# The ethics of radiation exposure in cancer-treated patients

## Editorial for: Frequent MUGA testing in a myeloma patient: a case-based ethics discussion

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Cardiovascular disease is the leading cause of mortality worldwide, accounting for more than 17.3 million deaths per year.[1] In the USA, cardiovascular disease is the most common cause of death, followed by cancer, which accounts for nearly 1 of every 4 deaths.[2] Cancer treatments may include potentially cardiotoxic agents, whose clinical utilization has become an impetus for intensifying surveillance imaging studies, besides those conventionally performed after chemotherapy to monitor for recurrence or development of new malignancies. However, some of these imaging studies are not risk-free and there is concern about their potential contribution to the development of a radiation-associated cancer.

The paper by Bhatti et al.[3] presents different perspectives and concerns regarding medical radiation risks from frequent MUGA testing, but also reflects the current dogma regarding medical imaging radiation carcinogenesis.

First-pass or equilibrium radionuclide angiography (also known as MUGA) is an imaging modality, whose clinical application for cardiotoxicity surveillance in patients treated with doxorubicin initially surfaced in the 1970s.[4] Its broad availability, few technical limitations, the accuracy and reproducibility of the measurements of left ventricular function, and the development of a standardized technique for monitoring anthracycline-induced cardiac dysfunction led the MUGA scan to become the preferred imaging modality in the 1980s[5] for monitoring of doxorubicin-associated cardiotoxicity, with serial MUGA assessments commonly performed for ongoing, interval surveillance of left ventricular function.[6,7] However, the later awareness of radiation risks and conscious efforts to reduce radiation exposure, along with the advent of 3D echocardiography, have contributed to serial MUGA falling out of favor for monitoring of LV function. Radiation exposure is considered to be the main disadvantage of MUGA and the limiting factor for serial MUGA scans, as each test, utilizing 20-30 millicurie (mCi) of 99mTc pertechnetate, is reported to be equivalent to 5-10 milli-Sievert (mSv) of radiation.[5]

According to the 2015 cancer statistics from the American Cancer Society, 86% of all cancers in the United States are diagnosed in people 50 years of age or older.[2] Of note, the majority of cardiac nuclear medicine procedures are performed in people >55 years, with a reported 71% of those procedures performed in 2003 in this age group.[8] While the adult population is exposed to more diagnostic medical radiation, the younger population (children and adolescents) is considered to be at greater risk for radiation-related cancer due to the rapid division of cells and organ development during youth, along with an estimated 10- to 40-year latency period preceding the manifestation of radiation-associated cancer.[8] In regards to gender, due to the radiosensitivity

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of the female breasts and lungs, women are deemed at greater risk for radiation-induced cancer.[8]

The association of diagnostic medical radiation and cancer risk has been reported in both the younger and adult population. A data linkage study of 11 million Australians documented a significant increase in cancer risk among people exposed to computed tomography (CT) scans during childhood or adolescence between 1985 and 2005, with an overall 24% increase in cancer incidence in the CT group (vs non-CT group), after accounting for age, sex, and year of birth (incidence rate ratio [IRR] 1.24; 95% confidence interval 1.20-1.29; $P < 0.001$).[9] A recent population-based case-control study revealed an increased risk for thyroid microcarcinoma in patients exposed to diagnostic radiation from CT scans and nuclear studies, with the highest risk observed in those patients, who underwent nuclear medicine examinations (excluding cardiology tests and thyroid uptake studies; OR 5.47, 95% CI 2.10-14.23), followed by chest CT (OR 4.30, 95% CI 1.66-11.14) and head and neck CT scanning (OR 3.88, 95% CI 1.75-8.63).[10]

The relative contribution of medical radiation to the overall ionizing radiation exposure in the US population substantially increased from 15% in the 1980s to 48% in 2006 (Fig. 1).[11]

Furthermore, while all radiographic, as well as conventional and interventional fluoroscopic procedures collectively accounted for 25% of the total dose from nontherapeutic radiation in 2006, CT imaging (49%) and nuclear medicine (26%) imaging tests were the major contributors to radiation exposure from imaging procedures.[8] Cardiac nuclear imaging comprised 57% of the nuclear medicine studies, and accounted for approximately 85% of the radiation dose.[12] Table 1 summarizes the estimated radiation doses of frequently performed diagnostic and therapeutic cardiovascular procedures.[13]

In an electronic survey on radiation exposure and dose reduction, which was conducted among oncologists at the top fifty National Cancer Institute-funded cancer centers in the USA, 82% of the participants reported patient/family anxiety about radiation dose from medical imaging.[14]

Two major initiatives, ''Image Gently'' (for the pediatric population)[15,16] and ''Image Wisely'' (for the adult population)[17] campaigns, were launched in an effort to minimize exposure to ionizing radiation by raising awareness about methods to reduce radiation doses of medical imaging studies.

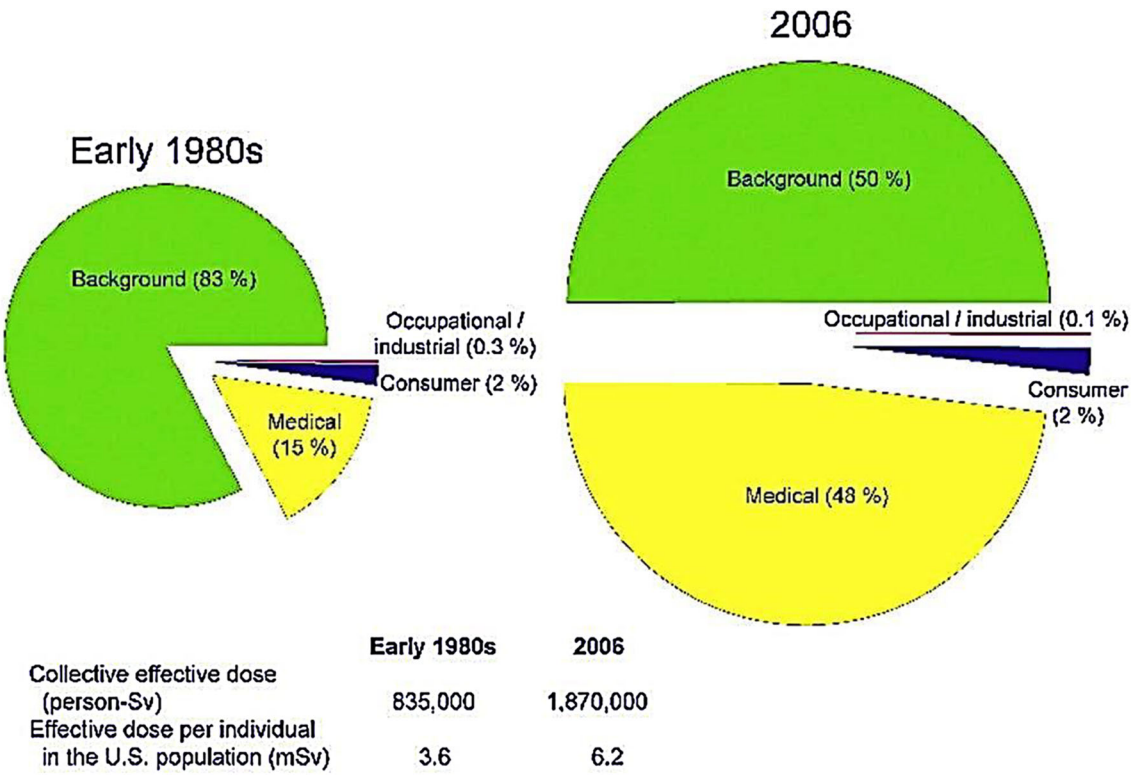


**Figure 1.** Ionizing Radiation exposure of the population of the United States. Comparison of sources of radiation exposure during the 1980s and 2006 in the US.[11] Reprinted with permission of the National Council on Radiation Protection and Measurements, http://NCRPonline.org.

**Table 1.** Estimated ED (mSv) for frequently performed diagnostic and therapeutic cardiovascular procedures.[13] Reprinted with permission from Elsevier, from JACC Cardiovascular Imaging

| Procedure/radionuclide | Dose (mCi) | ED (mSv) |
|---|---|---|
| $^{201}$Thallium (stress–rest) | 3.5 | 16.9 |
| $^{99m}$Tc-Sestamibi (stress–rest) | 27.5/10.0 | 10.7 |
| $^{99m}$Tc-Tetrofosmin (stress–rest) | 27.5/10.0 | 8.6 |
| $^{82}$Rubidium (stress–rest) | 50/50 | 12.8 |
| $^{13}$N-ammonia (stress–rest) | 15/15 | 2.3 |
| $^{18}$F-FDG | 10.0 | 6.4 |
| $^{99m}$Tc-labeled erythrocytes | 22.5 | 5.7 |
| CXR | | 0.1 |
| MDCT-CA | | 15.0 |
| Invasive-CA | | 7.0 |
| PCI | | 15.0 |
| RF arrhythmia ablation | | 15.0 |

Estimations take into consideration the tissue weighting factors from the most recent International Commission on Radiological Protection publication (Publication 103) for radiopharmaceuticals
*CA*, coronary angiogram; *CXR*, chest roentgenogram, *ED*, effective dose; *FDG*, fluorodeoxyglucose; *MDCT*, multidetector computed tomography; *PCI*, percutaneous coronary intervention; *RF*, radiofrequency; *Tc*, technetium

In 2012, escalating concern regarding cancer risks from medical radiation for diagnostic purposes prompted a symposium jointly sponsored by the National Heart, Lung, and Blood Institute and the National Cancer Institute, with subsequent development of three basic principles to guide imaging decisions. Those three principles were identified as follows: (1) *Justification* principle, risk-benefit ratio of all testing options, and avoidance of radiation exposure if not justifiable; (2) *Optimization* principle, adherence to the ''as low as reasonably achievable'' (ALARA) recommendation; and (3) *Responsibility* principle, accountability of both the ordering provider and the imaging provider for justification of the ionizing radiation exposure.[18] While this patient-centered imaging approach, with shared decision making and accountability, is an important step in managing radiation exposure risk, a basic understanding of radiation risk is necessary.

First of all, several issues regarding the accuracy of radiation risk assessment have been raised, including the appropriateness of extrapolating the estimated risks of radiation exposure secondary to medical radiation from epidemiologic data, which have been derived from exposure-outcome data in survivors of World War II atomic bomb explosions.[13] Although low levels of ionizing radiation [less than 100 mSv] are utilized in noninvasive cardiac imaging, tissue damage may still plausibly occur, as there is uncertainty of the dose-response relationship at lower levels.[13] While the current radiation risk exposure estimates are based on the theory that any level of ionizing radiation, however low, can cause a malignancy, with the risk of malignancy increasing linearly with an increase in radiation dose,[19] this model, known as the ''linear no-threshold'' [LNT] model, is not scientifically supported.[12] Other challenges in the estimation of radiation risk exposure include the measurement of the radiation dose absorbed by the patient and the determination of the attendant cancer risk; the inability to directly measure radiation dose to internal organs and organs distant from the irradiated anatomical area; as well as the unclear association between carcinogenesis and types of radiation used for medical imaging.[12] In the attempt to improve risk assessment related to radiation exposure, a common dose ''currency,'' the effective dose, has been adopted. The final goal is to facilitate a comparison between dose measurements of radiation produced by different sources (such as those accruing from external sources, like radiography, fluoroscopy, or CT and those released by internally administered agents, like nuclear imaging) and imaging tests involving radiation exposure of different anatomic areas. The effective dose, whose unit is Sv, affords comparisons by converting diverse radiation modalities and regional exposures to an equivalent whole-body dose. However, despite the clear improvement, even this approach is burdened with caveats, including (though not limited to) the inability to adequately measure the relative dose of radiation absorbed by different organs located within or outside the anatomic area irradiated by the different imaging tests. For instance, despite a lower radiation dose with a CT chest (whose effective dose is approximately 1 mSv), a young

female patient, due to inevitable breast exposure with the CT chest, may have a potential attendant risk by far superior to that of a CT pelvis (whose effective dose is approximately 10 mSv). While completely unconfirmed, a similar line of thinking might also apply to radiation released from internally administered agents, which could affect differently the various organs based on the specific organ tropism of the utilized agents.[20] Additionally, the issue of acute versus protracted exposure to radiation remains unanswered, as it is still undetermined whether a cumulative dose of radiation renders the same risk as multiple exposures at lower doses administered over a certain time period.[20]

Despite the general anxiety among patients about diagnostic radiation exposure, many remain uninformed about this issue. A recent survey to assess oncology patients' comprehension regarding the use of ionizing radiation in diagnostic imaging and their attitudes about radiation revealed a lack of basic understanding by the majority of patients and caregivers. Of the 5,462 respondents who had undergone a diagnostic imaging study at a comprehensive cancer center between November 1, 2013 and January 31, 2014, only 35.1% were aware that CT used ionizing radiation, while 29.4% incorrectly believed that MRI used ionizing radiation.[21] A disturbingly similar ignorance about ionizing radiation was discovered among physicians (including radiologists) in a survey conducted to assess physicians' knowledge and understanding of medical imaging radiation. There was a strong inverse relationship between the clinician's experience and his/her knowledge of CT radiation dose and risks. Additionally, 35.7% of physicians incorrectly believed that the typical nuclear medicine imaging study either did not involve ionizing radiation exposure, or that exposure was equal to or less than that of a standard chest x-ray.[22]

## THE MAGNITUDE OF RADIATION-INDUCED CANCER

Although it is a valid concern, the potential risk of radiation-induced cancer is significantly lower than the intrinsic risk of cancer.[8] In fact, natural cancer incidence was the major contributor to cumulative cancer incidence, compared to background radiation and medical radiation, from an hypothetical 1-day 99mTc sestamibi myocardial perfusion study, delivering at each scan 40 mCi (corresponding to approximately 12 mSv) and performed annually for 40 years in a female patient, beginning at age 40. As depicted in Fig. 2, the incidence of cancer observed in the background and medical radiation groups was substantially lower than the incidence of naturally occurring cancer.[8]

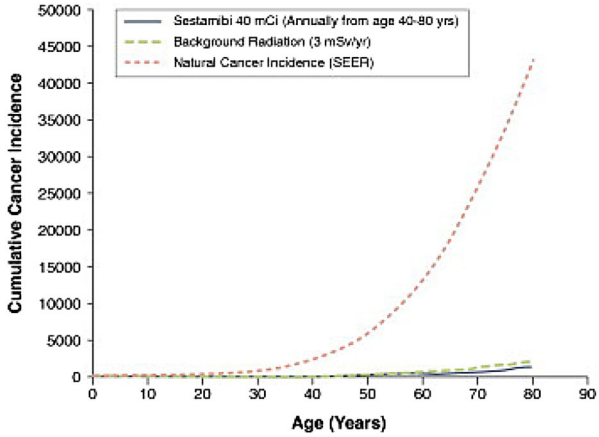


**Figure 2.** Cumulative Incidence of Cancer in Women. Cumulative cancer incidence (expressed as cases per 100,000 women) that can be attributed to background radiation (3 mSv), an annual dose of 40 mCi of technetium-99m sestamibi from age 40-80 years, and naturally occurring cancer. Data are based on the excess absolute risk model from the Biologic Effects of Ionizing Radiation VII report. *SEER*, surveillance, epidemiology, and end results. Figure courtesy of Michael O'Connor, PhD.[8] Reprinted with permission from Elsevier, from JACC Cardiovascular Imaging.

## THE NEED FOR MULTIDISCIPLINARY COLLABORATION

The case-based ethics discussion by Bhatti et al.[3] underscores the complexity of cancer treatment and the need for multidisciplinary collaboration (including cardio-oncology and imaging specialists). In addition to the medical radiation exposure for monitoring of LV function by serial MUGA assessments, it must be pointed out that, besides the risk of heart failure and LV dysfunction secondary to bortezomib,[23] the patient in this case study was exposed to other significant cardiotoxic side effects of bortezomib, a proteasome inhibitor, including the risks of acute myocardial infarction and pulmonary hypertension,[24] which cannot be detected by serial MUGA. Coordination of multidisciplinary care with regularly scheduled echocardiograms (preferably 3D) to assess cardiac function may have helped to avoid unnecessary radiation exposure [113 mSv] from excessive serial MUGA tests, while also helping to monitor for the development of these other cardiotoxic side effects.

Based on the 2009 ''Appropriate Use Criteria for Cardiac Radionuclide Imaging'' released, among the others, by the American Society of Nuclear Cardiology, serial MUGA testing is indicated and appropriate for cardiotoxicity monitoring.[25] However, when the three basic principles of justification, optimization, and responsibility[18] are applied, the request for serial MUGA assessments requires reconsideration.

Due to the paucity of clinical trials regarding detection and management of cardiotoxicity, evidence-based guidelines are virtually nonexistent. In an effort to meet the growing need for clinical recommendations/guidance, the American Society of Echocardiography and the European Association of Cardiovascular Imaging recently issued an expert consensus document[5] providing recommendations on multimodality imaging for cancer patients during or after treatment with potentially cardiotoxic agents (reviewed in[26]), with echocardiography identified as the method of choice for the evaluation of patients before, during, and after cancer therapy. Three-dimensional echocardiography (3DE) was indicated as the preferred technique for surveillance of left ventricular function and detection of cancer therapy-related dysfunction in patients with cancer.[5]

In conclusion, the current practice recommendation to maintain radiation exposure levels ''as low as reasonably achievable'' [ALARA] is prudent, especially in the oncology patient population, who is already at risk of recurrent or new malignancy, as well as at risk of cardiovascular disease with the likelihood of need for cardiac imaging. An educated assessment of the risk-benefit ratio and a sensible approach to diagnostic imaging are necessary. In regards to cardiac imaging studies using ionizing radiation, a science advisory statement by the American Heart Association recommends ordering such cardiac imaging studies ''only after thoughtful consideration of the potential benefit to the patient and in keeping with established appropriateness criteria.''[12] In summary, erudition, sound clinical judgment, and personalized care remain the best tools for today's healthcare providers.

## Disclosure

*All the listed authors reported no relationships relevant to the contents of this paper to disclose.*

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