

angiography improve risk stratification over coronary calcium scoring in symptomatic patients with suspected coronary artery disease? Results from the prospective multicenter international CONFIRM registry. *Eur Heart J Cardiovasc Imaging* 2013. doi:10.1093/ehjci/jet148. First Published online ahead of print August 21, 2013.

- Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. *J Am Coll Cardiol* 2007;**49**: 1860–70.
- Villines TC, Hulten EA, Shaw LJ, Goyal M, Dunning A, Achenbach S et al. Prevalence and severity of coronary artery disease and adverse events among symptomatic patients with coronary artery calcification scores of zero undergoing coronary computed tomography angiography: results from the confirm (coronary CT angiography evaluation for clinical outcomes: an international multicenter) registry. *J Am Coll Cardiol* 2011; **58**:2533–40.

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The intriguing issue of genetic predisposition and the importance of identification of pre-clinical markers of endothelial damage in radiotherapy-induced cardiotoxicity

We have read with great interest the article 'Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography' by Lancellotti et al.¹ Late cardiovascular complications after chest radiotherapy (RT), even modern RT techniques, are a remarkably increasing problem. Care of cancer survivors is becoming an emergent and topic issue especially after chest irradiation and more so for left breast cancer patients.² In this subset of patients, RT should be addressed a risk factor for coronary artery disease (CAD) and since vascular endothelium seems to be the first target of radiation, it should be our duty to detect early marker of endothelial damage long before clinical coronary events. In our institution, we are enrolling early left breast

cancer patients in a protocol study to estimate coronary flow reserve (CFR) by ^{99m}Tc-sestamibi SPECT Myocardial Perfusion Imaging before and after RT. Regional CFR is defined as the ratio between dipyridamole and baseline myocardial blood flow.³ In preliminary data, we have found ST segment and T wave of ventricular repolarization abnormalities registered soon after RT, coupled with myocardial perfusion defects (mostly in the apical region of the left ventricle) and with reduction of estimated values of CFR even in patients with no other risk factors for (CAD) besides chest RT. Our patients were all treated according to the Quantec constraints.⁴ We do not know yet the predicting role of CFR reduction for clinical coronary events, but while following up very closely our patients, we are aggressively treating their risk factors for CAD.

We are also intrigued by the genetic issue of RT-induced cardiotoxicity, and we are also trying to identify the genetic marker of increased risk. We have read the editorial by Kelsey et al.⁵ and the paper by Hilbers et al.⁶ about the association between genetic variants in Transforming Growth Factor β -1 and Plasminogen activator inhibitor-1 and an increased risk for cardiovascular diseases after RT for breast cancer. The authors say that, for the great majority of individuals, the normal tissue toxicity is influenced by the cumulative effect of multiple genetic polymorphisms. If these assumption are proved to be true, then we will be able to predict which patient are more exposed to toxicity and we can improve our 'tailored therapies' maximizing the therapeutic ratio of cancer therapies.

We would like to ask two questions:

- (1) What is your opinion on genetic determinants of RT-induced toxicity? The search for polymorphisms should be encouraged in Oncology Departments to modify therapeutic strategies. (For example, left mastectomy instead of breast-conserving surgery plus adjuvant RT if the risk of RT-induced cardiotoxicity is genetically increased.)
- (2) Do you think it is worthy to search for a suitable early marker of endothelial damage? And do you think CFR reduction could be such a preclinical marker? Would you suggest an ECG recording soon after RT to screen high-risk patients?

Conflict of interest: None declared.

References

- Lancellotti P, Nkomo VT, Badano LP, Bergler-Klein J, Bogaert J, Davin L et al. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular

Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2013;**14**: 721–40.

- Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;**368**:987–98.
- Storto G, Soricelli A, Pellegrino T, Petretta M, Cuocolo A. Assessment of the arterial input function for estimation of coronary flow reserve by single photon emission computed tomography: comparison of two different approaches. *Eur J Nucl Med Mol Imaging* 2009;**36**:2034–41.
- Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys* 2010;**76**(3 Suppl):S10–S19.
- Kelsey CR, Rosenstein BS, Marks LB. Predicting toxicity from radiation therapy: it's genetic, right? *Cancer* 2012;**118**:3450–4.
- Hilbers FS, Boekel NB, van den Broek AJ, van Hien R, Cornelissen S, Aleman BM et al. Genetic variants in TGF β -1 and PAI-1 as possible risk factors for cardiovascular disease after radiotherapy for breast cancer. *Radiother Oncol* 2012;**102**:115–21.

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The intriguing issue of genetic predisposition and the importance of identification of pre-clinical markers of endothelial damage in radiotherapy-induced cardiotoxicity: reply

We thank Dr Gallucci for her letter about the joint EACVI/ASE expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults.¹ As underlined, there is compelling evidence that chest radiotherapy can increase the risk of heart disease. Although modern radiotherapy techniques are likely to reduce the prevalence and severity of radiation-induced heart disease (RIHD), the incidence of RIHD is expected to

increase in cancer survivors who have received old radiotherapy regimens.

The pathophysiology of RIHD remains poorly understood. Genetic and exogenous factors certainly enhance the risk of RIHD and contribute to inter-patient disease expression differences.² As exogenous factors have been shown to result in genomic instability, and as low-dose radiation induces long-lasting genomic instability, synergistic interaction between radiation-induced effects and pathogenic events unrelated to radiation exposure is highly probable. When normal tissues are irradiated, identifying factors modulating their sensitivity to radiation is paramount but challenging. Little is known about the genetic variants of RIHD. Recently, single-nucleotide polymorphisms in a series of genes associated with DNA repair pathways, damage response, and angiogenesis regulating pathways have been identified. As an example, TGFβ1 29C>T polymorphism, which is associated with a lower TGFβ1 serum level, has been shown to be associated with a two-fold increase in cardiovascular disease risk in breast cancer survivors who were irradiated.³ Although these data are very promising, recommendations on the systematic assessment of these genetic polymorphisms cannot yet be drawn. Also, it would be premature at this time to use these preliminary results to modify the treatment strategies. Further confirmations are needed. However, building a bio-bank of blood samples for further targeted genetic analysis makes sense. Several exogenous factors potentiate the risk of RIHD. Younger age, cardiovascular risk factors (i.e. smoking and hypertension) or pre-existing cardiovascular disease, exposure to high doses of radiation (>30 Gy), concomitant chemotherapy, anterior or left chest irradiation location, and absence of shielding are the most common risk factors associated with RIHD.

In the present letter, Dr Gallucci elegantly pointed out that the 'primum movens' of RIHD relates to radiation-induced endothelial dysfunction. When coronary arteries are in the field of radiation, induced endothelial dysfunction may be translated into impaired coronary flow reserve (CFR). Several imaging methods, including MIBI SPECT-MPI (single-photon emission computed tomography myocardial perfusion imaging), can be used to identify reduced CFR.⁴ Dr Gallucci also reported

her preliminary data regarding an ongoing study in which CFR was assessed before and after radiotherapy in patients with left breast cancers. After treatment, a set of abnormalities (ST-T changes, myocardial perfusion defects in the left ventricular apical region, and reduction in estimated values of CFR) was found even in patients with no other risk factors for coronary artery disease other than chest irradiation. However, as the monitoring data are still ongoing, the impact of a reduced CFR on the outcome was not reported. In the meantime, these patients have been followed up closely and treated aggressively to correct any risk factor.

Even with technical improvements in radiotherapy delivery, a high incidence of left ventricular perfusion defects is found early after tangential radiotherapy for breast cancer.^{5,6} However, little is known about the time course and evolution of these perfusion abnormalities. In addition, whether these radiation-induced heart SPECT defects might persist or be the premises of later effects is still unknown. Microvascular disease, endothelial dysfunction, vascular spasm, or coronary artery disease might all contribute at various degrees to these perfusion abnormalities. Similar mechanisms contribute to stress-induced perfusion defects and reduced CFR during the provocative test. Therefore, they do not necessarily correspond to a typical coronary territory. So far, the clinical significance of these perfusion abnormalities remains unclear. So, although of potential interest, it is premature to consider the systematic evaluation of CFR as a preclinical marker of endothelial damage after thoracic radiotherapy. ECG represents the traditional support and completion to the clinical examination, but ECG ST-T abnormalities are often non-specific in cancer survivors. Moreover, in the short term, these ECG changes are often reversible and seem to be functionally insignificant.⁷

The adequate strategy for screening of RIHD remains a source of debate in the medical community. The lack of strong evidence has led the EACVI/ASE Writing Committee to suggest consensus statements rather than strict guidelines. Large prospective studies are thus required to confirm the clinical utility of non-invasive imaging for comprehensive screening and surveillance of asymptomatic cancer survivors. Other unsolved issues would deserve

specific actions: collection of standardized incidence data, trials to evaluate preventive measures, genomic testing to explain variability of incidence and onset, investigation of the impact on new agents that might share common signaling pathways with those involved in cardiac damage, and management of interventional strategies to reduce the burden of cardiovascular complications by acting simultaneously on multiple risk factors.

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References

1. Lancellotti P, Nkomo VT, Badano LP, Bergler-Klein J, Bogaert J, Davin L *et al.* Expert consensus for multimodality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2013;**14**:721–40.
2. Kelsey CR, Rosenstein BS, Marks LB. Predicting toxicity from radiation therapy: it's genetic, right? *Cancer* 2012;**118**:3450–4.
3. Hilbers FS, Boekel NB, van den Broek AJ, van Hien R, Cornelissen S, Aleman BM *et al.* Genetic variants in TGFβ1 and PAI-1 as possible risk factors for cardiovascular disease after radiotherapy for breast cancer. *Radiother Oncol* 2012;**102**:115–21.
4. Lancellotti P, Benoit T, Rigo P, Pierard LA. Dobutamine stress echocardiography versus quantitative technetium-99m sestamibi SPECT for detecting residual stenosis and multivessel disease after myocardial infarction. *Heart* 2001;**86**:510–5.
5. Seddon B, Cook A, Gothard L, Salmon E, Latus K, Underwood SR *et al.* Detection of defects in myocardial perfusion imaging in patients with early breast cancer treated with radiotherapy. *Radiother Oncol* 2002;**64**:53–63.
6. Sioka C, Exarchopoulos T, Tasiou I, Tzima E, Fotou N, Capizzello A *et al.* Myocardial perfusion imaging with (99 m) Tc-tetrofosmin SPECT in breast cancer patients that received postoperative radiotherapy: a case-control study. *Radiat Oncol* 2011;**6**:151.
7. Strender LE, Lindahl J, Larsson LE. Incidence of heart disease and functional significance of changes in the electrocardiogram 10 years after radiotherapy for breast cancer. *Cancer* 1986;**57**:929–34.

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