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Risks and safety aspects related to PET/MR examinations

Gunnar Brix · Elke A. Nekolla · Dietmar Nosske · Jürgen Griebel

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Abstract
Introduction The introduction of positron emission tomography (PET)/magnetic resonance (MR) systems into medical practice in the foreseeable future may not only lead to a gain in clinical diagnosis compared to PET/computed tomography (CT) imaging due to the superior soft-tissue contrast of the MR technology but can also substantially reduce exposure of patients to ionizing radiation. On the other hand, there are also risks and health effects associated with the use of diagnostic MR devices that have to be considered carefully.
Objectives This review article summarizes biophysical and biological aspects, which are of relevance for the assessment of health effects related to the exposure of patients to both ionizing radiation in PET and magnetic and electromagnetic fields in MR. On this basis, some considerations concerning the justification and optimization of PET/MR examinations are presented—as far as this is possible at this very early stage.
Discussion Current safety standards do not take into account synergistic effects of ionizing radiation and magnetic and electromagnetic fields. In the light of the developing PET/MR technology, there is an urgent need to investigate this aspect in more detail for exposure levels that will occur at PET/MR systems.

G. Brix · E. A. Nekolla · D. Nosske · J. Griebel
Department of Medical and Occupational Radiation Protection,
Federal Office for Radiation Protection,
Oberschleissheim, Germany

G. Brix (✉)
Abteilung für medizinische Strahlenhygiene und Dosimetrie,
Ingolstädter Landstraße 1,
D-85764 Oberschleissheim, Germany
e-mail: gbrix@bfs.de

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Introduction

Clinical adoption of combined positron emission tomography (PET)/computed tomography (CT) imaging has been surprisingly rapid and, despite an ongoing debate, the new technology has advanced the use of metabolic and molecular imaging [1], particularly for oncology [2, 3]. However, when discussing the immediate benefits of combined PET/CT examinations, the issue of patient exposure must be taken into account as well. As shown in a recent multicenter study, whole-body PET/CT examinations—comprising a PET scan after the administration of the glucose analogue 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) and a fully diagnostic contrast-enhanced CT scan—result in an effective dose to patients on the order of 25 mSv and thus mandate a thorough medical justification for each individual patient [4, 5]. A detailed analysis of protocols, which are representative for the imaging scenarios reported in the literature, revealed that up to 70% of the total exposure is contributed by CT [4, 5]. It would thus be very welcome from a radiation hygienic point of view, if PET/CT could be replaced whenever possible by PET/magnetic resonance (MR) as soon as the technical and methodological challenges related to the development of this new imaging technology have been solved.

As no ionizing radiation is used in MR, it is generally deemed safer than CT or PET procedures in terms of associated health risks. Nevertheless, there are possible risks and health effects associated with the use of diagnostic MR devices that have to be considered carefully [6–8]. In this context, a fundamental difference between ionizing and

non-ionizing radiation has to be noted: radiation doses related to CT or PET procedures may result in stochastic effects, while biological effects of magnetic and electromagnetic fields used in MR are of deterministic nature. In a stochastic process the exposure determines the probability of the occurrence of an event but not the severity of the effect. In contrast, the severity of a deterministic effect is related to the level of exposure, and a threshold may be defined [9]. As a consequence, the probability of detrimental effects caused by PET or CT examinations performed over many years accumulate, whereas biophysical and biological effects induced by magnetic and electromagnetic fields used for MR examinations (such as cardiovascular reactions or peripheral nerve stimulation) are related to the acute exposure levels of a particular examination and do not, to our present knowledge, accumulate over years.

This article provides an overview on biophysical and biological aspects relevant for the assessment of detrimental health effects related to the exposure of patients to ionizing radiation in PET and to magnetic and electromagnetic fields in MR. On this basis, some preliminary considerations on the justification and optimization of PET/MR procedures will be presented. A comprehensive discussion of aspects which are beyond the scope of this paper—as for example, radiation protection of the staff or layout and shielding of a PET facility—can be found in a safety report recently issued by the International Atomic Energy Agency [10].

PET: ionizing radiation

Detrimental health effects induced by ionizing radiation and principles of radiation protection

Detrimental effects of ionizing radiation, the most significant being the induction of cancer, have been identified in humans through various epidemiological studies at intermediate and high doses, i.e., organ or whole-body doses exceeding 50–100 mGy, delivered acutely or over prolonged periods of time. There is, however, considerable controversy regarding the radiological risk of low-level radiation, typical for diagnostic radiation exposures, since the stochastic risks evaluated at these dose levels are not based on experimental evidence but are rather extrapolated from effects observed at high doses [11, 12]. The extrapolation is based on the so-called linear non-threshold (LNT) hypothesis which assumes that (1) any radiation dose—no matter how small—may cause detrimental health effects and that (2) the probability of these effects is directly proportional to the dose absorbed in the tissue. Although the risk evaluated at low dose levels is thus hypothetical, it is prudent to assume that it exists and that the LNT model represents an upper limit for it. It is for this reason that current radiation protection standards as well as risk assessments are based on the LNT hypothesis.

In line with this philosophy, the "Directive on Health Protection of Individuals Against the Dangers of Ionizing Radiation in Relation to Medical Exposure", issued by the Council of the European Communities [13], requires that the following basic principles of radiation protection are applied:

- *Justification* (article 3): "Medical exposure... shall show a sufficient net benefit, weighting the total potential diagnostic or therapeutic benefits it produces... against the individual detriment that the exposure might cause, taking into account the efficacy, benefits and risks of available alternative techniques having the same objective but involving no or less exposure to ionizing radiation. In particular, (*i*) all new types of practice involving medical exposure shall be justified in advance before being generally adopted and (*ii*) all individual medical exposures shall be justified in advance taking into account the specific objectives of the exposure and the characteristics of the individual involved. ... Medical exposure for biomedical and medical research shall be examined by an ethics committee and/or by the competent authorities."
- *Optimization* (article 4): "All doses due to medical exposure for radiological purposes... shall be kept as low as reasonable achievable (ALARA principle) consistent with obtaining the required diagnostic information, taking into account social and economic factors." In case of biomedical and medical research projects, the Member States shall ensure that the individuals concerned are "informed about the risks of the exposure" and that "a dose constraint is established for individuals for whom no direct medical benefit is expected from the exposure."

Dose and risk estimation

The fundamental dosimetric quantity is the absorbed dose expressed in the unit Gray (1 Gy = 1 J/kg). It is defined as the radiation energy absorbed in a small volume element of matter divided by its mass. The absorbed dose averaged over the total mass of an organ or tissue T is denoted as *organ dose*, D_T.

Tissues and organs are not equally sensitive to ionizing radiation. Due to this reason, tissue weighting factors, w_T, are provided by the International Commission on Radiological Protection (ICRP; [14, 15]) for a reference population of equal numbers of both sexes and a wide range of ages. They indicate the relative proportion (i.e., $\sum w_T = 1$) of each organ or tissue to the total stochastic health detriment—in terms of the risk of fatal cancers and hereditary defects—resulting from a uniform irradiation of

the whole body. As indicated in Table 1, these factors have recently been changed for some organs. If the body is exposed in a non-uniform manner, as for example after the administration of a PET radiopharmaceutical, the sum of the products of the organ dose and the corresponding tissue weighting factor determined for each of the organs or tissues exposed has to be computed. The resulting quantity, $E = \sum_T w_T \cdot D_T$, is denoted as *effective dose* and expressed in the unit Sievert (Sv).

In case of PET examinations, organ doses can be estimated from the activity A of the radiopharmaceutical administered to the patient by using dose coefficients, Γ_T, computed by Monte-Carlo calculations for hermaphrodite mathematical models, i.e., $D_T = A \cdot \Gamma_T$. The effective dose is given by

$$E = \sum_T w_T \cdot D_T = A \cdot \sum_T w_T \cdot \Gamma_T = A \cdot \Gamma_E. \quad (1)$$

For PET tracers more frequently used in clinical routine [16], dose coefficients for the effective dose, Γ_E, are listed in Table 2 [17, 18]. It should be noted that the concept of the effective dose facilitates only an overall, but not an organ-specific assessment of stochastic radiation risks and is aimed at large, age- and gender-averaged collectives such as the working population or the whole population of a country. Nevertheless, it provides a rational framework for the justification and optimization of imaging procedures.

Table 1 Tissue weighting factors, w_T, given by the ICRP in 1990 [14] and 2007 [15] reflecting the relative susceptibility of various tissues and organs to ionizing radiation

Tissue or organ	w_T
ICRP, 1990	
Gonads	0.20
Bone marrow, lungs, colon, stomach	0.12
Liver, thyroid, esophagus, breast, bladder	0.05
Bone surface, skin	0.01
Remainder tissues [a]	0.05
ICRP, 2007	
Bone marrow (red), colon, lung, stomach, breast, remainder tissues [b]	0.12
Gonads	0.08
Bladder, esophagus, liver, thyroid,	0.04
Bone surface, brain, salivary glands, skin	0.01

The remainder tissues consists of a group of additional organs and tissues with a lower sensitivity for radiation-induced effects for which the average dose must be used:
[a] Small intestine, brain, spleen, muscle tissue, adrenals, kidneys, pancreas, thymus and uterus, extrathoracic region;
[b] Adrenals, extrathoracic region, gall bladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate, small intestine, spleen, thymus, uterus/cervix.

To assess adverse health effects to individuals, more complex radiation risk models based on radio-epidemiological data (e.g., A-bomb survivors) have to be used. The standard approach to generate age- and gender-specific risk estimates is based on the so-called *excess lifetime risk* (or lifetime attributable risk), which gives the additional risk, after an exposure at a specific age, to develop a radiation-induced (fatal) cancer later on in life [12, 19]. In Fig. 1, the excess lifetime risks for both cancer incidence and mortality are plotted for male and female patients undergoing an FDG-PET examination at different ages. The estimates were derived by applying the most recent risk models given by the Biological Effects of Ionizing Radiation (BEIR) VII committee in 2006 [12] and utilizing disease and life table data for a European (German) population.

In case of *pregnant patients* undergoing a PET examination—either based on a stringent clinical indication or due to the unawareness of pregnancy—the effective dose to the offspring as well as the resulting radiation risks have to be assessed carefully. In the early stage of pregnancy, the uterine dose is often used as surrogate for the embryonic dose. For [^{18}F]FDG, the dose coefficient for the uterine dose is 21 μSv/MBq [17].

MR: Non-ionizing radiation

Interaction mechanisms and biological effects of magnetic and electromagnetic fields

In MR imaging and spatially localized MR spectroscopy, three variants of magnetic fields are employed to form cross-sectional images of the human body: (1) a high static magnetic field generating a macroscopic nuclear magnetization, (2) rapidly alternating magnetic gradient fields for spatial encoding of the MR signal, and (3) radio-frequency (RF) electromagnetic fields for excitation and preparation of the spin system.

The basic actions of *static magnetic fields* are (1) magnetomechanical effects, including the orientation of magnetically anisotropic molecules or structurally ordered molecule assemblies in uniform fields as well as the translation of paramagnetic or ferromagnetic materials in magnetic field gradients, (2) electrodynamic interactions with ionic conduction currents (i.e., moving ionic charge carriers), and (3) effects on electron spin states of chemical reaction intermediates [20]. A large number of studies have been conducted to detect biological responses to static magnetic fields with flux densities ranging from mT to several T. These studies have been reviewed comprehensively—among others—by the International Commission on Non-Ionizing Radiation Protection (ICNIRP; [21]) and

Table 2 Dose coefficients to estimate the effective dose related to PET radiopharmaceuticals frequently administered in clinical routine [17, 18]

Nuclide	Radio-labeled compound	Function	Dose coefficent Γ_E (μSv/MBq)
^{11}C	L-Methionine	Amino acid transport and protein synthesis	7.4
	Acetate	Myocardial oxidative metabolism	3.5
^{13}N	Ammonia	Myocardial blood flow	2.0
^{15}O	Water	Regional blood flow	0.93
^{18}F	2-Fluoro-2-deoxy-D-glucose (FDG)	Glucose transport and phosphorylation	19.0
	L-Dopa	Presynaptic dopaminergic function	25.0
	Fluoride	Bone metabolism	24.0
^{82}Rb	Rubidium chloride	Myocardial blood flow	3.4

Values were calculated using the tissue weighting factors given in ICRP Publication 60 under the assumption that the bladder is emptied at 3.5 h after tracer administration. They hold for a standard patient with a body weight of about 70 kg.

the World Health Organization [22]. Overall, there is little convincing evidence from cellular, animal, and epidemiological studies for biologically harmful effects of short-term exposure resulting from static magnetic fields with strength up to several Teslas > T. Until now, most MR examinations have been performed using static magnetic fields up to 3 T, although whole-body MR systems with static magnetic fields up to 9 T are already used in clinical tests. The literature does not indicate any serious adverse health effects from the exposure of healthy human beings up to 8 T. However, sensations of nausea, vertigo, and metallic taste may occur in magnetic fields above 2 T [23]. The greatest potential health hazard comes from metallic, ferromagnetic materials, in particular, such as scissors, coins, pins, oxygen cylinders that are accelerated in the inhomogeneous magnetic field in the periphery of an MR system and may become dangerous projectiles. This risk can only be minimized by a strict and careful management of both patients and staff.

Rapidly switched *magnetic gradient fields* induce electric fields in the human body, the strength of which is proportional to the rate of change of the magnetic field, dB/dt. In conductive media, such as biological tissues, the electric fields result in circulating eddy currents. In general, rise times of magnetic gradients in MR are longer than 100 μs, resulting in time-varying electric fields and currents with frequencies below 100 kHz. Within this frequency range, the conductivity of cell membranes is several orders of magnitude lower than that of the extra- and intracellular fluid [24]. As a consequence, the current flow is restricted to the extracellular fluid, and voltages are induced across the membrane of cells. When these voltages are above a tissue-specific threshold level, they can stimulate nerve and muscle cells [25]. The primary concern with respect to time-varying magnetic fields is cardiac fibrillation because it is a life-threatening condition. In contrast, peripheral nerve stimulation is of practical concern because uncomfortable or intolerable stimulations would interfere with the examination (e.g., due to patient movements) or would even result in a termination of the examination [26]. Bourland et al. [27] analyzed stimulation data in the form of cumulative frequency distributions that relate a dB/dt level to the number of healthy volunteers that had already reported on perceptible, uncomfortable, or even intolerable sensations. Their results indicate that the lowest percentile for intolerable stimulation is approximately 20% above the median threshold for the perception of peripheral nerve stimulation. The threshold for cardiac stimulation is well above the median perception threshold for peripheral nerve stimulation, except at very long pulse durations which are, however, not relevant for clinical MR examinations (Fig. 2, [25]).

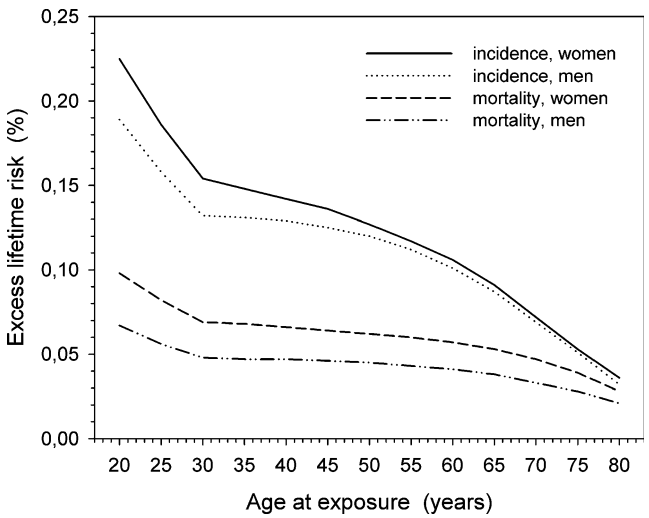

Fig. 1 Excess lifetime risks for both cancer incidence and mortality for a male/female patient attributed to the administration of 370 MBq FDG at different ages. The radiation-induced risks estimated by means of the most recent radio-epidemiological models [12] are at least two orders of magnitude lower than the corresponding baseline lifetime risks (cancer incidence and mortality for males/females aged 20 years in Germany: 47/39% and 26/21%, respectively)

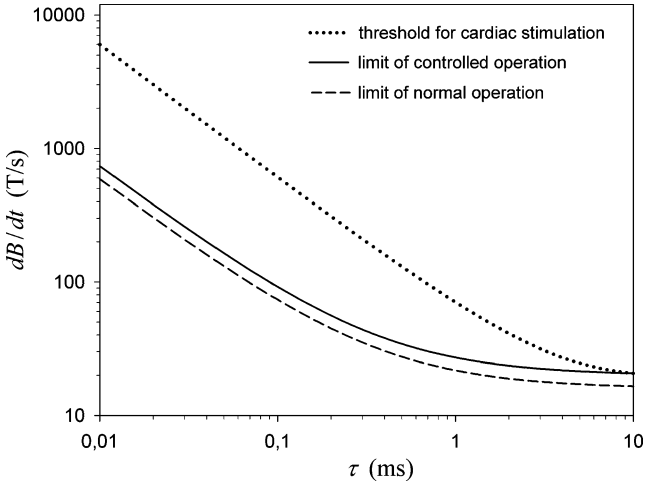

Fig. 2 Limits for the normal and controlled operating mode of an MR gradient system expressed as d*B*/d*t* as a function of the effective stimulus duration τ. The limit for the controlled operating mode is given by the median perception threshold for peripheral nerve stimulation. For comparison, the threshold for cardiac stimulation is also plotted [25]

Time-varying magnetic fields used for the excitation and preparation of the spin system in MR have typically frequencies above 10 MHz. In this RF range, the conductivity of cell membranes is comparable to that of the extra- and intracellular fluid which means that no substantial voltages are induced across the membranes [24]. Due to this reason, stimulation of nerve and muscle cells is no longer a concern. Instead, thermal effects due to tissue heating become important. The increase in tissue temperature depends not only on the local power absorption and the duration of RF exposure but also on the heat transfer and the activation of thermoregulatory mechanisms leading to thermal equalization within the body. According to published studies, no adverse health effects are expected if the RF-induced increase in body-core temperature of healthy persons does not exceed 1°C [23]. Since temperature changes in the various organs and tissues of the body during an MR procedure are difficult to measure in clinical routine, RF exposure is usually characterized by means of the *specific absorption rate* (*SAR* in W/kg), which is defined as the average energy dissipated in the body per unit of mass and time.

Safety regulations and operating modes

To minimize health hazards and risks to patients undergoing MR procedures, exposure limits for the three different magnetic fields used in MR are specified in

- the product standard IEC 60601-2-33 provided by the International Electrotechnical Commission [28] for manufacturers of MR equipment to follow and
- the safety recommendation issued by ICNRIP [23].

In order to reflect the persistent uncertainty about deleterious effects of magnetic and electromagnetic fields and to offer the necessary flexibility for the development and clinical evaluation of new MR technologies, both safety guidelines give exposure limits for three different modes of operation:

- *Normal operating mode*: Routine MR examinations that do not cause any field-induced physiological stress to patients.
- *Controlled operating mode*: Specific MR examinations outside the normal operating range where discomfort and/or physiological stress to some patients may occur. Therefore, a clinical decision must be taken to balance such effects against expected benefits, and exposure must be carried out under medical supervision.
- *Experimental operating mode*: Experimental MR procedures with exposure levels beyond the controlled operating range. In view of the potential risks for patients and volunteers, special ethical approval and adequate medical supervision is required.

All major manufacturers of MR equipment have adopted the regulations of the IEC product standard and ensure compliance with the specified exposure limits for magnetic gradient and RF fields by integrated monitor systems. With respect to the examination of patients in clinical routine, both the IEC standard and the ICNIRP guidelines recommended the following exposure limits:

- *Static magnetic field:* The recommended upper limit for the normal and controlled operating mode is 2T and 4T, respectively.
- *Magnetic gradient fields:* The maximum recommended exposure level is set equal to a d*B*/d*t* value of 80% of the median perception threshold for normal operation and 100% of the median for controlled operation. To this end, perception threshold levels have to be determined by the manufacturers for a given type of gradient system by means of experimental studies on human volunteers. As an alternative, the empirical hyperbolic strength-duration expressions shown in Fig. 2 can be used.
- *RF fields:* The increase in body-core temperature is limited to 0.5°C and 1.0°C in the normal and controlled operating mode, respectively. The relatively low temperature threshold of the normal operating mode takes into account that heat tolerance or thermoregulation may be compromised in some individuals, such as the elderly, infants, patients with certain medical conditions and/or taking certain medications. For MR practice, the SAR limits summarized in Table 3 have been derived on the basis of experimental and theoretical studies. They should not be exceeded in order to limit the temperature rise to the stated values.

Table 3 SAR limits for patients (and volunteers) undergoing MR procedures [23, 28] in clinical routine, which holds at environmental temperatures below 24°C

	Averaging time: 6 min					
	Whole-body SAR (W/kg)	Partial-body SAR (W/kg)		Local SAR (averaged over 10 g tissue) (W/kg)		
Body region → Operating mode ↓	Whole-body	Any region, except head[a]	Head[b]	Head	Trunk	Extremities
Normal	2	2–10	3.2	10	10	20
Controlled	4	4–10	3.2	10	10	20
Short-term SAR	The SAR limit over any 10 s period shall not exceed 3 times the corresponding average SAR limit					

[a] Partial-body SARs scale dynamically with the ratio r between the patient mass exposed and the total patient mass: normal operating mode: SAR=(10−8×r) W/kg; controlled operating mode: SAR=(10−6×r) W/kg.
[b] Partial volume SARs given by IEC; ICNIRP limits SAR exposure to the head to 3 W/kg.

Contraindications

MR examinations of patients with *passive implants* (e.g., vascular clips and clamps, intravascular stents and filters, vascular access ports and catheters, heart valve prostheses, orthopedic prostheses, sheets and screws, intrauterine contraceptive devices), *active implants* (e.g., cardiac pacemakers and defibrillators, cochlear implants, electronic drug infusion pumps), or other objects of ferromagnetic or unknown material (pellets, bullets) are always associated with a serious risk, even if all procedures are performed within the established exposure limits summarized in the previous section. This risk can only be minimized by a careful interview of the patient, evaluation of the patient files, and contacting the implanting clinician or the manufacturer for advice on MR safety and compatibility of the implant. MR examinations of patients with active implants are strictly contraindicated, provided that the patient implant card does not explicitly state their safety in the MR environment. Comprehensive information on the MR compatibility of implants and other metallic objects is available in a reference manual published by Shellock [29] and online at www.MRIsafety.com. In contrast, side effects associated with the use of iron oxide or other metal-based pigments in tattoos occur extremely seldom and should not prevent patients—after informed consent—from undergoing a clinically indicated MR procedure [30].

Pregnant females undergoing MR examinations are exposed to the combined magnetic and electromagnetic fields discussed above. The few studies on pregnancy outcome in humans following MR examinations have not revealed any adverse effects, but are very limited because of the small numbers of patients involved and difficulties in the interpretation of the results [23]. It is thus advisable that MR procedures may be performed in pregnant patients, in particular, in the first trimester, only after critical risk/benefit assessment and with informed consent of the expectant mother [31].

Justification and optimization of combined PET/MR examinations

At present, possible clinical indications for PET/MR can only be speculated on. In any case, not only the improvement in diagnostic accuracy achieved by this new imaging modality will be of relevance, but also its practicability, availability, and cost effectiveness. From a radiation hygienic point of view, it is obvious that a PET/MR examination is (1) justified, when there is an indication for a PET scan, and should (2) be performed instead of an PET/CT examination whenever possible. Nevertheless, there will be a whole string of clinical situations in which PET/CT will remain the method of choice, as for example, when CT data are required for radiation treatment planning, when CT is indicated instead of MR for morphological imaging, or when an MR examination is contraindicated in patients due to implants or metallic objects.

In case of combined PET/MR examinations, optimization of the entire procedure with respect to the exposure of patients to ionizing radiation reduces to the question, what activity of the radiopharmaceutical has to be administered for the emission scan. FDG activities administered for PET/CT examinations vary between about 200 MBq and 450 MBq [10] depending on the detector material and count rate behavior of the PET system as well as on the acquisition mode used (2D vs. 3D). They will presumably also be adequate for PET/MR examinations.

From a clinical point of view, lower activities will eventually result in longer emission scan times, and thus longer overall examination times. However, excessive

examination times should be avoided in multimodality imaging as they may result in patient discomfort and, thus, in motion-induced misregistrations of the complementary images. Thus, diagnostic reference levels for [^{18}F]FDG studies performed at conventional PET scanners—that have meanwhile been established by most European states—may not be appropriate for combined PET/MR examinations. To balance the potentially higher activities that are injected into patients in an attempt to reduce emission scan time, voiding of the bladder should be forced, e.g., by oral hydration with water or the administration of a diuretic. This is a very effective measure because FDG in the bladder is the major source of internal exposure to the bladder itself as well as to neighboring organs.

In contrast to CT, the acquisition of whole-body MR images for transmission correction of emission data and morpho-functional image correlation is much more challenging [32]. To realize short examination times, the measurement has to be performed with fast MR sequences relying on the use of high-performance gradient and RF systems. At least at high-field MR systems, it will therefore be necessary to carefully optimize the imaging sequences, as for example by utilizing SAR reduction techniques like parallel imaging or hyperechos. In this context, it has to be noted that—contrary to a common opinion held among MR users—the SAR limits given in Table 3 do not relate to an individual MR sequence, but rather to running SAR averages computed over each 6-min period, which is assumed to be a typical thermal equilibration time [33]. This means that sequences can be employed for which SAR levels exceed the defined limits, if the acquisition time is short in relation to the averaging period and energy deposition has been low previous to the applied high-power sequence.

Research needs

The data and considerations presented in this review provide an appropriate foundation for the initial assessment of possible health risks for patients undergoing combined PET/MR examinations. It has to be noted, however, that they are based solely on established biophysical and biological effects related to the exposure of either ionizing radiation or magnetic and electromagnetic fields, whereas synergistic or antagonistic effects are not taken into account. There are a few studies indicating that static [34] and low-frequency [35–38] magnetic fields might enhance the genotoxic potential of ionizing radiation. Moreover, it is well recognized that mild hyperthermia, as for example caused by RF fields, has a radiosensitizing effect in tumors [39, 40]. In the light of the developing PET/MR technology, further biological studies are thus required to investigate—for exposure levels and examination scenarios that will occur at PET/MR systems—whether there are synergistic effects in normal tissues and, if so, to clarify their relevance for risk assessment of patients that will be examined with this innovative imaging modality.

Conflict of interest There are no conflicts of interests for any of the authors.

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