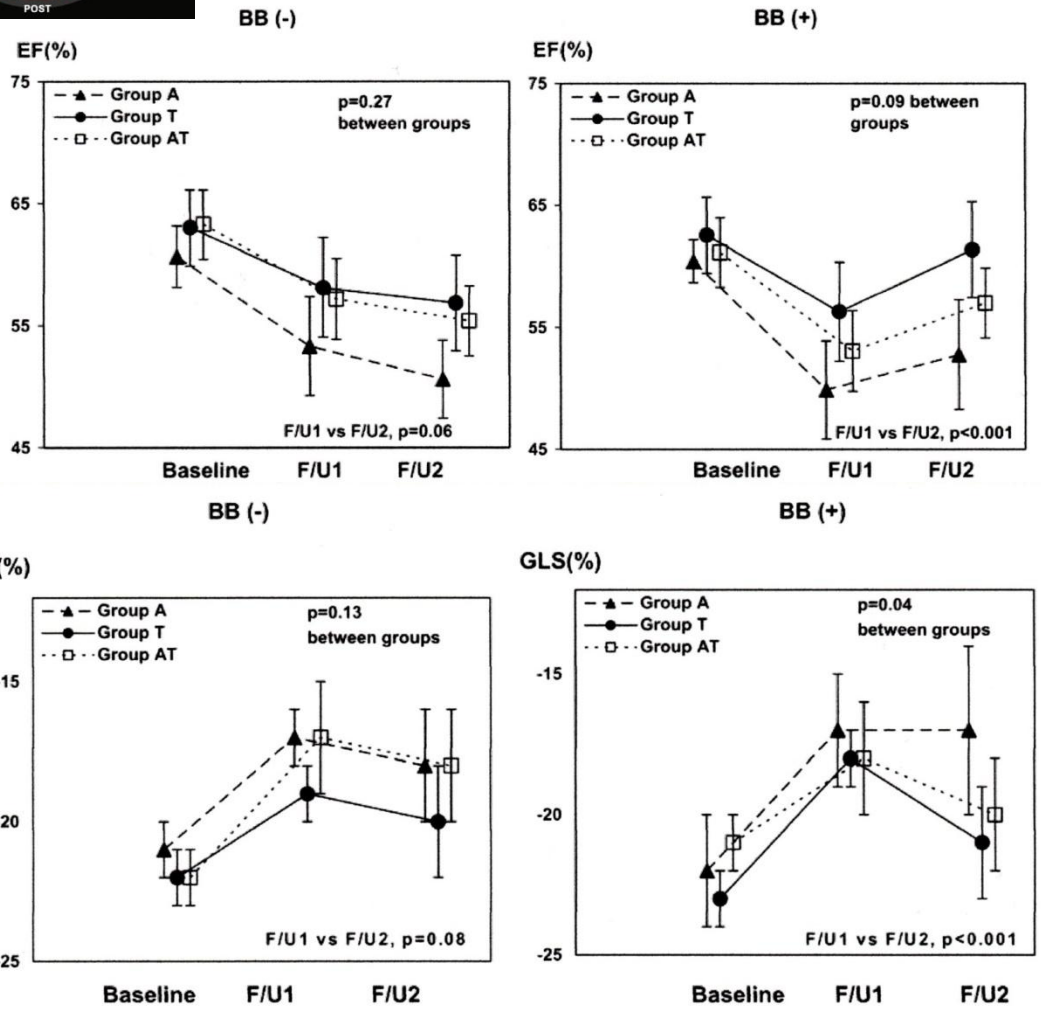
GLS x EF x kardiotoxická chemoterapie

Curr Cardiol Rep 2016;18:7-12
Doi 10.1007/s11886-016-0776-z

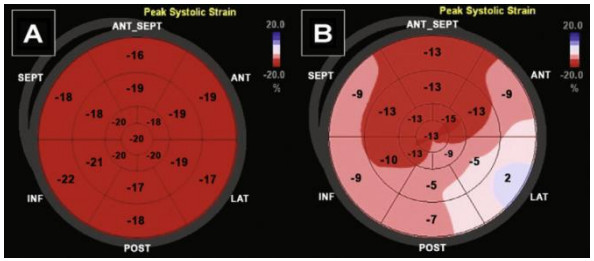
EF	%GLS	Kardiol	Onkol
≥ 55% (53)	< 10-15%	Vyloučit jiné příčiny symptomů	Pokračovat v léčebném režimu
≥ 55% (53)	≥ 10-15%	Biomarkery před každým cyklem: • Negat: EF, GLS po 3M • Pozit: EF, GLS před každým cyklem	Pokračovat v léčebném režimu
< 55% (53)	≥ 10-15%		
1. 40-54%		Biomarkery před každým cyklem: • Negat: EF, GLS po 1M • Pozit: EF, GLS před každým cyklem	Pokračovat v léčebném režimu
2. 35-39%		Vide supra	Alternativní režim
3. < 35%		Individuální kardiologický program	Přerušit terapii

GLS x EF x kardiotoxická chemoterapie x kardioprotekce

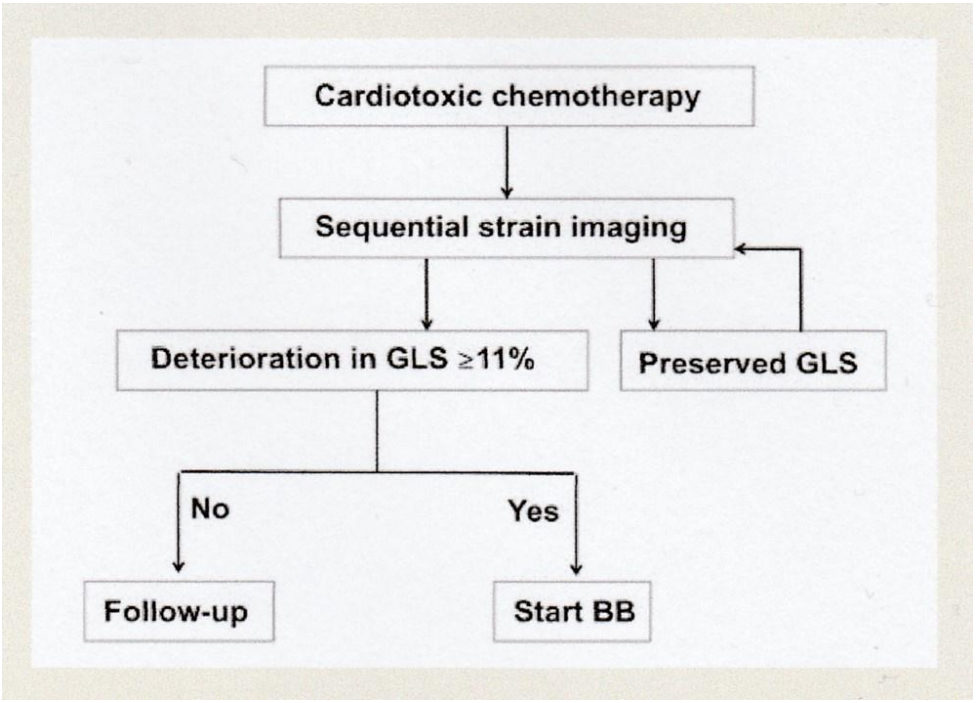


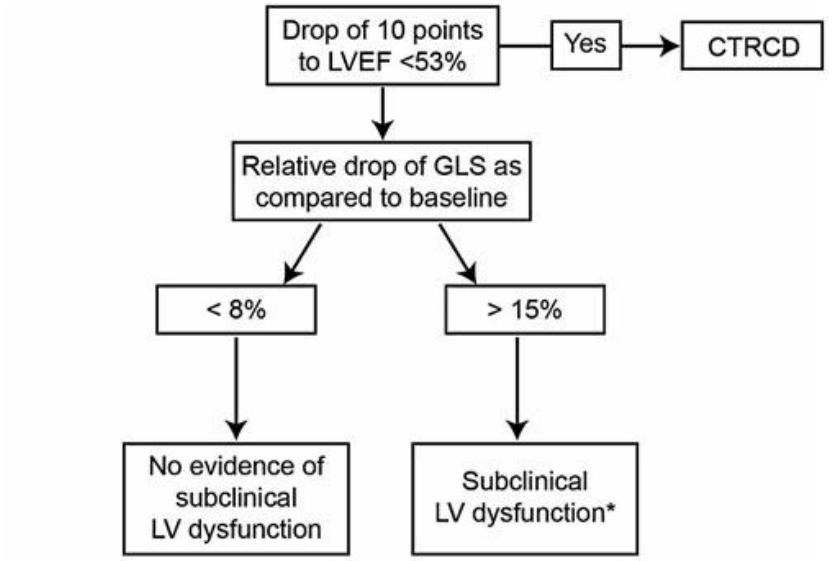


Negishi K et al. EHJ - Cardiovasc Imaging 2014;15:324-331
doi 10.1093/ehjci/jet159



GLS x EF x kardiotoxická chemoterapie x kardioprotekce





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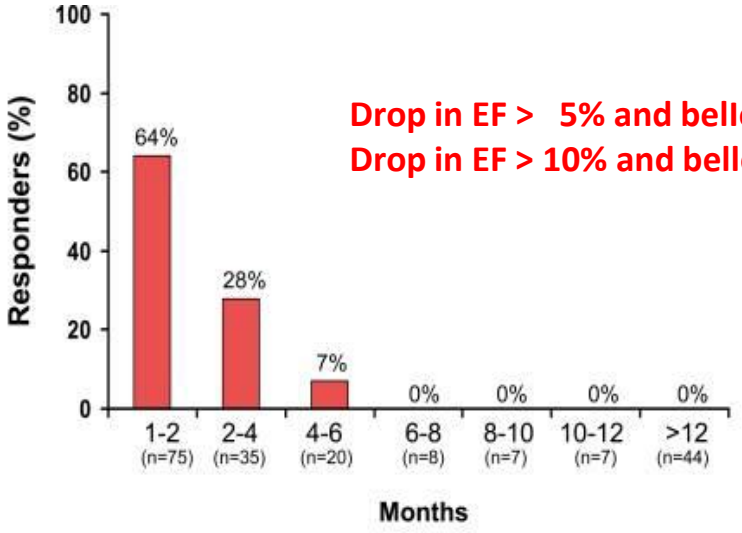
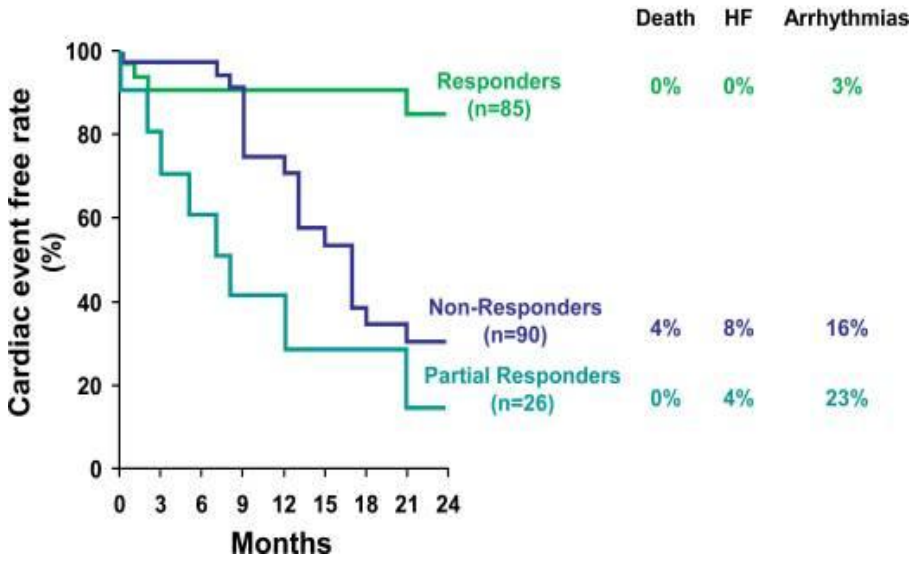
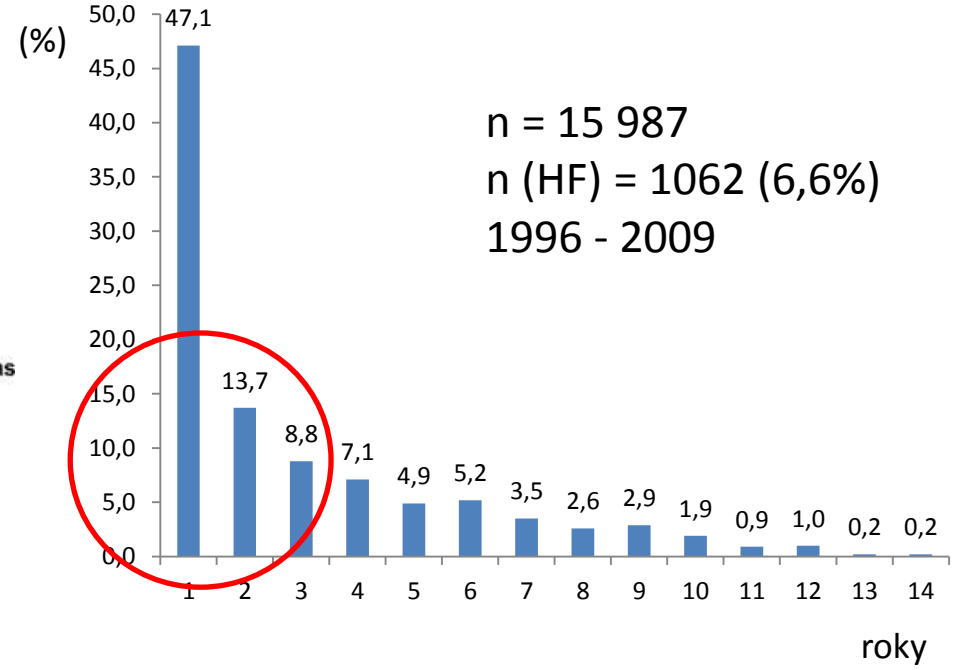


Drop in EF > 5% and bellow 55%
Drop in EF > 10% and bellow 55%



Doba od diagnosy nádoru po první hospitalizaci pro srdeční selhání po kardiotoxické terapii



n = 15 987
n (HF) = 1062 (6,6%)
1996 - 2009

Heart failure following cancer treatment: characteristic, survival and mortality of linked health data analysis.
Clark RA et al. Royal Austr Coll Physiol 2016;12:1297-1305.
doi: 10.1111/imj.13201

Evaluation and Management of Patients With Heart Disease and Cancer: Cardio-Oncology
Herrmann J et al.
Mayo Clin Proc. 2014 Sep; 89(9): 1287–1306.
doi: 10.1016/j.mayocp.2014.05.013

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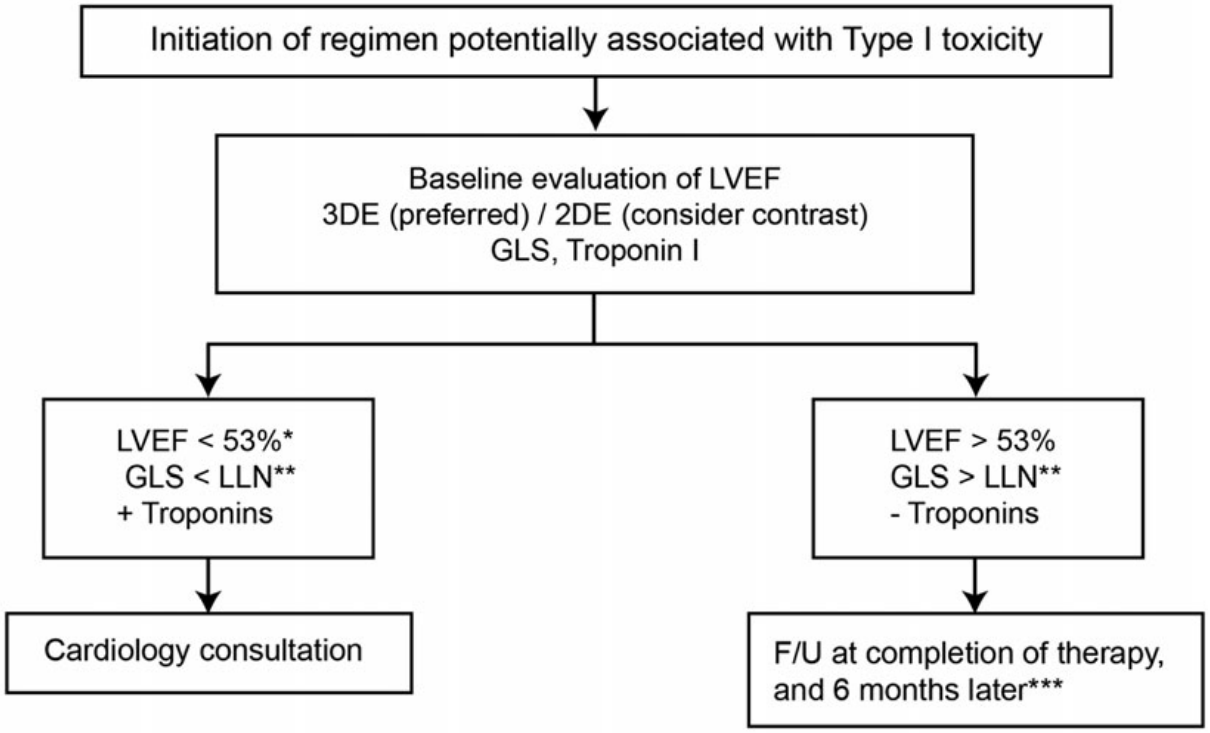

* Consider confirmation with CMR.

** LLN = Lower limit of normal. Please refer to Table 5 for normal GLS values based on vendor, gender and age.

*** If the dose is higher than 240 mg/m^2 (or its equivalent), recommend measurement of LVEF, GLS and troponin prior to each additional 50 mg/m^2.

1) Risk Assessment

Tests: TTE with strain, EKG, cTn

Medication-related risk

High (risk score 4):
Anthracyclines, Cyclophosphamide, Ifosfamide, Clofarabine, Herceptin

Intermediate (risk score 2):
Docetaxel, Pertuzumab, Sunitinib, Sorafinib

Low (risk score 1):
Bevacizumab, Dasatinib, Imatinib, Lapatinib

Rare (risk score 0):
e.g. Etoposide, Rituximab, Thalidomide

Patient-related risk factors

- Cardiomyopathy or heart failure
- CAD or equivalent (incl. PAD)
- HTN
- Diabetes mellitus
- Prior or concurrent anthracycline
- Prior or concurrent chest radiation
- Age <15 or >65 years
- Female gender

Overall risk by Cardiotoxicity Risk Score (CRS)
(risk categories by drug-related risk score *plus* number of patient-related risk factors:
CRS >6: very high, **5-6:** high, **3-4:** intermediate, **1-2:** low, **0:** very low)

2) Monitoring recommendations

Very high cardiotoxicity risk: *TTE with strain before every (other) cycle, end, 3-6 months and 1 year , optional EKG, cTn with TTE during chemotherapy*

High cardiotoxicity risk: *TTE with strain every 3 cycles, end, 3-6 months and 1 year after chemotherapy, optional EKG, cTn with TTE during chemotherapy*

Intermediate cardiotoxicity risk: *TTE with strain, mid-term, end and 3-6 months after chemotherapy, optional EKG , cTn mid-term of chemotherapy*

Low cardiotoxicity risk: *Optional TTE with strain +/- EKG, cTn at end of chemotherapy*

Very low cardiotoxicity risk: *None*

3) Management recommendations

applies as preventive measures before and with abnormalities during/after chemotherapy

Very high cardiotoxicity risk: *initiate ACE-I / ARB, Carvedilol, and statins , starting at lowest dose and start chemotherapy in 1 week from initiation to allow steady state, up-titrate as tolerated*

High cardiotoxicity risk: *initiate ACE-I / ARB +/- Carvedilol +/- statins*

Intermediate cardiotoxicity risk: *discuss risk and benefit of medications*

Low cardiotoxicity risk: *none, monitoring only*

Very low cardiotoxicity risk: *none, monitoring only*

ECHOKARDIOGRAFIE V KARDIO-ONKOLOGII

1. Nejčastěji užívaná zobrazovací modalita pro skrínink kardiotoxicity
2. Nejčastěji preferována v řadě klinických doporučení pro monitorování
3. Jednoduchá interpretace:

    1. Symptomatický pacient: pokles EF > 5% a pod dolní limit (50/53/55%)
    2. Asymptomatický pacient: pokles EF > 10% a pod dolní limit

4. GLS: redukce > 10% senz. 78-79% spec. 79-82%
5. 2DE –TTE EF x MRI r= 0,69 3DE-TTE EF x MRI r=0,95
6. Nutnost korelací 3DE-TTE EF s klinickými výsledky !
7. Vyřazení standardních ukazatelů diastolické funkce
8. Může rozhodovat o nasazení kardioprotekce