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Should the 'echo guidelines' be followed in cancer patients?

“The goal remains clear in that suitable efforts should be made to prevent the development of symptomatic heart failure given its prognostic implications.”

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Which cardiac monitoring guidelines apply to cancer patients? Never before has this question generated more interest; in fact, this topic and the cardiovascular care of cancer patients in general has led to a whole new discipline, which has become known as ‘cardio-oncology’. In keeping with traditions, most attention in this field has been devoted to the deteriorating effects of cancer therapies on cardiac structure and function, even though cancer in itself might have an impact on the heart and its treatment can lead to vascular complications, QTc prolongation and other consequences as well. Accordingly, much of the contributions to this emerging field have been made by investigators with an interest in cardiac imaging, especially in echocardiography.

Not surprising then, the key multimodality cardiac surveillance recommendations for cancer patients were published by the European and American Societies of Echocardiography: one for patients after radiation therapy and one for patients undergoing chemotherapy [1,2]. In both consensus statements, echocardiography takes a central role but recommendations

are more refined for patients undergoing active chemotherapy. Accordingly, in case of exposure to agents with known cardiotoxicity risk, the first recommendation is to pursue a baseline echocardiogram – with (2D speckle) strain imaging if available – and to obtain cardiac troponin (cTn) levels (assay and sensitivity level not specified). If the LVEF is less than 53%, global longitudinal strain (GLS) is below the lower limit of normal, and/or cTn levels are elevated, the recommendation is for a Cardiology consultation and discussion of the pros and cons of continuing with planned cancer therapy and the initiation of ‘cardioprotective’ agents. Otherwise, the recommendation is for repetition of the outlined tests before each additional cycle if abnormalities were noted or a cumulative dose of 240 mg/m² has been reached, and then again at the completion of therapy and 6 months after for patients receiving anthracyclines. For those patients receiving trastuzumab, the same parameters are to be obtained every 3 months during treatment (same with VEGF signaling inhibitors or tyrosine kinase inhibitors but one additional assessment after the first month),

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and in case of anthracycline therapy, assessment is to be done at completion and also 6 months after therapy. Any cTn elevation (before and at 24 h after chemotherapy) is deemed abnormal and should prompt a consultation and discussion as outlined above, whereas the cutoffs for echocardiography are an absolute drop in LVEF of more than 10% to less than 53% or a relative decline in GLS by more than 15%. Both of these scenarios are deemed to represent cancer therapy-related cardiac dysfunction (in the absence of another plausible cause).

These 'guidelines' extend on the previous algorithm for cardiac surveillance for anthracyclines by Schwartz *et al.* as well as the multiple algorithms for cardiac monitoring for patients undergoing therapy with trastuzumab [3–5]. The main distinction is the LVEF cutoff of 53% compared with the previously used 50%. This resides in the fact that the average 'normal' cardiac function in the most recent clinical trials was 63% with a standard deviation of 5%. Thus, considering a margin of 2 standard deviations, 53% would be the lower limit of normal. While the EAE and ASE recommendation is for LVEF determination by 2D echocardiography using the modified Simpson method, the shortcomings of this technique need to be acknowledged. First, there is significant variability and a 10% margin alone is required to conclude on a real change for 2D echocardiography [6]. Second, 2D echocardiography might overestimate LVEF and was found in one study to be only 25% sensitive in detecting patients with an LVEF <50% [7]. The use of 3D echocardiography was 50% more sensitive, but using a cutoff of 60% on 2D echocardiography yielded an even better sensitivity of 75%. In situations of uncertainty, especially with consideration of alteration and discontinuation of cancer therapy (and the related potentially significant implications for the oncology/hematological outcome), cardiac MRI is recommended. While multigated blood pool imaging (MUGA) remains an option for reliable and reproducible LVEF assessment, it is burdened by radiation exposure and does not provide information on pericardial and valvular disease or right-sided pressures. Accordingly, standard echocardiography is considered to be a gatekeeper and the results need to be interpreted in the entire clinical and pathophysiological context.

Both, LVEF and GLS are depending on volume and pressure loading conditions and thus may vary over time based on these parameters

alone. In case of any noteworthy change, the recommendation is thus to reassess with a repeat echocardiogram after 3 weeks [2]. The main advantage of 2D speckle GLS is the angle-independence and the less variable (and thus statistically more robust and earlier emerging) decline than LVEF (Figure 1). The endpoint used in most of these studies to define cardiotoxicity, however, has been the LVEF decline itself measured by echocardiography with all its inherent shortcomings [8–11]. There is, however, emerging data that abnormal strain may, indeed, provide prognostic information on all-cause mortality in patients undergoing chemotherapy [12]. Provision of prognostic implication has been the main advantage of cTn, and its major role in the current cardio-oncology resides in this fact. Patients who have cTn elevation during chemotherapy are at intermediate risk (37%) and those with cTn elevation during and one month after chemotherapy are at highest risk (84%) for heart failure, arrhythmias, or cardiac death within the first year after therapy after which time the risk abides [13,14]. For 6 and 12 months outcomes of LVEF, strain imaging is superior to cTn, and the addition of cTn to strain imaging may not increase the already very high negative predictive value of 90+% [9,10]. Thus for both, GLS and cTn, the main merit is in predicting who is not at risk of an LVEF decline while the positive predictive value of these tests is not as high.

Seminal studies in the 1970s outlined the principle that a drop in LVEF precedes the development of heart failure in cancer patients, and this adverse clinical outcome can be prevented when the decline in LVEF is recognized, chemotherapy is held and LVEF stabilizes [15]. These findings have since governed surveillance protocols up to this date. Early algorithms were based on radionuclide LVEF and anthracycline dose, and validation studies confirmed that adherence leads to far superior and essentially always heart failure-free survival [3]. It is the expectation but has not yet been proven that the current and maybe slightly more complicated echo 'guidelines' accomplish the same and may be even superior as they aim to shift towards even earlier prediction of LVEF decline and heart failure risk.

It is of note that the current 'echo' guidelines appear to emphasize trastuzumab in their outline although listing many more agents with similarly reversible, thus mainly functional (type II) cardiotoxicity. On the contrary, the

Figure 1. Illustration of the time sensitivity of change with cardiac troponin and echocardiographic parameters, the most established early parameter being global longitudinal strain. A significant decline in LVEF is often noticed later but has been associated more clearly with the risk of clinical heart failure. Similarly, clinical events are predicted by cardiac troponin elevations (solid lines). On the contrary, there is no established association between other echo parameters and clinical events (dashed lines).

LVEF: Left ventricular ejection fraction.

point out agents with presumably irreversible, structural and functional (type I) cardiotoxicity risk in the algorithm in relative generic terms which might indicate a similarly broad class of drugs although, in reality, only one class is of consideration: anthracyclines. This might be conceived as confusing; however, in truth there are only very limited studies on serial evaluations for type II cardiotoxicity agents other than trastuzumab [16,17]. The most reasonable recommendation thus has been to reassess cardiac function at 1 month after start of therapy with tyrosine kinase inhibitors and VEGF inhibitors and every 3 months thereafter while on therapy [2]. Of note though, the need for three monthly echocardiographic surveillance even for patients on trastuzumab is not without debate and future recommendations might revise the screening interval.

The main current shortcoming at the present time is the lack of solid long-term follow-up recommendations. A number of proposals have been made by a number of groups over the past years, especially for pediatric cancer survivors. These were recently unified in the publication of the ‘International Late Effects of Childhood Cancer Guideline Harmonization Group’,

which recommended echocardiography surveillance starting 2 years after therapy, repeated 5 years after diagnosis, and every 5 years thereafter in those exposed to ≥ 250 mg/m² doxorubicin equivalent, ≥ 35 Gy chest radiation, or ≥ 100 mg/m² doxorubicin equivalent plus ≥ 15 Gy chest radiation (high risk individuals) [18]. In distinction, there is no recommendation regarding the timing of initiation and follow-up intervals of cardiac surveillance of adult cancer patients who received anthracyclines. Should it be the same as for pediatric cancer survivors?

The ‘guidelines’ on cardiac surveillance after radiation therapy suggest follow-up every 5 years starting 5 years after therapy for those at high risk and otherwise at 10 years. The truth of the matter, however, is that adult cancer patients may develop heart failure sooner after anthracycline therapy and ischemic heart disease events earlier after chest therapy than children (due to underlying/concomitant heart disease, reduced reserve) [19,20]. A longer lag-time to surveillance might therefore not be justifiable. Furthermore, in both, adult and childhood cancer survivors, dynamics of a reduced contractile reserve due to a cancer therapy-induced cardiomyopathy

process could be detected earlier with functional tests rather than relying on resting echocardiograms [21]. This might be particularly useful in those with normal cardiac surveillance parameters during treatment. The value of resting strain imaging in comparison with functional assessments remains unknown. Also, the cost-effectiveness of these tests needs to be taken into consideration. For instance, for childhood cancer survivors, 2D echocardiograms have not been deemed cost effective in those with anthracycline exposure $<250 \text{ mg/m}^2$ but every other year evaluations do might meet cost-effectiveness margins of US\$100,000 per quality life-year gained in those with greater dose exposure [20]. The most recent recommendations by the 'International Late Effects of Childhood Cancer Guideline Harmonization Group' might therefore be the most efficient and effective statutes at present [18]. In addition, as new chemotherapy agents are being developed, regardless of drug class, there will always be a concern for short- and long-term cardiotoxicity, which will make surveillance intervals difficult to determine. Finally, there are virtually no long-term

data to determine when it is considered 'safe,' as in recurrent/secondary malignancy screening, to decrease the frequency of cardiotoxicity surveillance or to stop screening at all.

The goal remains clear in that suitable efforts should be made to prevent the development of symptomatic heart failure given its prognostic implications (Figure 2). Echocardiography has largely replaced radionucleotide scans, and serial echocardiograms for patients undergoing chemotherapy have been considered appropriate by the appropriate use criteria for echocardiography [22]. Reasonable protocols exist for the monitoring of cardiac function and guidance of therapy at the time of chemotherapy, and these should be followed as the weight of collateral evidence would support their benefit for patient outcomes. On the contrary, the best long-term cardiac surveillance strategy remains unknown, especially in adult cancer patients. Should the 'echo' guidelines be followed in cancer patients? The answer is 'yes' as this is the best we currently can do for this increasing patient population but refinements are to be expected in the future, the future of oncology.

Figure 2. Illustration to the American Heart Association stages of heart failure and the goal of cardiac surveillance after exposure to cardiotoxic cancer therapy: detection of dynamics of cardiac dysfunction before symptoms of heart failure develop, and most importantly, prevention of refractory heart failure.

HF: Heart failure; LV: Left ventricular.

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