Whole-body MR diffusion imaging in oncology: origins, practice, and outlook

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Background

1905 was one of Albert Einstein's most productive years, his acclaimed *annus mirabilis* (from Latin meaning "extraordinary year"), in which he made a substantial contribution to the foundation of modern physics. In addition to other findings and innovations, Einstein extended Brown's theory about the random motion of particles [1]. Robert Brown, a Scottish botanist, was the first to notice the motion of particles in water; but he was not able to determine the underlying mechanisms of this motion. This was not the case for the German-born Nobel Prize winner. The first part of Einstein's theory was to determine how far a particle travels in a given time interval, and the second related the diffusion constant to physically measurable quantities, such as the mean squared displacement of a particle in a given time interval. Einstein observed, understood, and ultimately quantified water diffusion.

In 1974, R.V. Damadian patented the first magnetic resonance (MR) scanner as a "method for detecting cancer in tissue [2]." In this context, diffusion-weighted imaging played no significant role. This technical innovation was widely reported in the international media and had a significant impact on public opinion. In fact, with this new electronic device, Damadian claimed to be able to locate cancer across the whole body, raising expectations of the potential benefits of this innovation for oncology.

More than a decade later, a French physician named Denis Le Bihan came up with the intuitive idea of merging these two findings. Le Bihan showed that water diffusion could be displayed in the human brain through magnetic resonance imaging and, in 1985, produced the first diffusion-weighted image with MRI [3]. Since 1990, diffusion-weighted imaging (DWI) has become a standard neuroradiology tool for diagnosing ischemia. In 2004, Takahara et al. made a pioneering contribution to the development of DWI, by introducing a technology called diffusion-weighted whole-body imaging with background suppression (DWIBS), in which radiological images are acquired during free respiration, suppressing background signals and allowing volumetric acquisitions and multiple section excitations of the whole body [4]. Thanks to these developments regarding the role of diffusion in magnetic resonance imaging, the scientific community finally had a method for quantifying the microscopic motion of water molecules in biological tissues over the entire body. Over the past decade, medical technology suppliers have launched incredible technological developments enabling whole-body MRI (WB-MRI), including morphological and diffusion-weighted images, to be performed in just 30–45 minutes. Moreover, clinicians have found many exciting uses for this radiation free technique for the management of malignancies and cancer screening.

Guidelines and key uses of WB-MRI by cancer histotype

Following growing evidence of its effectiveness in the management of cancer patients, the use of WB-MRI has increased exponentially over the last decade [5]. Encouraging results in the management of a variety of different cancer histotypes, in some cases substantiated

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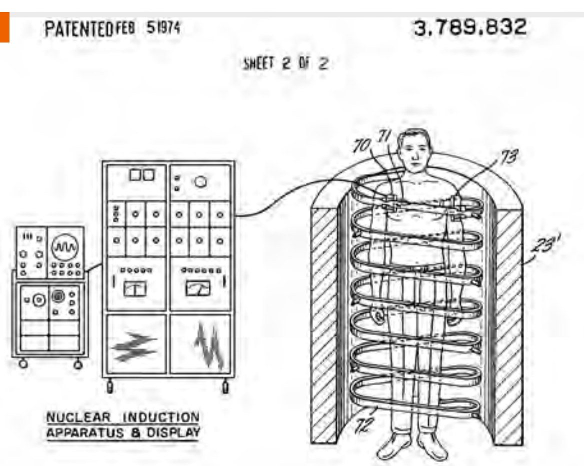


Figure 1:
Damadian's whole body MRI device, excerpt from the original U.S. Patent No. 3789832, Feb. 5, 1974.

by the highest level of scientific evidence [6], consolidated the role of WB-MRI in the management of several malignancies. In recent years, certain clinical guidelines have recommended the use of WB-MRI and important uses for this technique have been found in modern oncology.

Multiple myeloma

Multiple myeloma (MM) is a haematological cancer characterized by the accumulation of neoplastic plasma cells in the bone marrow. Bone disease, distinguished by the presence of bone fractures, osteolytic lesions, or osteoporosis, is a significant cause of morbidity and mortality in multiple myeloma [7]. Thus, according to the guidelines of the International Myeloma Working Group (IMWG), the presence of even asymptomatic bone disease on conventional radiography should be considered a criterion of symptomatic MM requiring treatment [8]. In a series of 611 MM patients, MRI detected more focal lesions than lytic lesions in whole-body X-rays of the spine (78% versus 16%; P 0.001), pelvis (64% versus 28%; P 0.001), and sternum (24% versus 3%; P 0.001) [9], which are the most common areas of MM systemic spread. Moreover, in a study of 41 patients with newly-diagnosed multiple myeloma, WB-MRI proved superior to conventional whole-body CT screening in detecting lesions of the skeleton. WB-MRI should thus be used to detect regions with bone marrow infiltration for both diagnosis and monitoring of treatment response. According to the guidelines on the role of imaging in patients with MM, produced by the British Society for Haematology [10], WB-MRI is recommended for staging all forms of multiple myeloma (Grade of Recommendation A, GR A, reflecting the highest level of evidence-based medicine). It is also recommended for the monitoring of oligosecretory and non-secretory myelomas (Level of Evidence, LoE 1B [11]) as well as for extramedullary disease (LoE 1B [12]). The GR A recommendation also indicates that WB-MRI should be used for the staging of solitary bone plasmacytoma (SBP), an early stage malignancy with a clinical course between MGUS and multiple myeloma.

Prostate cancer

Prostate cancer is the most common histotype among men. While some types of prostate cancer grow slowly and may need only minimal or even no treatment, others may develop aggressive behavior, requiring accurate systemic staging and follow up.

In high-risk patients, guidelines developed by the European Association of Urology recommend cross-sectional abdominopelvic imaging and a bone-scan, as a minimum (GR A, LoE 2A [14]). However, the guidelines suggest that MRI is more sensitive (97%) than choline PET/CT (91%) and bone scans (78%) for detecting bone metastasis. This was confirmed in a recent meta-analysis conducted by Shen et al. on 18 studies comparing the diagnostic accuracy of these three imaging techniques [15]. Moreover, the radiological assessment of metastasis also has prognostic value and changes treatment management protocols [16].

In advanced prostate cancer (APC) the management of metastasis is crucial: skeletal metastases are present in more than 90% of patients who die of the disease. In metastatic castrate-resistant prostate cancer (mCRPC) patients being treated with enzalutamide and abiraterone and radium-223, up to one disease progression in three is detected radiologically with no clinical symptom or PSA (prostate serum antigen) progression [17, 18]. Moreover, PSMA PET/CT may fail to provide information on tumor viability during androgen receptor inhibition. Two recent reviews identified the potential of WB-MRI to address the unmet need for robust imaging that allows us to monitor the response of bone metastases to treatment [19, 20]. The St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) presented clear recommendations about castrate-resistant patients. The recommendations confirm that PSA alone is not reliable enough for monitoring disease activity in mCRPC (since metastases may develop without a rising PSA) and that imaging should be conducted before starting a new line of treatment [21]. Moreover, the APCCC recommendations affirm that "disease monitoring in the bone is especially difficult with well-described bone lesion are phenomena both on CT and bone scans, [...] and it is recognised that planar bone scintigraphy has short-comings and is less sensitive than other newer imaging technologies such as MRI of the whole body." Finally, although it acknowledged the "limited availability of these newer imaging technologies," the APC Consensus Conference confirmed that "advanced spinal/whole-body MRI techniques are also better able to identify and gauge the extent of bone disease than planar bone scans."

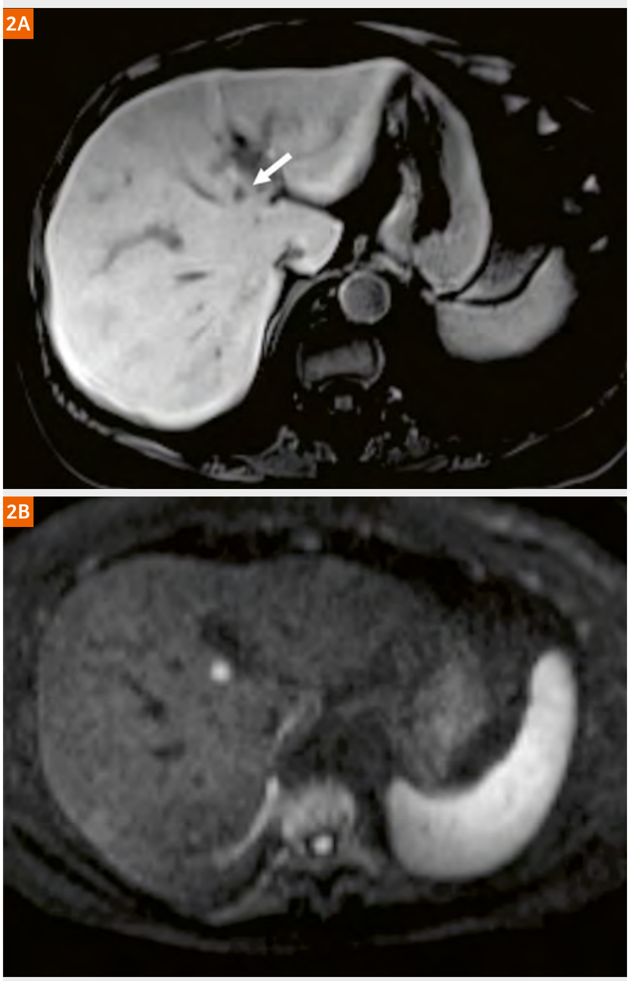
Melanoma

Although we have seen significant developments in the clinical management of advanced melanoma in recent years, most patients with stage IV melanoma will still die of the disease. For this reason, guidelines for the treatment of malignant melanoma have been published since 2001, providing feasible practical recommendations for clinicians and surgeons. Several meta-analysis and systematic reviews have established WB-MRI as a valid alternative method to PET/CT in oncology [22, 23]. Further studies have confirmed that WB-MRI is highly sensitive in detecting extracranial metastases in melanoma patients [24]. Although MRI with hepatobiliary contrast agents is considered the best imaging strategy for identifying hepatic secondary lesions, small liver metastases can also be confidently detected with diffusion-weighted imaging as the sole method, as briefly reported in the case study (Fig. 2).

Moreover, studies are investigating recent developments in non-standard ultra-short TE (UTE)[1] MRI sequences [25] as a viable radiation-free alternative to reference CT scans in detecting small metastatic lesions in the lungs from melanoma (Fig. 3). In a study conducted on behalf of the German Dermatological Society and the Dermatologic Cooperative Oncology Group [26], Pflugfelder et al., strongly recommend WB-MRI for cross-sectional imaging of advanced melanoma (stage III or worse), asserting that the efficacy of this method is equivalent to whole-body CT and PET/CT. Moreover, WB-MRI is also recommended for the follow-up in patients with melanoma staged from IIC to IV [27].

[1] WIP, the product is currently under development and is not for sale in the US and in other countries. Its future availability cannot be ensured.

Figure 2: Hepatic metastases: do we really need contrast?



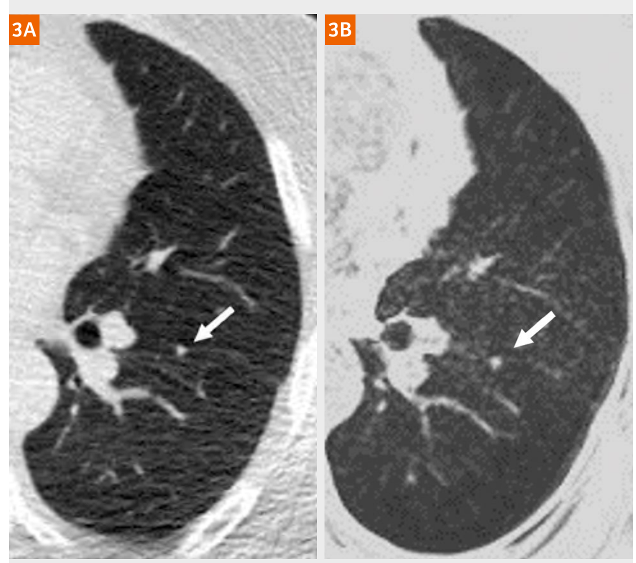
A patient with a stage III melanoma undergoes WB-MRI with hepatobiliary-specific contrast agent (gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid, Gd-EOB-DTPA). The late hepatobiliary phase, 20 minutes after injection **(2A)**, reveals the presence of a 9 mm metastasis in the fourth segment (white arrow). The same lesion is clearly detectable in the high b-value (900 s/mm^2) diffusion-weighted image performed in the same session **(2B)**.

Breast

Breast cancer is the second leading cause of death among women. An epidemiological study based on 25,336 women diagnosed with primary invasive breast cancer, confirmed bone as the most common site of metastasis [28]. The widely accepted RECIST criteria (Response Evaluation Criteria in Solid Tumors) should not be used for monitoring bone lesions, as they are considered non-measurable. Moreover, the revised RECIST 1.1 failed to fully address this point. According to the new criteria bone metastases are only measurable once they have spread to the surrounding soft tissue with a mass larger than at least 10 mm in diameter [29]. This does not occur in the majority of the cases.

Since being introduced in clinical practice, conventional MRI has proven capable of supplying extremely precise imaging of the bone marrow which, in some cases, would be unachievable using other imaging techniques [30]. In

Figure 3: Lung metastasis in CT and MRI



A patient with stage IV melanoma undergoes a follow-up examination with low-dose CT of the lung and WB-MRI. A subcentimetric metastasis in the left inferior lobe is identified on the axial CT image (arrow in **3A**) as well as on the axial T1-weighted image (arrow in **3B**).

a meta-analysis conducted by Yang et al. on 145 studies comprising 15,221 patients with bone metastasis, WB-MRI showed better sensitivity for lesion detection (97%) than FGD-PET (91%)and bone scan (79%) [31]. In some instances conventional MRI could have shortcomings, however. For instance, a phenomenon known as T1 pseudo-progression can occur. This is when a strong response to therapy results in a bone marrow edema, which is visible as a T1 hypo-intensity and can be misclassified as progression. In such cases, the addition of DWI to T1-weighted images allows both the presence of the bone marrow edema and an absence of restrictions for water molecules to be identified, thus avoiding misdiagnosis [32]. The sclerotic response occurs when, after treatment, bone metastases appear unchanged on morphologic T1 images, but a response is clearly visible on the ADC map. The response is identified by an increase in the ADC value to over 1,500 µm²/s, which is a well-documented threshold for response to therapy (Fig. 4).

Studies are underway to evaluate the impact of the superior diagnostic performance of WB-MRI compared to conventional imaging techniques on the management of cancer patients and, ultimately, on their survival. In a recent study, Kosmin et al. [33] compared the findings of 210 paired WB-MRI scans and computed tomography of chest, abdomen, and pelvis (CT-CAP) performed at the same time (within 14 days) for follow-up in patients with metastatic breast cancer. They observed that therapy changes were made due to progressive disease (PD) detected in the imaging in 46 pairs of scans; in 16 of these pairs (34.7%), PD was only visible in the WB-MRI scans and was not diagnosed by CT examination. This observation emphasizes the additional value of performing WB-MRI scans as opposed to CT-CAP in actual clinical practice. There are several recognized breast cancer histotypes that have different gene expression profiles and thus need to be managed differently. In some cases, these types of breast cancer benefit from targeted therapies [34]. Clinical practice in treating invasive lobular breast cancer (ILC) has recently revealed an important use for WB-MRI scans in breast cancer patients. In ILC, the second most common histological subtype, the spread of metastases differs from invasive ductal breast cancer (IDC), the most common histological subtype. ILC is

Figure 4: Pseudo-progression of bone metastases

45-year-old woman with metastatic breast cancer. WB-MRI examinations before and after third-line systemic treatment with capecitabine and vinorelbine.

(4A) On T1-weighted sagittal images a diffuse reduction in signal intensity is identified in the whole spine following chemotherapy. However, it is impossible to assess whether this is consistent with progressive disease, stable disease, or response to therapy. This finding can sometimes be observed when bone metastases respond to cytotoxic chemotherapy. It is due to the increase in extracellular water in the bone marrow, which reduces signal intensity on T1-weighted images thus mimicking disease progression. Maximum intensity projection (MIP) in the high b-value (900 s/mm²) diffusion-weighted images reveal a decrease in signal intensity after therapy, related to decreased cellularity that is in fact consistent with response to therapy.

(4B) WB-tumor load segmentation undertaken on *syngo*.via Frontier[2] MR Total Tumor Load software (Siemens Healthcare; released research prototype). The MIP images in the high b-value (900 s/mm²) are overlaid with ADC value color classes using the thresholds indicated. The green voxels are values ≥1500 µm²/s (representing voxels that are 'highly likely' to be responding). The yellow voxels are set to lie between the 95th centile ADC value of the pre-treatment histogram (1390 µm²/s) and 1500 µm²/s thus representing voxels 'likely' to be responding. Red voxels represent mostly untreated and still active disease. A reduction in the volume of the active disease is measured (418 mL before therapy and 255 mL after therapy), with an overall increase in ADC values (946 µm²/s and 1742 µm²/s) on the corresponding relative frequency histograms. Note: the decreased extent and volume of red voxels are consistent with disease response (94% before therapy and 56% after therapy). The residual red regions on the post-therapy scan are likely to represent residual active disease with low ADC value, in the spine, pelvis, and limbs.

[2] *syngo*.via Frontier is for research only, not a medical device.

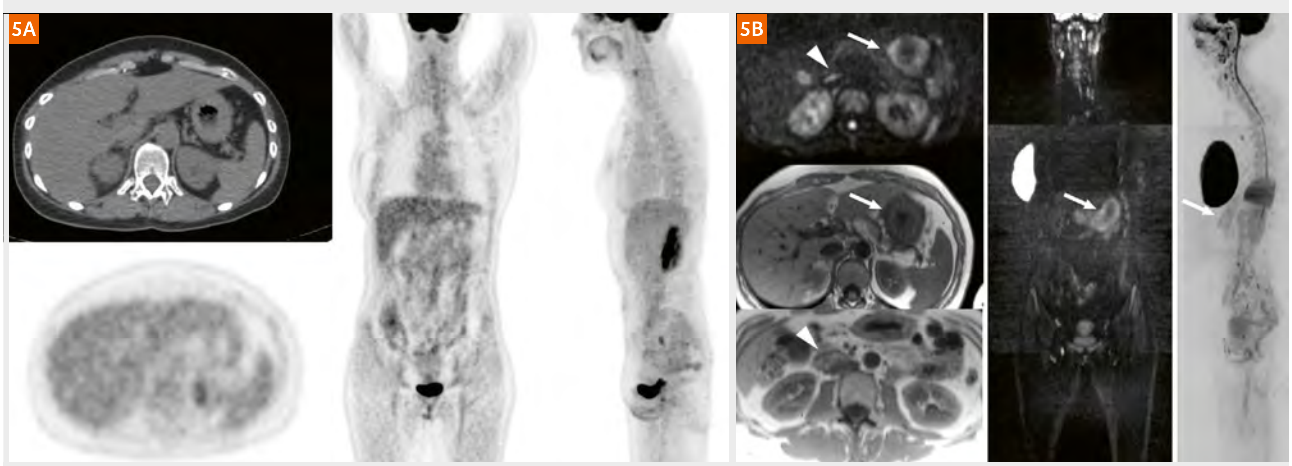
statistically more likely than IDC to spread to gastrointestinal (GI) organs, the peritoneum and retroperitoneum, the gynecological system, and the pleura, which are anatomical sites that are notoriously challenging to explore using PET and CT techniques [35]. Moreover, metastases from ILC are less FDG avid than other breast cancer histotypes [36] and therefore less visible on FDG-PET scans. This is associated with the reduced (to absent) E-cadherin membrane expression, which provides cell-to-cell adhesion and facilitates permeation through tissue planes. In ILC cancer cells this feature is responsible for the characteristic spread of the disease. This is known as "Indian file" neoplastic growth and involves neoplastic cells infiltrating the parenchyma around non-neoplastic ducts of GI organs or spreading to the peritoneum or retroperitoneum [37]. In our experience, thanks to the superior contrast resolution in WB-MRI compared to CT scans and the 'aspecific' nature of diffusion-weighted imaging (hyper-cellular lesions are always visible irrespective of the glucose metabolism), they are often able to depict the presence of neoplastic spread of disease into GI organs or the peritoneum/retroperitoneum earlier and more effectively than CT and FDG/PET-CT scans (see Fig. 5). Lastly, WB-MRI has demonstrated extraordinary results in detecting and staging breast cancer during pregnancy. In 40% of these cases, breast cancer presents at an advanced stage, which is 2.5 times the rate of the general breast cancer population. This means that accurate staging of bone, liver, and chest malignancies is crucial. However, imaging techniques involving ionizing radiation and the administration of intravenous contrast agents should be limited during pregnancy making WB-MRI the imaging technique of choice for systemic staging in pregnant women with breast cancer [38].

Lymphoma

FDG-PET/CT is the recommended imaging technique for the most common lymphomas, including DLBCL, follicular lymphoma, and Hodgkin lymphoma [39]. However, its diagnostic performance depends on glucose metabolism and patients with severely altered glucose metabolism may not be ideal candidates for this imaging technique. The aim of WB-MRI, on the other hand, is to investigate hypercellularity across the whole body. This technique is thus likely to be less histology-dependent than FDG-PET and therefore more suitable for patients with lymphomas with poor or no FDG avidity. In a prospective study of 140 patients, WB-MRI demonstrated better diagnostic performance than both FDG-PET/CT and CE-CT in patients with lymphoma subtypes with variable FDG avidity (the majority were MALT lymphomas) [40].

Another important use that is on the rise for WB-MRI is in young (< 35-year-old) lymphoma patients. Over the last decade, there have been promising increases in the survival rates for lymphomas, particularly among young patients. Nevertheless, NCCN guidelines still recommend repeated CT or PET/CT examinations every year, including in the clinical management of low stage lymphomas [41]. WB-MRI has shown diagnostic performance comparable

Figure 5: Gastric and peritoneal metastases from lobular breast cancer



A 44-year-old woman with lobular breast cancer post-surgery undergoes several FDG PET/CT scans due to suspected disease recurrence based on a persistent and continuous rise in CA 15.3. No suspicious findings are visible on FDG PET/CT **(5A)**. A WB-MRI performed 15 days later **(5B)** reveals a thickening of the gastric wall, with corresponding abnormally high signal intensity in the high b-value images b-900 DWI (white arrows), and suspicious solid tissue on the right anterior renal fascia (white arrowhead). A second WB-MRI examination performed two months later showed the same findings. Gastroscopy with multiple punch biopsies of the gastric wall has been performed, confirming the presence of malignant infiltration of lobular breast cancer cells.

to that of PET/CT both in staging and follow-up. Thus, following the introduction of a dose-saving criterion for the younger patients, WB-MRI could be considered as an alternative to PET/CT and CT in the young lymphoma patient subgroup.

Cancer screening and WB-MRI

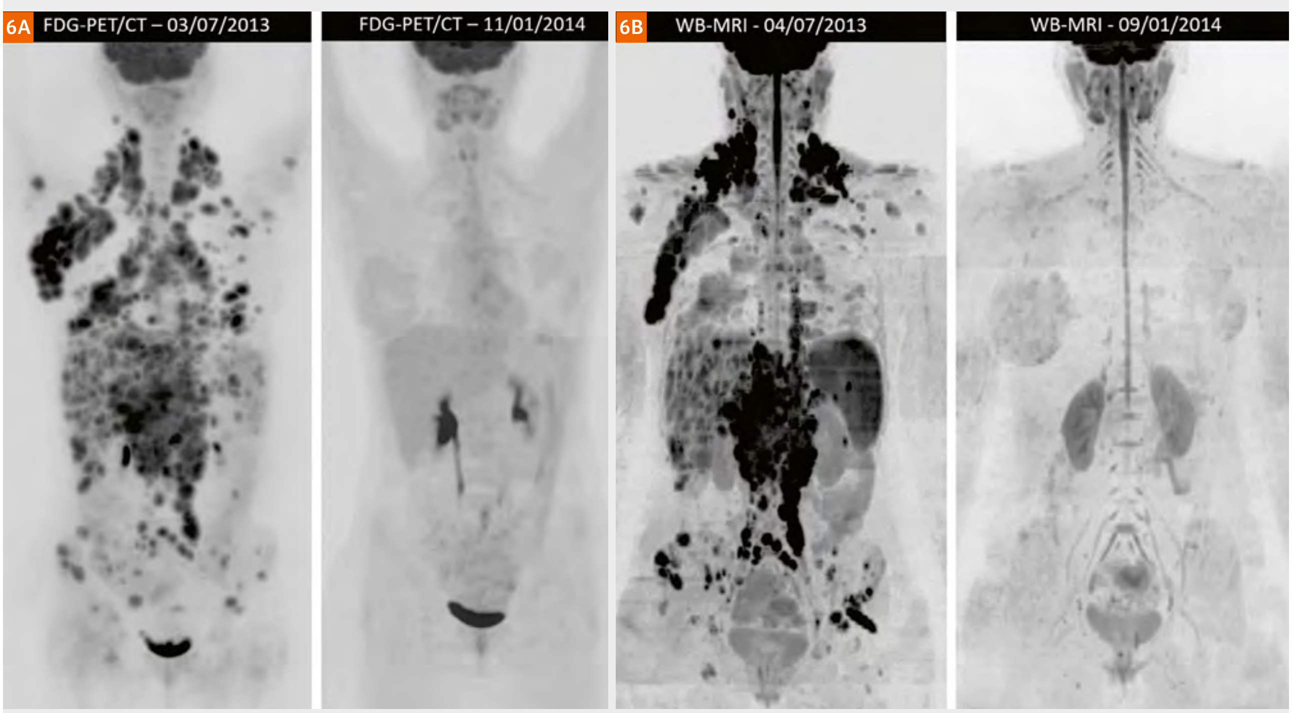
The aim of cancer screening is to detect cancer before symptoms appear. Several screening tests have proven to help detect cancer early and reduce the chance of dying from that disease [42]. Having saved thousands of lives, Pap tests, breast mammography for women, and FOBT for both women and men therefore became standard in many countries [43]. However, standard screening tests are not considered adequate for subjects genetically predisposed to cancer, such as those with Li-Fraumeni syndrome (LFS) and neurofibromatosis (NF). For patients with these conditions, advanced screening using WB-MRI is recommended. Moreover, there are high expectations of the benefits of advanced screening for the general population of asymptomatic subjects.

Li-Fraumeni syndrome

First described in 1969, Li-Fraumeni syndrome (LFS) is a highly penetrant cancer prone syndrome [44] caused by germline mutations of the TP53 tumor suppressor gene. Essentially, this rare, autosomal dominant, hereditary disorder, pre-disposes carriers to the development of a wide variety of cancer types. For this reason, it is also known as the sarcoma, breast, leukaemia, and adrenal gland (SBLA) syndrome. A recent meta-analysis validates the first statistically robust estimate of the clinical utility of WB-MRI in screening TP53 mutation carriers [45]. In addition, results from the UK SIGNIFY study on the cancer detection rate in this group of subjects argue for the adoption of at least a baseline whole body MRI scan [46]. Furthermore, the MD Anderson Cancer Center jointly with LFSA, the world largest LFS patients association, produced the first screening guidelines for the early detection of the syndrome. Guidelines developed by LEAD (Li-Fraumeni Syndrome Education and Early Detection) recommend WB-MRI for pediatric patients[1] between the age of 1 and

[1] Siemens Healthineers Disclaimer does not represent the opinion of the authors: MR scanning has not been established as safe for imaging fetuses and infants less than two years of age. The responsible physician must evaluate the benefits of the MR examination compared to those of other imaging procedures.

Figure 6: Assessment of post-treatment response



After multiple lines of systemic treatments, a 22-year-old woman with a relapse of non-Hodgkin lymphoma (Ann Arbor stage IVb) undergoes new chemotherapy combined with the ESHAP scheme and peripheral blood stem cell transplant. The patient undergoes FDG PET/CT and WB-MRI scans before treatment and six months post-treatment. Response assessment with PET/CT **(6A)** reveals a complete resolution of the abnormal FDG uptake across all body regions consistent with complete response (CR). Response assessment using WB-MRI at the same points in time **(6B)** is equally effective at showing CR.

10 years affected by sarcomas related to LFS, as well as for patients aged 10 or above, suffering from sarcomas, brain or adrenocortical tumors [47].

Lastly, according to a recent National Comprehensive Cancer Network (NCCN) recommendation, annual screening of LFS patients including WB-MRI should be a reference standard [48].

Neurofibromatosis

Neurofibromatosis is a genetic disorder causing tumors to form on nerve tissue. These tumors can develop anywhere across nervous system, including the brain, spinal cord, and nerves. Neurofibromatosis is usually diagnosed in childhood or early adulthood. Identifying pre-malignant and malignant tumors is essential for the clinical management of patients with NF, yet achieving this goal has remained challenging because of the heterogeneity of neurofibromas. Diffusion-weighted imaging is a particularly attractive technique for children[1] as most pediatric malignancies are small round cell tumors with impeded water diffusion. Moreover, WB-MRI has proven its efficacy in detecting and staging the three main clinical manifestations of NF: neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and schwannomatosis (SWN).

The National Cancer Institute has already recommended the development of practical guidelines to introduce WB-MRI for the detection of malignant peripheral nerve sheath tumors (MPNST) [49]. About half of all MPNST are diagnosed in people with neurofibromatosis and the lifetime risk of patients with NF1 developing this rare malignancy is between 8 and 13%. Moreover, a study conducted by Cashen et al. [50] showed an overall survival rate of 84% among treated patients emphasizing the key role of advanced imaging in early diagnosis and treatment management. The Response Evaluation in Neurofibromatosis and Schwannomatosis International Collaboration (REiNS) is in the process of developing official recommendations for the use of WB-MRI in NF [51]. The Neuro Foundation, the largest NF patient foundation in the UK, already recommends MRI for investigating preliminary signs of neurofibromatosis across the whole body [52].

Asymptomatic subjects and screening

Although current paradigms and treatments for cancer have resulted in substantial progress, oncologic diseases frequently evade long-term monitoring and cure. Thus, early detection and diagnosis in asymptomatic patients, before the systemic spread of the primary neoplasm, are critical. Early detection of subclinical disease may enable more efficient and effective initiation of preventive measures and treatment interventions at the early rather than later stages of disease. Imaging findings may thus result in the identification of early, and potentially curable, disease. Moreover, the role of the radiologist is crucial in deciding whether an image feature is normal or whether it potentially needs further examination.

The implementation of advanced imaging techniques in large cohort studies is an approach that has increasingly been used in epidemiologic research. The Framingham Heart study [53], the Multi-Ethnic Study of Atherosclerosis [54], and the Rotterdam study [55] have already demonstrated the invaluable scientific contribution of such techniques. In addition, advanced imaging has also improved our understanding of complex disease processes, as well as our ability to identify novel imaging biomarkers as precursors for subsequent disease states. The largest study using WB-MRI in asymptomatic subjects is the currently ongoing German National Cohort, a multicentric population-based study on 30,000 asymptomatic subjects. The study aims to identify risk and protective factors for population-relevant diseases and to provide new information that can be translated into primary prevention measures [56].

Several other studies regarding the use of WB-MRI for cancer screening have appeared in recent years. The first, published in 2008 by Gladys Lo et al. [57], described the incidental findings in a population of 132 doctors at Hong Kong Sanatorium and Hospital, who volunteered to undergo a WB-MRI for cancer screening. Various other studies have also been published over the last decade. The largest of these included 666 asymptomatic subjects in which a 1.05-percent rate of malignant cancers was determined [58].

Similar preliminary observations were made by the Advanced Screening Centers (ASC Italy), a recently founded social enterprise, originating from a collaborative partnership between a group of entrepreneurs and long-term supporters of cancer research, the European Institute of Oncology of Milan, and a panel of international experts in oncological WB-MRI, devoted exclusively to performing WB-MRI for cancer screening in asymptomatic subjects. From January 2017, when it was opened, to October 2017, ASC performed WB-MRI for cancer screening on 394 asymptomatic subjects.

The scans showed no abnormalities in just 12 of these subjects, which is actually consistent with the abnormality rates reported in the scientific literature. At least one abnormality was reported per 382 subjects (97% of the total).

However, for almost 80 percent of these subjects, no further investigation was requested, while 75 subjects were referred for follow-up. Further examinations were only requested for 9 subjects, and in 4 of these (1%) the presence of malignant cancer was confirmed histologically and the subject was informed.

However, the introduction of WB-MRI for screening the general population of asymptomatic subjects is still a long way off. First, it has to be proven that advanced cancer screening using WB-MRI, as opposed to screening that targets the most common malignancies (as per current standard practice) is scientifically relevant. Second, the diagnostic performance of WB-MRI in many cancer histotypes is well known, but it still needs validation for use in different populations (such as asymptomatic subjects). Third, there are practical issues associated with the relatively high cost of the equipment as well as the examination itself that present obstacles for the widespread use of WB-MRI. Lastly, but equally important, as with every practice in medicine, interpreting WB-MRI scans is heavily dependent on the experience of the reader. There is still inadequate standardization of image interpretation and reporting, as well as a lack of proper understanding of the learning curve required to be able to read an image effectively. Research to examine these issues is ongoing.

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