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Radiation protection issues in dynamic contrast-enhanced (perfusion) computed tomography

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ABSTRACT

Dynamic contrast-enhanced (DCE) CT studies are increasingly used in both medical care and clinical trials to improve diagnosis and therapy management of the most common life-threatening diseases: stroke, coronary artery disease and cancer. It is thus the aim of this review to briefly summarize the current knowledge on deterministic and stochastic radiation effects relevant for patient protection, to present the essential concepts for determining radiation doses and risks associated with DCE-CT studies as well as representative results, and to discuss relevant aspects to be considered in the process of justification and optimization of these studies.

For three default DCE-CT protocols implemented at a latest-generation CT system for cerebral, myocardial and cancer perfusion imaging, absorbed doses were measured by thermoluminescent dosimeters at an anthropomorphic body phantom and compared with thresholds for harmful (deterministic) tissue reactions. To characterize stochastic radiation risks of patients from these studies, life-time attributable cancer risks (*LAR*) were estimated using sex-, age-, and organ-specific risk models based on the hypothesis of a linear non-threshold dose–response relationship.

For the brain, heart and pelvic cancer studies considered, local absorbed doses in the imaging field were about 100–190 mGy (total $CTDI_{vol}$, 200 mGy), 15–30 mGy (16 m Gy) and 80–270 mGy (140 mGy), respectively. According to a recent publication of the International Commission on Radiological Protection (ICRP Publication 118, 2012), harmful tissue reactions of the cerebro- and cardiovascular systems as well as of the lenses of the eye become increasingly important at radiation doses of more than 0.5 Gy. The *LAR*s estimated for the investigated cerebral and myocardial DCE-CT scenarios are less than 0.07% for males and 0.1% for females at an age of exposure of 40 years. For the considered tumor location and protocol, the corresponding *LAR*s are more than 6 times as high. Stochastic radiation risks decrease substantially with age and are markedly higher for females than for males.

To balance the diagnostic needs and patient protection, DCE-CT studies have to be strictly justified and carefully optimized in due consideration of the various aspects discussed in some detail in this review.

1. Introduction

Technical innovations in multi-detector computed tomography (CT) allow for larger volume coverage in shorter scan times and have thus stimulated the application of dynamic contrast-enhanced (DCE) CT techniques in clinical practice. Since the temporal change of CT densities (in Hounsfield units, HU) upon administration of an extracellular CT contrast agent (CA) is related to the regional blood supply and the extravasation of the CA, DCE-CT is a valuable tool for rapid and non-invasive characterization of tissue microcirculation.[1] It has been established in medical care for

[1] "DCE imaging" is frequently used in the medical literature synonymous with "perfusion imaging". In this paper, the latter denotes more specifically any imaging technique (CT, MRI, SPECT) that aims primarily at the assessment of tissue blood flow (perfusion) as an important but not the only relevant feature of tissue microcirculation. Accordingly, the term "CT perfusion imaging" specifically refers to a DCE-CT study optimized to acquire serial CT data during the first-pass of a rapidly injected CA bolus through the terminal vascular bed, from which the perfusion can be determined.

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improved diagnosis and treatment of cerebral ischemia and infarction [1–4] and is increasingly investigated in clinical trials to define its role in the diagnosis, management, and prognosis of patients with coronary artery disease (CAD, [5–7]) and cancer [8,9]. The most recent state of the art is summarized in this special issue.

As compared to DCE magnetic resonance imaging (MRI), the CT technique offers the major methodological advantage of a direct and almost linear relationship between the CA-induced density increase and the local CA concentration. Moreover, it has practical advantages in that the examination is fast, commonly available and better applicable for critically ill and intensive care patients than MRI. But there are also two serious and interconnected shortcomings: First, the relatively small CA-induced increase in CT densities in most (in particular ischemic) tissues as compared to the noise level of the acquired density–time curves and, second, the exposure of patients to ionizing radiation.

Although the effective dose resulting from a DCE-CT study is typically less than about 30 mSv, local doses in the examined body region are rather high and may result in harmful radiation damages when the examination is repeated several times or combined with other high-dose angiographic or interventional procedures. Imanishi et al. reported on temporary bandage-shaped hair loss occurring in three patients with cerebrovascular disorders who underwent several CT perfusion studies and two angiographies of the head within a few days [10]. In the United States, approximately 385 patients from six hospitals were exposed to excess radiation during CT brain perfusion scans using inadequate protocols. Some of these patients reported obvious signs of excessive radiation exposure following their scans, such as hair loss or skin redness, which called attention to the problem [11]. But even if radiation exposures are not high enough to produce obvious signs of radiation injury, it can place patients at increased risk for long-term radiation effects, in particular cancer [11].

It is thus the aim of this review article (*i*) to briefly summarize the current knowledge on deterministic and stochastic radiation effects relevant for radiation protection of patients, (*ii*) to present the essential concepts for estimating radiation doses and risks associated with DCE-CT studies as well as representative results, and (*iii*) to discuss in detail the various aspects that have to be considered in the process of justification and optimization of DCE-CT studies as summarized in Fig. 1.

2. Biological effects of ionizating radiation

According to how the tissue response relates to the radiation dose, radiological protection deals with two types of adverse health effects. (*i*) Stochastic radiation effects (cancer or heritable effects due to cell transformation), which may be observed as a statistically detectable increase in the incidences of these effects occurring long after radiation exposure in the affected individuals or their offspring. (*ii*) Deterministic radiation effects (harmful tissue reactions due to cell killing), which occur at higher doses exceeding tissue-specific thresholds, often of an acute nature [12]. Most recent scientific data question this mainstream classification to a certain extent (see below) and may call for a modified concept for categorizing radiation effects [13,14].

2.1. Stochastic radiation effects

Radiation effects at the cellular or molecular level may result in viable but genetically modified cells, which may initiate cancerogenesis in case of somatic cells or may lead to inherited disease in case of germ cells. These all-or-nothing single-cell effects occur by chance (i.e., in a stochastic manner without a threshold), which implies that their probability but not the severity of the resulting detriment is proportional to the radiation dose.

In the context of radiation protection, the main stochastic effect is the occurrence of cancer several years to decades after the exposure has taken place (latency time). Radiation-associated cancers do not differ in their clinical appearance from cancers that are caused by other factors. They can thus not be recognized as such, and it is only by means of epidemiological studies that increases in the spontaneous cancer incidence rates of irradiated groups can be detected.

Increased cancer rates have been demonstrated in humans through various radio-epidemiological follow-up studies at organ or whole-body doses exceeding about 50 mGy, delivered acutely or over a prolonged period. The so-called Life Span Study (LSS) of the survivors of the atomic bombings in Hiroshima and Nagasaki is the most important of these studies [15,16]. The follow-up of the atomic bomb survivors has provided detailed knowledge of the relationships between radiation risk and a variety of factors, such as the absorbed dose, the age at exposure, the age at diagnosis and other parameters. The LSS yields cancer incidence [15] and mortality data [16] with good radio-epidemiologic evidence due to the large size of the study population (about 86,600 individuals with individual dose estimates), the broad age- and dose-distribution, the long follow-up period and an internal control group (individuals exposed only at a minute level or not at all). It is, therefore, the major source for predicting radiation-associated risks for the general population. The risk estimates from the LSS are largely supported by a multitude of smaller studies, mostly on groups of persons exposed for medical reasons, both in diagnostics and therapy [17].

Since experimental and radio-epidemiological studies do not provide conclusive evidence for the carcinogenicity of low levels of radiation (<about 50 mGy), there is a considerable controversy on the validity of the widely used linear non-threshold (LNT) response model to describe stochastic radiation risk in this low-dose range [18–21]. According to the "International Commission on Radiological Protection (ICRP)", the long standing question on the validity of the LNT model in the low-dose range may well prove to be beyond definitive scientific resolution and "weight of evidence" arguments and practical judgments are likely to continue to apply in the foreseeable future [12]. Based on a review of mechanistic studies, the "United Nations Scientific Committee on the Effects of Atomic Radiation" (UNSCEAR) concluded in a recently published summary on low-dose radiation effects on health that the current balance of available evidence tends to favor an LNT response for the mutational component of radiation-associated cancer induction at low doses [22].

Even for doses between about 50 and 200 mSv, frequently occurring in the body region exposed in DCE-CT studies, the scientific evidence for carcinogenic radiation effects is still somewhat fuzzy [21]. Nevertheless, estimation of stochastic radiation risks associated with DCE-CT studies by means of the LNT model is the most prudent and precautionary approach for radiation protection of patients [12].

2.2. Deterministic radiation effects (harmful tissue reactions)

At higher doses there may be a substantial amount of cell killing, sufficient to result in detectable tissue reactions [12,23]. Above organ-specific threshold doses, which may vary somewhat by individual, the severity of harmful tissue reactions increases with dose. According to the existing evidence, acute absorbed doses (see below) up to around 100 mGy produce no functional impairment of (most) tissues [24]. Typical examples of deterministic effects with a relatively high dose threshold are radiation-induced damages to the skin and hair losses.