Integrated Whole Body MR/PET Imaging. First Examples of Clinical Application

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Introduction

Over the last decade, development of hybrid-imaging instrumentation has been among the innovations with the strongest impact on diagnostic imaging in clinical everyday routine. The driving force behind these developments is the considerable extent to which several different imaging modalities show complementary rather than redundant features. Consequently, it is logical to bundle the particular strengths of different modalities, and to compensate particular deficits of one modality with capabilities of another by combination of the different modalities into one hybrid instrument. Hybrid PET/CT entered the market in around 2000 and became a major success, thereby quickly obviating the demand for PET-only scanners. This success has been strongly driven by oncological applications, combining the high sensitivity of PET with the anatomical precision of CT. The coupling of ^{18}F-FDG, a tracer for metabolic activity with CT, has especially proved highly valuable: FDG-PET allows the sensitive detection of tumor cells and the estimation of their viability (e.g. for therapy control); CT complements the exact anatomic localization of suspect lesions and has a very high sensitivity for small lesions which are missed by PET due to limited resolution or movement artifacts (e.g. in the lung).

However, CT has some specific limitations, the most apparent being the relatively low soft-tissue contrast. This represents a disadvantage particularly for diagnostic questions directed to body regions which are defined by a complex regional arrangement of different adjacent soft tissue structures, e.g. the brain, the head-and-neck region or the pelvis. In contrast to CT, MR-imaging is distinguished by the ability to provide excellent soft-tissue contrast. This is the main reason why corresponding diagnostic problems are typically directed to MRI as the first-line imaging procedure of choice rather than to CT. This includes questions concerning e.g. neurological disorders, brain tumors, conditions in the head and neck region, abdominal/hepatic and pelvic masses and musculoskeletal problems.

For many of these diagnostic questions, PET has demonstrated a high added value as a complementary test in itself, whilst frequently being performed in addition to mandatory MRI-tests (see A. Padhani 'Multiparametric imaging of tumors – an emerging paradime', MAGNETOM Flash #45 3/2010, Research Supplement). Thus, the value of a combination of PET with MRI seems obvious. However, the development of such hybrid MR/PET instrumentation has been hampered for a long time primarily by technical obstacles which have been harder to overcome compared to the combination of PET and CT. Whereas the latter both represent modalities working with radiation (although in different wavelengths) and can thus be combined more easily, PET and MRI are based on entirely different image acquisition principles. The strong magnetic field required for MR-image acquisition is severely affecting the acquisition of the PET-signal. In particular, the conventional photomultiplier technique commonly used for obtaining the PET signal does not work properly in a magnetic field. To circumvent this limitation, platforms have been developed in which spatially separate MR- and PET-scanners are connected by means of a moving table. The patient is positioned on this table and undergoes first PET and then MR imaging, without having to get up from the table between the scans. However, these solutions do not allow simultaneous image acquisition and they are of course associated with lengthy examination protocols and with the risk of patient movement.

With the introduction of the so-called APDs (Avalanche Photodiodes) into PET-

instrumentation this problem has been solved more elegantly. APDs function in strong magnetic fields and can be used to substitute conventional photomultipliers to acquire information in the MR-scanner. The advent of this technology has allowed the industry to produce a first generation of hybrid MR-scanners in which a true integration of both modalities in a single machine has been realized (see H. Quick 'Whole-body MR/PET hybrid imaging' page 88 in this issue of MAGNETOM Flash). This principle was first successfully demonstrated by means of small head-only PET-scanners (PET-insert) which have been installed in conventional MR-scanners (see T. Beyer et al. 'MR/PET-hybrid imaging for the next decade', MAGNETOM Flash #45 3/2010 Research Supplement). Several studies have been performed in this prototype system since and proved the practicability of the concept [1–4].

On the basis of this prototype, a dedicated whole-body MR/PET system has now been developed. In November 2010, the world's first integrated clinical whole-body MR/PET scanner (Siemens Biograph mMR) was installed in the Department of Nuclear Medicine at the Technische Universität München (TUM), in Munich, Germany. The scanner is now operated by a consortium between the directors of Nuclear Medicine (Prof. Dr. Markus Schwaiger) and Radiology (Prof. Dr. Ernst Rummeny) from TUM and the directors of Nuclear Medicine (Prof. Peter Bartenstein) and Radiology (Prof. Dr. Maximilan Reiser) from the Ludwig-Maximilians-Universität, München. The setup of the first scanner of this type in Germany (and of three identical scanners which will be established in 2011 in Essen, Leipzig and Tübingen) has been made possible by funding of the German Research Foundation (DFG, Deutsche Forschungsgemeinschaft).

The Biograph mMR MR/PET-scanner is constituted by a high end 3T MR-scanner which harbours a fully functional state-of-the-art PET system within the gantry. The PET-system covers a field of view (25.8 cm) which is larger than in any other existing PET-camera. This allows to obtain multimodal (MR&PET) image information simultaneously in an extended region and to cover the entire body with a limited number of bed positions in short time. For further technical details on the system see page 88 in this issue of MAGNETOM Flash.

Opportunities of the MR/PET-system

From a clinical point of view, this system offers a number of obvious advantages:

1. Reduction in examination time

In comparison to clinical CT-examinations, MR-scans can often be relatively time-consuming. The recently introduced whole-body MR/PET scanner now allows the acquisition of MR and PET information in a truly simultaneous approach, i.e. in regional alignment at exactly the same time, thereby reducing not only the number of examination appointments (i.e. the visits patients have to make to the imaging department) but also cutting the required examination time approximately in half (as compared to two separate examinations). This option of 'one-stop shop' examinations represents a major gain in patient comfort for patients requiring both MR and PET examinations and also reduces the required time of the medical personnel to acquire the requested imaging information.

2. Regional coregistration

The acquisition of PET and MR-information in exactly overlapping anatomical positions also offers clear advantages: Precise coregistration of the PET-signal with the underlying anatomical information is assured as the risk of patient movement or changes in organ position (e.g. in bowel positions, different bladder filling status) between the acquisition of the two modalities is reduced, and thus potential misalignment is minimized. Due to the lack of radiation exposure by the MR-image acquisition, anatomical scans can be added/repeated to achieve optimal anatomical information.

3. Simultaneity of acquisition

The newly introduced integrated MR/PET scanners for the first time allow truly simultaneous acquisition of imaging information from two different modalities of the same region at the same time. This opens a completely new dimension in hybrid imaging. Even established PET/CT technology only allows the acquisition of CT and PET in the same system but not at exactly the same time and region, as the two modalities/acquisition procedures are cascaded one after the other. The simultaneous acquisition of MR and PET information opens the opportunity to address many new scientific questions, which may be translated into clinical application, e.g. to cross-evaluate the value of different imaging tests under identical examination conditions or to improve understanding of disease pathophysiology by shedding light on the interrelation between different pathological processes. Simultaneous acquisition may also allow the following of organ and/or patient movement over time allowing for motion correction [2] and also the combination of information on motility with other functional information provided by PET (e.g. information on viability/perfusion derived from PET-imaging with information on wall movement in cardiac examinations).

4. Exposure to ionizing radiation

Radiation exposure based on clinical imaging tests is currently a much-discussed topic. Compared to PET/CT, hybrid MR/PET offers the chance to reduce ionizing radiation exposure without loss of diagnostic information. MRI will probably allow anatomical allocation of the PET-signal with comparable precision as known from CT. In some cases the combination of PET-imaging with appropriate diagnostic MR-imaging procedures may be of superior diagnostic value with considerably lower radiation exposure as compared to the combination of PET and diagnostic CT.

5. Complementary/superior diagnostic value of MR/PET compared to PET/CT
It is well known that MRI has complementary features to CT. The most obvious being the higher soft-tissue contrast. As mentioned above, combined MR/PET may be of obviously higher diagnostic value compared to PET/CT for indications and in body regions which would usually be approached using MRI rather than CT (see clinical examples below). In this regard MR/PET may represent a complementary imaging technique to PET/CT in the future just as MR itself represents a complementary imaging technique to CT nowadays.

6. Opportunities for scientific applications
The MR/PET-system opens a large number of potential scientific applications. Among these is the unique option to establish previously unknown interrelations between different measures of pathology and physiology in the human body such as structure and function, perfusion and metabolism, tissue diffusivity and cell proliferation etc. This may allow to improve the understanding of healthy organ function and to detect causal relationships in disease pathogenesis potentially leading to new therapeutic approaches.
For clinical diagnosis, combined MR/PET may allow the development of integrated multiparametric markers for more sensitive and more specific diagnosis, therapy planning and evaluation [5]. Several previous studies using separate modalities point to a potentially high scientific and clinical benefit from multimodal imaging approaches using MR/PET [e.g. 5–7].

Challenges of the MR/PET system

Like every new system, combined MR/PET still has a number of apparent challenges:

1. Attenuation correction
In PET/CT systems, low-dose CT scans are used to estimate the expected attenuation of the radiation emitted from a specific body region. In contrast to CT, MR imaging does not provide information on tissue specific photon absorption, but rather on tissue type/class. However, it has been demonstrated that by means of a set of specific MR-sequences (Dixon imaging or chemical shift imaging) suitable attenuation maps can be calculated, which allow an approximation of 511 keV photon attenuation correction with sufficient reliability [8]. The dual point VIBE T1-weighted Dixon sequence used for attenuation correction in the Biograph mMR can be acquired quickly for each bed position (e.g. in the thorax during one breathhold), practically not increasing the examination time. However, the current approach of tissue classification with the Dixon sequence is not yet fully satisfying, it is prone to metal artifacts, attenuation by bones is not considered and truncation artifacts may occur due to the limited transaxial field-of-view of the MR/PET scanner (particularly of the upper limbs). The compensation for these artifacts is currently a matter of ongoing research. Moreover, it can be anticipated that different sequences for attenuation correction will be used in specific areas of the body. For the head e.g., bone probably cannot be neglected completely for truly accurate AC, especially for the skull base. Therefore in this region, the application of ultrashort TE (UTE) sequences might be favourable, which allows for delineation of the bone, thus leading to more exact attenuation maps (μ-maps) as compared to the Dixon imaging approach.

2. Anatomical allocation of PET-findings
The low dose CT scan of the whole body as acquired in conventional PET/CT provides limited diagnostic information but it allows a rough anatomical allocation of suspect PET-findings with sufficient reliability in many cases. For precise attribution diagnostic contrast-enhanced CT scans can be acquired in very short time and provide excellent anatomical information. By contrast, MR-sequences can be comparably slow and it may not be feasible to always acquire whole-body MR-information with high resolution in due time. However, it seems likely that the Dixon-sequences used for attenuation correction of the PET-data also can be used for anatomical allocation of PET-findings with very satisfying results. These whole-body images can then be complemented by added high-resolution MR-sequences in particular regions of interest.

3. MR-specific diagnostic limitations
It is expected that MR/PET will be inferior to PET/CT for indications which are commonly addressed with better diagnostic value by CT, e.g. small pulmonary lesions. It remains to be evaluated for which indications MR/PET is superior or equal to PET/CT and for which indications PET/CT will remain the method of choice.

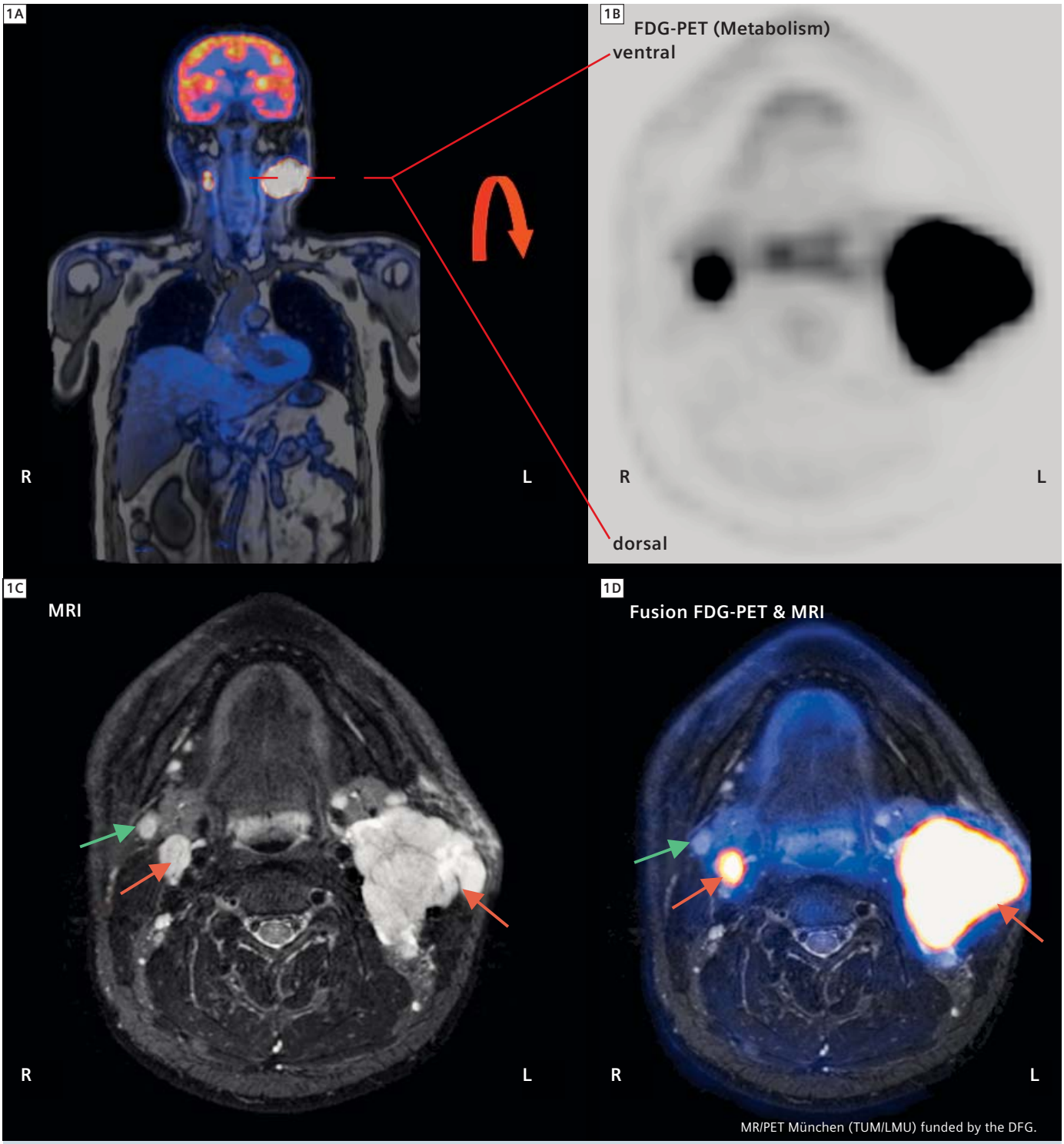
4. Workflow
The high costs for this type of imaging instrumentation will require elaborate logistics regarding patient flow, occupancy of the scanner, selection of examination procedures etc., to assure efficient utilization of the scanner. The combined acquisition of MR and PET information defines the need for specially educated medical personnel experienced with both modalities.

5. Design of suitable imaging protocols
The large number of available MR-sequences and of different PET-tracers exponentiates the number of potential combinations of imaging tests. This will define the need to develop optimized imaging algorithms for specific diagnostic questions, which ensure the selection of the most beneficial combinations.

Examples for clinical applications

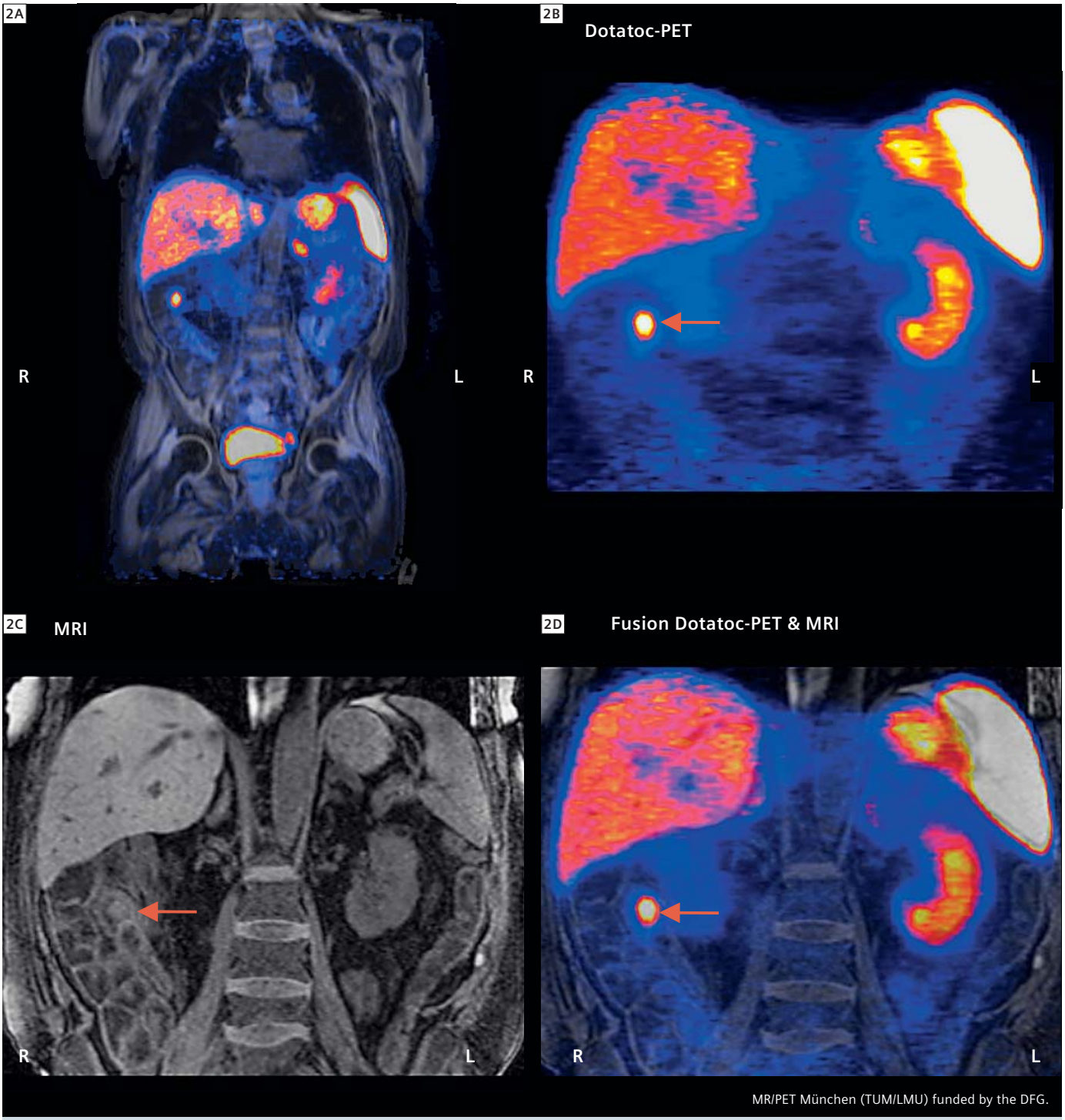
1. Oncology

Case 1 Patient with a cervical Non-Hodgkin lymphoma.



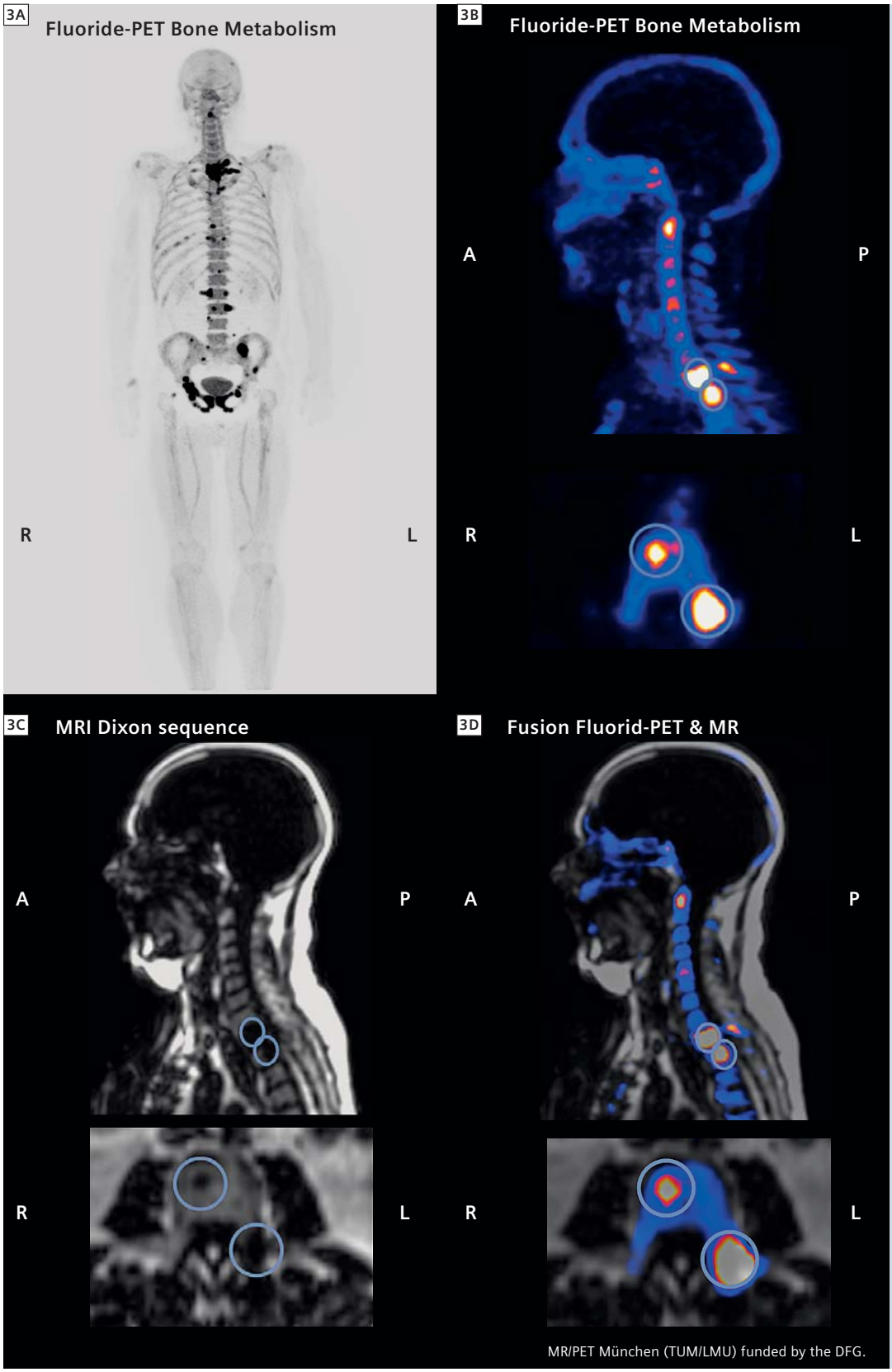
1 **A:** Overview using the opposed phase of the MR AC Dixon sequence. **B:** Axial slice of the ^{18}F-FDG-PET image, demonstrating tumor-suspect increased metabolism in two lesions (left and the right lateral). **C:** Axial MRI (STIR sequence) demonstrating the high tissue contrast. Several cervical lymph nodes are apparent, some enlarged. **D:** Overlay of PET and MRI, easily tumor-typical (red arrows) and non tumor-typical findings (green arrow) can be identified and allocated anatomically.

Case 2 Patient with a Neuroendocrine tumor.



2 **A:** Overview using the water image of the MR AC Dixon sequence. Note the area of intense focal tracer uptake in the right upper quadrant of the abdomen, projecting on the region of the terminal ilium. There is a small bladder diverticulum of the left lateral bladder wall with tracer retention as accidental finding. **B:** PET-findings with ^{68}Ga-DOTATOC, a tracer binding to somatostatine-receptors which are expressed frequently on neuroendocrine tumors. An intense focal tracer-uptake can be found in the abdomen. **C:** MR-image, fat-suppressed coronal T1w breathold VIBE sequence. **D:** Fusion of PET and MR-findings. An excellent identification and anatomical allocation of the tumor is possible by combination of PET and MRI findings. No additional suspect lesions are apparent.

Case 3 Patient with bone metastases of a prostate cancer.

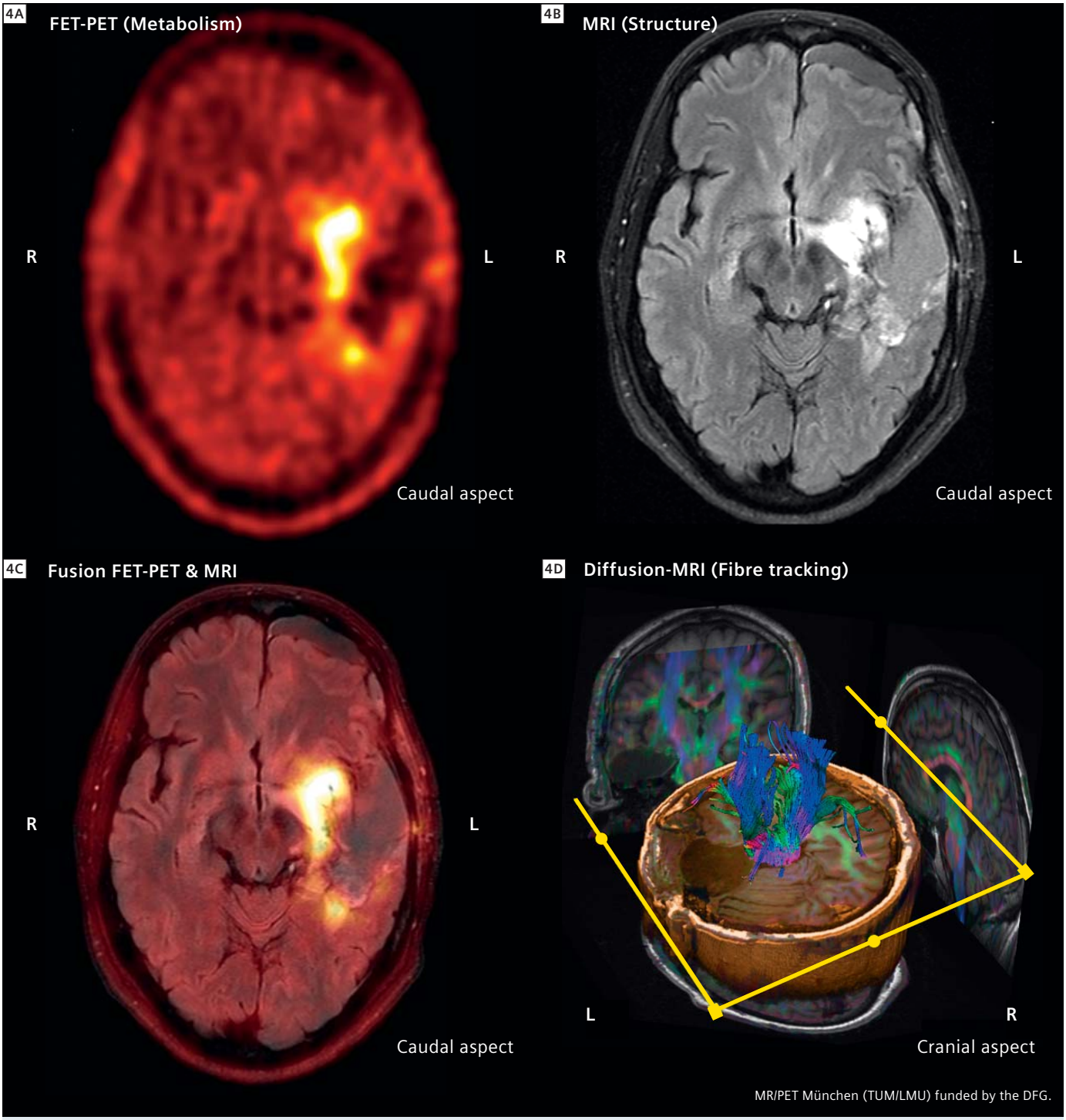


MR/PET München (TUM/LMU) funded by the DFG.

3 **A:** Overview of the ^{18}F-Fluoride PET scan. **B:** PET-findings. **C:** MR-image, sagittal fat-weighted MR AC Dixon sequence. **D:** Fusion of PET and MR-findings. Upper row: sagittal slices, Lower row: axial slices. The Fluoride-PET scan shows a number of suspect lesions in the skeleton, likely corresponding to bone metastases of the prostate-cancer. On the MR- and the fusion-images it is apparent that in the region of the increased PET-tracer uptake, displacement of the bone marrow has occurred, underlining the suspicion of bone metastases.

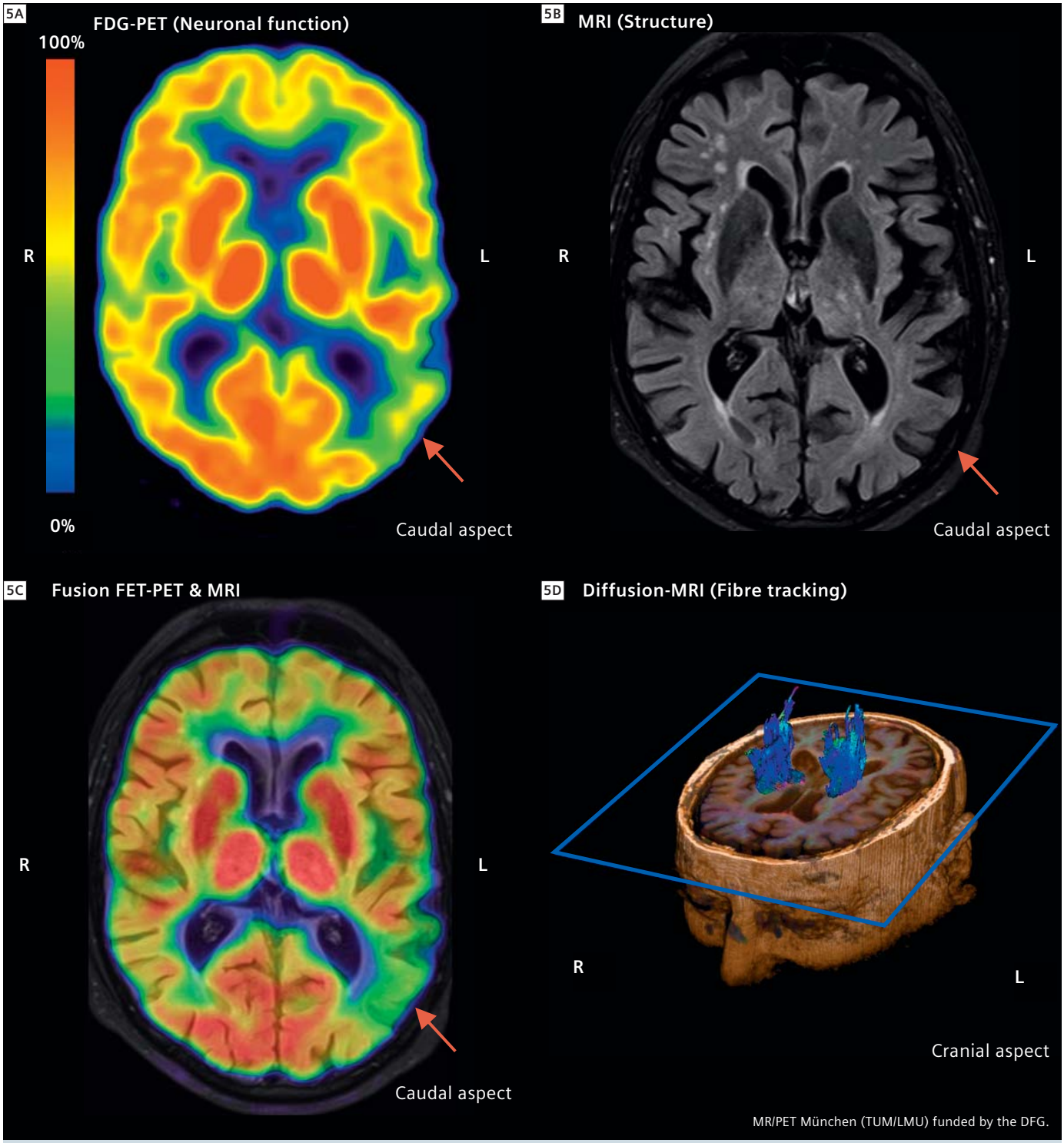
2. Neurology

Case 4 Patient with a glioblastoma multiforme.



4 **A:** ^{18}F-FET PET scan. The tracer FET represents a measure of the amino acid metabolism and allows the sensitive identification of brain tumor tissue which is characterized by high amino acid turnover, in contrast to healthy brain tissue. A strong tracer uptake is visible around a previous resection area, suspect for remaining/recurrent brain tumor tissue. **B:** MR-image, axial FLAIR-sequence, demonstrating a region of hyper intensity around the area of resection, potentially representing edema and/or gliosis, but also vital tumor tissue cannot be excluded. Moreover, a left frontopolar hygroma is seen. **C:** Fusion of PET and MR-findings, allowing excellent anatomical allocation of the vital tumor tissue in reference to anatomical structures and abnormalities in the MR-image. **D:** Fibre-tracking based on a diffusion-tensor MR dataset, demonstrating the course of neuronal axons alongside the resection area.

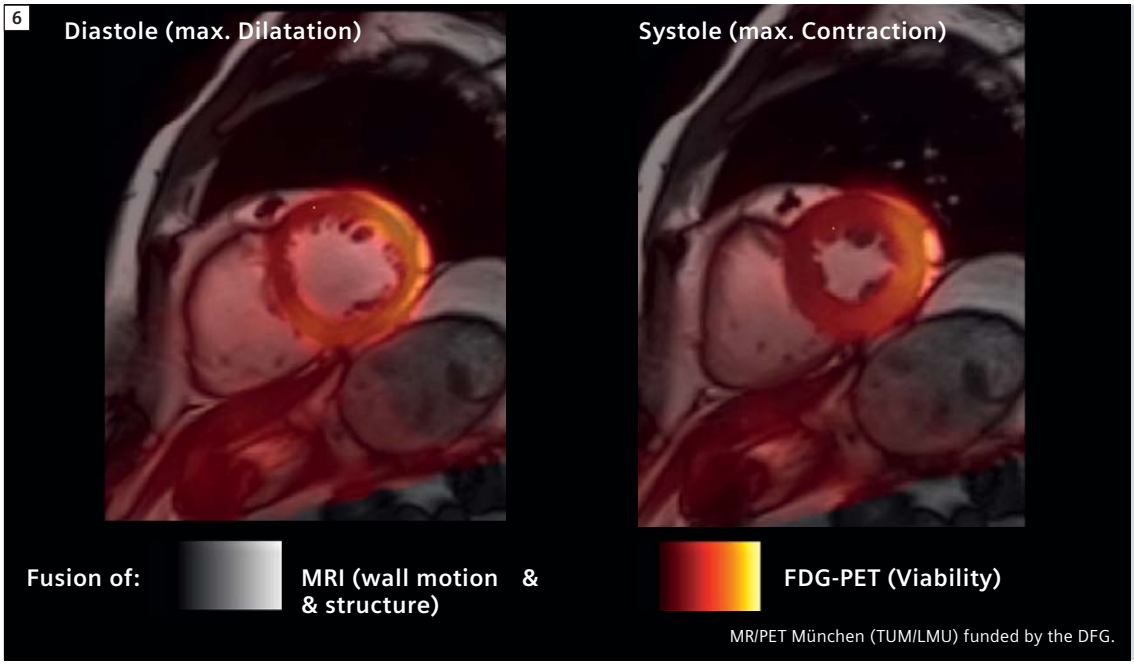
Case 5 Patient with Alzheimer's disease.



5 **A:** ^{18}F-FDG-PET of the brain, which represents a measure of neuronal function. Areas with reduced neuronal function in consequence of ongoing neurodegenerative processes are displayed in green-yellow (left temporoparietal cortex, see red arrow), healthy brain regions in orange-red. **B:** MR-image, axial FLAIR-sequence. Brain anatomy can be displayed in high resolution, cerebral atrophy is apparent in widespread regions, predominantly on the left side. **C:** In the MR/PET fusion regional allocation of hypometabolism and brain substance loss is possible. **D:** Fibre-tracking based on a diffusion-tensor MR dataset, demonstrating the course of neuronal axons in the brain of the patient.

3. Cardiology

Case 6 MR/PET of the heart.



6 Assessment of the metabolism of cardiac tissue with the tracer ^{18}F-FDG allows the identification of viable myocardium. Simultaneous acquisition of wall motion and myocardial anatomy can be performed using MRI. The combination allows the exact attribution of functional aspects to underlying regional metabolic conditions/viability.

Conclusions

- First clinical imaging studies demonstrate successful clinical applicability of integrated whole body MR/PET.
- Attenuation correction of the PET signal using appropriate MR-derived attenuation maps appears to be feasible with sufficient reliability for most cases. Some problems (lack of accurate bone-detection, truncation artifacts) are a matter of ongoing research.
- From a diagnostic perspective, superiority of MR/PET compared to PET/CT can be foreseen for indications/body regions, which would preferably be approached by MRI rather than by CT, due to the superior soft tissue contrast of MRI. Examples are:
  Oncology: Head and neck tumors, masses in the pelvis/abdomen (e.g. prostate cancer), carcinoma of unknown primary, whole-body imaging
  Neurology: Brain tumors, epilepsy, dementia, stroke
  Cardiology: Regional function (wall motion) and scar detection (late enhancement) versus myocardial perfusion and tissue viability
- It remains to be evaluated for which indications MR/PET is superior or equal to PET/CT and for which indications PET/CT will remain the method of choice. MR/PET will probably be inferior to PET/CT for indications which are commonly addressed with better diagnostic value by CT, e.g. pulmonary lesions.
- The expected high costs for this type of imaging procedure will require elaborate logistics regarding patient flow, examination procedures, occupancy of the scanner etc., to ensure efficient utilization.
- The large number of available MR-sequences and of different PET-tracers exponentiates the number of potential combinations of imaging tests. This will define the need to develop optimized imaging algorithms for specific diagnostic questions.

References

1 Catana, C., et al., MRI-assisted PET motion correction for neurologic studies in an integrated MR-PET scanner. J Nucl Med. 52(1): p. 154-61.
2 Catana, C., et al., Toward implementing an MRI-based PET attenuation-correction method for neurologic studies on the MR-PET brain prototype. J Nucl Med. 51(9): p. 1431-8.
3 Herzog, H., et al., High resolution BrainPET combined with simultaneous MRI. Nuklearmedizin. 50(2).
4 Schlemmer, H.P., et al., Simultaneous MR/PET imaging of the human brain: feasibility study. Radiology, 2008. 248(3): p. 1028-35.
5 Beer, A.J., et al., Radionuclide and hybrid imaging of recurrent prostate cancer. Lancet Oncol. 12(2): p. 181-91.
6 Metz S, Ganter C, Lorenzen S, van Marwick S, Herrmann K, Lordick F, Nekolla SG, Rummeny EJ, Wester HJ, Brix G, Schwaiger M, Beer AJ. Phenotyping of tumor biology in patients by multimodality multiparametric imaging: relationship of microcirculation, alphavbeta3 expression, and glucose metabolism. J Nucl Med. 2010 Nov; 51(11):1691-8. Epub 2010 Oct 18.
7 Drzezga A, Becker AJ, Van Dijk K, Sreenivasan A, Talukdar T, Sullivan C, Schultz AP, Sepulcre J, Putcha D, Greve D, Johnson KA, Sperling RA. Neuronal dysfunction and disconnection of cortical hubs in non-demented subjects with elevated amyloid-burden. Brain. 2011, in press.
8 Martinez-Moller, A., et al., Tissue classification as a potential approach for attenuation correction in whole-body PET/MRI: evaluation with PET/CT data. J Nucl Med, 2009. 50(4): p. 520-6.

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