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Whole-body Diffusion Weighted and Proton Imaging: A review of this emerging technology for monitoring metastatic cancer

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Introduction

Cancer is a potentially curable disease and the combined effects of early detection and adjuvant systemic therapy are likely the key elements that explain the observed reduction in cancer mortality over the last 20 years (1). Although our current paradigms and treatments for cancer have resulted in substantial progress, the disease frequently evades long term control and cure. It is imperative that we continue to search for new possibilities in detection, assessment of progression and monitoring of treatment of cancer. Thus, early detection and diagnosis before metastasis is critical (1,2). The development of skeletal or organ metastasis is often difficult to detect and usually not found until clinical symptoms present or is discovered during tumor staging with radiological imaging. In general, metastatic lesions usually present with clinical symptoms of pain and or abnormal serum results, such as, elevations of carcinoembryonic antigen (CEA—a protein that is typically increased with breast tumors or colon tumors), cancer antigen 15-3 (CA-15) or prostate specific antigen (PSA). If metastatic disease is present, the usual sites are in bones, liver, brain, and lung. For example, metastatic breast and prostate cancer usually prefers the axial skeleton (~90%), e.g., vertebrae, pelvis, ribs, femur, and skull, whereas, colon cancer prefers viscera, e.g., liver (3-5). The types of metastatic lesions that can arise within the bony structures are osteolytic (~75%; bone reabsorption—usually in the marrow), osteoblastic (~15%; bone formation—usually in the cortical or trabecular structure), or mixed (10%) (5,6).

Determination of metastatic disease is accomplished using radiological imaging, such as plain film X-ray, Tc99m bone scintigraphy, computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI) and the radiological characteristics of bony metastatic disease are detailed in Figure 1. Indeed, these radiological procedures are the cornerstone for the detection and staging of metastatic lesions, and, if possible, classifying the type of lesion as well as the extent and localization of metastatic sites (5). However, until

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recently, most sensitive radiological procedures were limited to only “regional” or “local” coverage and could not interrogate the full body. Tc99m bone scintigraphy is a true whole-body method, but usually exhibits lower specificity due an increased false-positive rate related to different disease processes, such as, trauma, degenerative changes, inflammation, or benign disease (4,5,7,8). In some cases, there is a need for additional radiological imaging for clarification of the findings (9). False negatives can occur when osteolytic lesions grow rapidly or have slow bone regeneration (4,5,10). In addition, for monitoring therapeutic response, Tc99m bone scans can be unreliable (6,11). To augment Tc99m bone scans, CT scans are used for metastatic screening(12). Computed tomography has a high sensitivity (~72-90%) for detecting metastatic lesions in the cortex of the bone and is sensitive to bone marrow changes from metastases that result from bone destruction which causes increased attenuation(13). However, CT does not give any “functional” information about the status of cells and movement of water within the tissue and is less sensitive in the early development phases of metastatic disease in bone marrow or in soft tissue other than the lung. CT can show some changes in the bony structure, but repeated CT scans, at the intervals needed to gauge early response to treatment, are associated with increased levels of radiation (approximately 15mSv per scan) (14-17). Positron emission tomography imaging is now clinical standard for staging and/or detecting metastasis with near whole body coverage and has moderate to high sensitivity and moderate specificity in tumors(18-21). When PET is combined with CT (PET/CT), the lower spatial resolution PET image is fused onto a CT image for anatomical localization. Moreover, a quantitative measure of glycolic activity in tumors can be obtained using a metric called Standardized Uptake Value (SUV) from PET data. SUV is defined as

$$SUV = \frac{Activity(\mu Ci/g)}{[injected\ dose(\mu Ci/g)/weight(kg)]} \quad (1)$$

where activity (the tissue activity obtained from the PET images), the injected dose ($\mu Ci / g$) of ^{18}F FDG, and weight of the patient are considered. In general, a normal SUV is low (~1) and any change above 2.5 is considered suspicious and requires correlation with clinical and other radiological findings (22). However, there are some practical limitations to PET/CT imaging; for example, repeat scans required to gauge treatment response can be logistically difficult and there is a substantial increase in radiation dose of approximately 22mSv. Finally, magnetic resonance imaging (MRI) is a very sensitive method for the *localized* detection of metastatic lesions in viscera and bone, using either T₂- or T₁-weighted images with fat-suppression and Short tau inversion recovery (STIR) methods (23-28). However, although sensitive, T₁ and T₂-weighted images do not provide “functional” information on the status of the lesion and until recently have been limited to localized regions of interest and it not clear if they can be used to monitor treatment response.

New paradigms for whole-body imaging using magnetic resonance imaging

As discussed above, prior radiological studies of metastatic lesions have been performed in using combinations of modalities such as, Tc99m bone scans, CT, PET/CT, and T₁- STIR and T₂-weighted MR examinations in locoregional areas or near whole-body imaging. In addition, if the threshold of uptake is not sufficient within the region of interest some bony metastatic lesions may go undetected on either bone scan or CT or if the scan is aimed at specific regions of the body, it may miss an area of interest(29-32) Some potential limitations of these radiological procedures include incomplete interrogation of the whole body and a lack of functional or metabolic information (3-5,33-35).

Some of these limitations may be overcome with recent developments in the field of MR technology, including gradient systems, RF coils, and “rolling bed” methods which allow

whole-body coverage using anatomical T₁-STIR or T₂-weighted imaging (see Figure 2). These improvements have been demonstrated during the last few years with encouraging results that demonstrate both oncological and non-oncological indications compared to more conventional imaging methods (17,28-32,36-44). Indeed, regions of metastatic lesions detected by STIR T₁ or T₂ are very sensitive; but they exhibit little functional or metabolic information. However, one could use diffusion weighted imaging (DWI), which provides physiological information that would complement routine T₁- and T₂-weighted imaging.

Diffusion weighted Imaging

Diffusion-weighted imaging provides important information about the movement and functional status of the microenvironment of water in tissue. Changes in diffusion of water within pathological tissue may occur before they are seen on standard MR imaging (45-49). In addition, these changes between normal and pathological tissue results in differences (increases or decreases) in the signal intensity of DWI. The reason for these signal intensity changes on DWI are not exactly known; however, there is evidence that these changes may be attributable to many factors, such as shifts of water from the extracellular space to the intracellular space, increased tortuosity of the diffusion pathways, restriction of the cellular membrane permeability, cellular density, and disruption of cellular membrane depolarization (50-54). Moreover, DWI also provides an important quantitative biophysical parameter, called the apparent diffusion coefficient (ADC) of water. The ADC is an indicator of the movement of water within the tissue. It gives an average value of the flow and the distance a water molecule has moved. A “decreased” ADC is interpreted as “reduced” (restricted) flow of water, whereas an “increased” ADC indicates no restricted water flow within the tissue. The ADC map will reflect these changes and potentially serve as a radiological biomarker of tissue response. These changes on the DWI are seen *before* they are seen on a T₁ or T₂-weighted image (46-49). In general, water movement can be restricted by compacted or proliferating cells. ADC is a marker of tumor density or cellularity, such that, a highly dense region will have low ADC and an area with low density will exhibit a high ADC. It has been demonstrated that there are differences in the ADC value between benign and malignant lesions (35,55-63) and vertebral metastatic lesions (64-68); or ischemic events (e.g., stroke) (45-48). These applications of DWI/ADC mapping have been primarily used for localized imaging of specific organs. In this paper, however, we will detail the novel application of using whole body DWI (WB-DWI) with ADC mapping for the detection of malignant lesions. To date, there are a few reports in the literature about using WB-DWI for the detection of metastatic lesions (42,67,69-75) and a paucity of systematic studies (74).

Whole-body Diffusion Weighted Imaging

As noted above, DWI provides a radiological biomarker for monitoring disease states via the ADC map. In general, ADC is a marker of tumor density or cellularity, such that a highly dense region will have a low ADC and an area with low density will exhibit a high ADC. However, it has been demonstrated that there are changes in the ADC parameters for different tissues, particularly in benign and malignant lesions. Moreover, suspicious areas detected by T₁ or T₂ have no functional or metabolic information (e.g., DWI/ADC). There are a few reports in the literature about the feasibility of using WB-DWI in different cancers (42,67,69-74). It is clear that by combining T₁- and T₂-weighted imaging with WB-DWI, early changes within the tumor and metastatic sites can be visualized and can provide important information about treatment response, which would enable individualized treatment regimens. Therefore, using these methods for the detection, classification, and monitoring of treatment are clearly attainable goals in the near future. Figure 3 demonstrates the use of axial WB-DWI/ADC mapping at 1.5T on a 64 y/o patient with known prostate cancer. The Tc99m bone scan demonstrates multiple areas of increased uptake in the calvarium, sternum, ribs, vertebra,

pelvis, and femur suggestive of metastatic sites. However, there are some false-positives (degenerative and inflammatory changes) noted in the left knee and left ankle (post fracture due to fall—dotted arrow). Whole-body DWI ($b=0$, 600 s/mm^2) demonstrated multiple metastatic sites and the corresponding ADC map values obtained from both normal tissue and suspected metastatic sites were consistent with altered pathological states. In addition, Figure 4 demonstrates WB-DWI at 3T on a normal female 35 y/o volunteer. We constructed full coronal T_2 WI and ADC maps for visualization of the soft tissue and bones. These examples demonstrate the potential of WB-DWI.

Technical Issues for whole-body imaging

Gradients and radio frequency coils

In order to be able to realize whole-body MR examination which is required to cover a large examination volume, special demands for the gradient systems and RF coils are required. A fast gradient slew rate as well as a high gradient amplitude are prerequisites for achieving short repetition and echo times (TR and TE), in order to allow fast imaging and shortest possible scan time(76). A typical high-performance gradient system is as follows; maximum gradient amplitudes in all spatial directions are around 40 mT/m with minimum rise times of $5.9 \mu\text{s}/(\text{mT/m})$ and maximum slew rate of 170 T/m/s. For RF systems, the RF coils are required to excite a large examination volume as homogeneously as possible. In terms of signal reception, the built-in body coil of the scanner with a signal reception over large examination regions can be used. However, this necessitates a high demand for the homogeneity of the signal reception and has limited attainable SNR. Alternatively, a series of dedicated RF surface coils, adapted to the respective examination region, can be placed over each body region to achieve complete head-to-coverage, as shown in Figure 5. With this setup, no time-consuming patient repositioning is needed and which significantly shortens the total examination time with increased SNR. Surface coils are further combined as phased-array coils to facilitate parallel imaging and achieve high spatial resolution. A typical state-of-the-art RF receiver system offers the connection of up to 76 array elements from multiple phased-array surface coils and simultaneous signal reception from up to 32 independent receiver channels(76).

Whole-body coverage typically requires scanning a number of (four to nine) regions of the body in multiple steps with so called multistation techniques to achieve an extended longitudinal FOV. The MR system automatically moves the patient table with the patient to discrete stations and images are acquired as soon as the table is stopped (77). To cover each station, either the body coil or dedicated surface coils for each body region are used for signal reception. Further, the images acquired from all stations are merged, either composed or reformatted, to generate composite whole-body images from head to toe. With the typical high-performance gradients and RF coil system as indicated above, a total scan range of approximately 205cm with head-to-toe coverage and large field-of-views (400-500 mm) can be achieved with parallel imaging sequences while maintaining high spatial resolution and a reasonable examination time.

Whole body coverage via built-in body coil or whole body surface coil design

As discussed above, to achieve whole-body coverage, the scan must be performed at multiple stations to achieve extensive longitudinal FOV coverage. Conventionally, when surface coils are used, the patient must be repositioned and the surface coils reconfigured at each station, all of which is significantly time consuming. Therefore, instead of using surface coils, several vendors, including Philips and General Electric, utilize the built-in body coil as both the excitation and receiver coil, with an automatic moving tabletop (later with an tabletop extension), to achieve whole-body coverage (30,73). However, this demands high homogeneity of the signal reception of the body coil over a large examination volume, and the

SNR and CNR are inferior to surface coils. Later, a rolling table platform mounted on the top of the original patient table, with an integrated phased-array surface coil, was introduced (AngioSURF and BodySURF, MR-Innovation, Essen, Germany) (78). The “patient holder” glides in between a “coil sandwich” comprised of the spine coil integrated into the patient table and the phased-array surface coil attached to the patient table in the bore. The use of the surface coil permits a higher spatial resolution while maintaining a sufficient SNR. Recently, Siemens introduced a whole-body surface coil design technology, the so-called TIM (Total Imaging Matrix). The TIM technology combines a seamlessly integrated coil element with independent RF channels that can be freely and flexibly combined to cover the whole body from head to toe like a matrix. Up to 76 coil elements from multiple phased-array surface coils can be connected to the scanner with simultaneous signal reception from up to 32 independent receiver channels, which allow large anatomical coverage (up to 205cm) and image acquisition, with no time lost due to patient repositioning and coil reconfiguration(79). As indicated, all major MR vendors recognize the clinical need, as well as the future potential of WB-MRI, and both hardware and software are being actively developed to further push the limit of this emerging technology.

Pulse sequences

The choice of which MR pulse sequence to use depends on the desired application and type of cancer. The choice of which MR pulse sequence to use depends on the desired application and type of cancer. Most WB-MR studies have been performed using fat suppressed (FS), T₁- and T₂-weighted sequences (T₁WI and T₂WI), with newer studies using WB-DWI. In addition, most T₁WI, T₂WI, and DWI sequences utilize parallel imaging sequences for reduced scanning time and reduction of artifacts (80,81). For example, typical T₂WI parameters are repetition time/echo time (TR/TE)=6640/84ms, NEX=1, field of view (FOV)=40×40cm², imaging matrix=256×256, slice thickness(ST)=4mm, bandwidth (BW)=250Hz and T₁WI are TR/TE=259/13ms, flip angle 180, NEX=4, FOV=40×40cm², imaging matrix=256×256, ST=4mm, BW=110Hz. The WB-DWI (spin echo, echo planar imaging (EPI)) sequences should have a least two different b values and a minimum TR (81,82). Typical WB-DWI parameters are TR/TE=3900/78, NEX=3, ST=4mm, 2mm gap, imaging matrix=128×128, BW=min of 1700 Hz and b = 0 -1000 s/mm². These parameters can be modified according to the organ of interest (42). The acquisition of different b-values allows for the creation of trace apparent ADC maps on a pixel-by-pixel basis for quantitative analysis according to the equation.

$$ADC = \sum_{i=1}^n \frac{\ln \left(\frac{S_i}{S_0} \right)}{b_i} \quad (1)$$

where b_i = the diffusion gradient values; (b=γ²G²δ²(Δ-δ/3), γ= gyromagnetic ratio, G=gradient strength, δ=diffusion gradient duration, Δ= time between diffusion gradient pulses, S₀ = 1st image (b=0), and S_i = ith image.

Diffusion weighted imaging with background body signal suppression (DWIBS)

A unique concept of whole-body DWI, called “diffusion-weighted whole-body imaging with background body signal suppression” (DWIBS) was first described by Takahara et al. (67) at 1.5T. DWIBS uses a free breathing approach during scanning with multiple thin axial slices and large signal averages (NEX). In addition, fat suppression is applied by either STIR or other robust methods. In essence, DWIBS exploits both intravoxel incoherent motion (IVDM) and

intravoxel coherent motion which uses free breathing during scanning to visualize the organ of interest(45,70,75,83). Notably, for accurate background suppression, both large b values (>500) and NEX, thus longer acquisition times are needed (67,69,70,73,75). Figure 6 shows some typical results from various WB-DWIBS reports.

Field Strength

The magnetic field strength most widely used in WB-MR and WB-DWI is 1.5 Telsa. Research studies using 3T WB-MRI have been reported from others(69) and by our group (84). However, there are some advantages and challenges when moving pulse sequences to higher magnetic field strengths. The advantages include increased signal-to-noise ratio (SNR) and spatial resolution, but the disadvantages include the following: (1) susceptibility artifacts (variation of local magnetic field at the boundaries between different types of tissues); (2) B₁ inhomogeneities due to increased wavelengths and variations; (3) nonuniform fat suppression for large fields of view; (4) increased eddy currents; and (5) large chemical shift artifacts. As expected, Murtz, et al. reported increased SNR and CNR at 3T versus 1.5T and increased motion artifacts due to increased scan times(69). They reported longer imaging times than those at 1.5T presumably due to increased specific absorption rate (SAR) and increased TR(69).

Summary and Protocols

Although the techniques for WB-MR/DWI are not standardized and still investigational, several principles from the above discussion may be applied to the development of a clinical WB-MR/DWI protocol. In general, all WB protocols will need to acquire images from the head to the mid-femur, covering approximately 200cm with a large FOV (400-500 mm), and using either T₁ WI and T₂ WI for anatomical morphology. Diffusion-weighted sequences should have at least two different b-values for creation of ADC maps, as discussed above. In addition, other MR sequences, such as dynamic contrast imaging (DCE) or magnetic resonance spectroscopy (MRS), can be incorporated in the WB-MR scan and is an area of active research.

Current Clinical Indications for Whole-body Imaging

The indications for WB-MR/DWI are listed in Table 1 and discussed below.

Detection of metastatic disease

Treatment planning for patients depends on staging of the primary tumor. Thus, the search of metastatic disease in patients is important for long-term prognosis. The power of WB-MR for the detection of metastasis has been demonstrated in a handful of recent reports using T₁-STIR or T₂-weighted imaging sequences(17,28-32,37,40,85). For example, Lauenstein et al. (78) investigated the use of whole-body imaging using various T₁ and T₂ sequences compared to bone scans. These investigators found a sensitivity of 88% and a specificity of 88%. Similar results were found by Antoch et al., (86), where the authors reported a diagnostic accuracy of 93% for whole-body MRI, compared to a diagnostic accuracy of 94% for PET-CT for assessment of the M stage in the Tumor Nodal Metastasis (TNM) staging criteria (41). Moreover, others have reported high sensitivities using WB-MR, ranging from 71%-95% (17,28,29,31,^{32,36,39}-44,85,87,88). The ability to obtain high spatial resolution and “functional” images of the whole body for assessment of pathological disorders is of major importance to the oncologist, radiologist, and more importantly, the patient. In a recent editorial in the *Journal of the American Medical Association (JAMA)*, Blomqvist and Torkzad (16) eloquently stated, “*the planning treatment for metastatic patients relies heavily on imaging information to establish tumor stage at presentation and to assess tumor response to treatment. ... Because different imaging modalities have different inherent soft tissue contrast properties, use of several imaging modalities in a stepwise approach is common.*” The authors further

elaborated that “...one of the most important, if not the only, indication for whole-body imaging is the search for metastases. Somewhat surprisingly, results of whole body MRI reported by Antoch et al. (⁸⁶) were comparable with PET/CT.” Moreover, the use of WB-MRI represents a future setting where the patient will be imaged using a single modality and, within minutes to hours, a complete diagnosis and treatment plan could be available(16). Therefore, this “future setting” is becoming a reality; few radiological procedures can achieve either partial or whole-body imaging in one setting. For example, radiological procedures that can obtain full or partial whole-body coverage are bone scintigraphy, PET/CT, and CT alone, and, more recently, WB-MRI. The introduction of whole-body MRI allows for rapid imaging of the whole body with high spatial resolution and has the potential to evaluate skeletal and visceral metastatic regions throughout the body.

Tumor staging and screening of high risk patients (T3 or greater)

Tumor staging and screening is very important in determining the type of therapeutic options that are available for a patient. These treatment options range from neoadjuvant, surgical, adjunctive, and/or palliative; therefore, methods that can define and guide these decisions are crucial. Tumor staging is defined by size and nodal involvement, and metastasis, if present, and is recorded on the TNM scale. The T (size) and N (nodal) stage is defined by palpation, histology, or through radiological imaging. Lymph nodes have characteristic appearances on T₁ WI and T₂ WI MR Images, and metastatic lymph nodes usually present with a low ADC map value. Finally, the M stage is determined using radiological imaging, as described above (e.g., bone scintigraphy, PET/CT) and this is the stage at which the use of WB-MR/DWI will be most advantageous, and can be extended to investigate high-risk patients for additional cancers or other diseases. This is possible due to the increased soft tissue resolution and distinct radiological biomarkers (ADC mapping) compared to other imaging modalities with near whole-body coverage. Indeed, a recent study demonstrated the ability of WB-DWI to accurately classify lesions according to the TMN staging system. Ohno, et al. in a prospective study of non small cell lung cancer (NSCLC) patients (n=203), compared WB-MR with and without WB-DWI to PET/CT in determining the M stage of the tumor (74). They reported that WB-DWI compared favorably with PET/CT. WB-DWI alone had a sensitivity/specificity of 0.57 and 0.79, and 0.70/0.87 when combined with WB-MR, whereas, PET/CT demonstrated a sensitivity/specificity of 0.62/0.94. Indeed, in another small study of 29 patients (solid and liquid tumors), similar results were noted, and these results are shown in Figure 7 (73). In addition, Komori et al. reported that 25/27(92.6%) of the malignant lesions were detected visually with WB-DWIBS imaging, whereas, 22/27 malignant tumors (81.5%) were seen with PET/CT imaging(70). However, surprisingly, they found no difference between benign and malignant lesion ADC values, contrary to several other reports (56,58,59,72,89-91). This difference between benign and malignant lesion ADC values may be related to the difference in DWI sequences, sample sizes, and other technical factors. Nonetheless, the combination of WB-DWI/ADC mapping and PET/CT radiological parameters will be very useful for screening of cancer patients. Indeed, a review of the literature demonstrates better sensitivity and specificity for WB-MR and WB-DWI compared to bone scintigraphy and equal sensitivity and specificity for PET/CT imaging of tumors which is summarized in Table 2.

Monitoring treatment response

The advantage of monitoring treatment response is a critical need. Our limited ability to predict early on which patients will benefit from therapy (overall or individual regimens) makes it difficult to select the treatment most likely to help, while minimizing exposure to potentially ineffective and toxic regimens. The proposed WB-MR/DWI technology will advance clinical radiological diagnostic tools for the detection and classification of treatment response, as well as distant metastasis, with high specificity and sensitivity. Currently, there is a lack of

standardization of functional MRI parameters to monitor treatment. However, through the use of WB-DWI, we believe that radiological biomarkers can be developed for monitoring metastatic disease. The concept of a WB-MR/DWI imaging modality for accurate detection and monitoring of treatment is needed, ensuring that accurate treatment planning can be defined.

Pediatric Whole-body imaging

One area of real advancement for WB-MRI will be in imaging children. Current whole-body methods are x-ray, bone scans, CT, and PET. These methods all involve ionizing radiation, which may be detrimental to children. However, WB-MRI (T_1 OR T_2 WI) or WB-DWI could be utilized to minimize radiation dose and increase soft tissue delineation. Recent reports have shown the potential of WB-MRI in children (92). For example, Daldrup-Link et al compared WB-MRI to standard radiological imaging methods (e.g, PET and bone scintigraphy) for the evaluation of potential metastatic disease in children and reported comparable sensitivities between PET and WB-MRI (90% vs 82%) which were higher than bone scans (71%) (39). Other groups have shown similar results using WB-MRI (93-95). The use of WB-DWI in children has not been explored and is actively being pursued. However, there are some limitations in the use of WB-MR in children, such as sedation and normal bone and marrow changes that could mimic disease. But, in the future, the potential of WB-MRI and WB-DWI to become excellent screening tools in children is high.

Conclusion

The ability to use WB-MR and WB-DWI/ADC mapping at both 1.5T and 3T holds great promise, and has shown utility in the identification and, potentially, the characterization (WB-DWI/ADC) of both bony and visceral metastasis. However, more optimization is required for WB-DWI to become a routine screening tool, and large-scale studies are needed to fully gauge its impact in oncology. However, WB-MRI and WB-DWI will be increasingly used in pediatric applications and other systemic disorders as a non-invasive method to detect and monitor patients. The utility of this new imaging method is just now being realized and will increase in the near future.

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Figure 1.

Figure 2.

Figure 3.

Figure 4.

Figure 5.

Figure 6.

Figure 7.

Table 1

Indications for whole-body MR and diffusion weighted imaging

1. Detection of metastatic disease
2. Screening of high risk patients (T3 or greater)
3. Monitoring treatment response
4. Pediatric screening

Table 2

Review of whole-body MR and DWI literature

Author	Year	Patients	Screening Method	Sensitivity	Specificity	Whole Body MR	Sensitivity	Specificity
Eustace(29)	1997	25	Bone Scan	72	98	STIR	97	100
Daldrup-Link [*] (39)	2001	39	Bone Scan/PET	71/90	NR	T ₁ /T ₂	82	NR
Lauenstein(78)	2002	26	Bone Scan	NR	NR	STIR	88	88
Antoch(86)	2003	98	PET/CT	93	95	T ₁ /T ₂	90	95
Lauenstein(85)	2004	51	Bone Scan/CT/MR	NR	NR	STIR	100	100
Stienborn(37)	2004	18	Bone Scan	85	NR	STIR	91	NR
Engelhard (32)	2004	22	Bone Scan	83	80	STIR	92	90
Ohno ^{**} (74)	2008	203	PET/CT	63	95	T ₁ /T ₂	56	92
Author						WB-DWI		
Komori(70)	2007	16	PET/CT	82	NR	WB-DWI	93	NR
Barcelo(96)	2007	24	PET/CT	71	80	WB-DWI	100	90
Ohno ^{**} (74)	2008	203	PET/CT	63	95	WB-DWI	67	88
Steeco(43)	2008	29	PET/CT	NR	NR	WB-DWI	89	98

DWI=diffusion weighted imaging; STIR-short tau inversion recovery;

PET/CT=positron emission tomography/computed tomography

NR=not reported; no data reported on sensitivity/specificity

^{*} =children; no true negatives recorded

^{**} =Non small cell lung cancer