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Original Research Article

Detectability of Spinal Metastasis in Known Malignancies: A Comparative Study between 1Tesla MRI and F18 Sodium Fluoride PET- CT

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Abstract

Background: The development of spinal metastasis is a seminal event in the progression of common malignancies and their early detection plays a critical role in deciding the treatment protocol and assessing prognosis. There is no consensus in the literature regarding the preferred imaging modality. The study was undertaken with the objective to compare the efficacy of Magnetic Resonance Imaging (MRI) as against 18F Sodium Fluoride (Positron Emission Tomography- Computed Tomography) PET-CT in detection of spinal metastatic lesions.

Methods: A total of 32 patients with biopsy-proven malignancy and clinical and laboratory suspicion of metastases were taken up for this study. All patients underwent spinal MRI and whole body 18F Sodium Fluoride PET-CT scan using standard techniques. The MR images and 18-F Sodium Fluoride PET-CT scans was read independently by an experienced Radiologist and an experienced Nuclear Physician respectively, who were blind to the results of the other study.

Results: A total of 1056 vertebrae of 32 patients were examined by both PET CT and MRI. On MRI 148 total lesions were detected whereas on PET CT scan 199 lesions were found. Analyzing the data by using Mc Nemar's chi square statistics assuming 18F NaF as case and MRI as control, it is found that p value is 0.000. That means statistically 'highly significant difference' were seen in detection of vertebral metastasis by PET CT than MRI as PET CT picked up more number of lesions.

Conclusion: Combined 18F NaF PET CT scan showed superior to MRI in the detection of spinal metastatic lesions. Consequently18F NaF PET CT has a better impact on clinical management compared to MRI, which will help in staging and reducing the morbidity associated with advanced malignancy.

Keywords: 18F Sodium Fluoride PET-CT (18F NaF PET-CT), Magnetic Resonance Imaging (MRI), Spinal Metastasis.

Introduction

Skeletal metastasis is the third most common location of metastasis after liver & lungs[1]. Skeletal metastasis is most commonly seen in carcinomas of the breast (47-85%), prostrate (54- 85%), lung (32%), kidney (33-40%), and thyroid (28-60%) [2].

Most bone metastases are haematogenous in origin, although contiguous and intra-spinal spread may occur [3].

Spine is the most common site for skeletal metastases because of the abundant vascularity and red bone marrow [4]. Most of the metastases are located in the lumbar spine, less frequently in the thoracic, and rarely in the cervical spine. The metastasis are osteolytic (60%), osteosclerotic (20%) or mixed pattern (20%) [5].

Magnetic Resonance Imaging (MRI) has emerged as a sensitive method of detecting intramedullary metastases in vertebral bodies, which has large marrow content [6]. Despite this the use of MRI in metastases detection has been limited due to cost, long examination times and convenience. With the advent of faster sequences, there has been a renewed interest in MRI as a screening tool for early spinal metastases.

Various MR sequences have been used to evaluate spinal tumors [6]. Most investigators advocate a combination of T1-weighted spin-echo and T2-Weighted spin-echo sequences [7]. In recent years, faster acquisitions of STIR images have gained popularity to evaluate the bone marrow [8].

Because bone marrow (including hematopoietic or “red marrow”) contains a high percentage of fat, it is reliably imaged with T1-weighted spin-echo techniques because the marrow fat provides a nearly homogenous, high intensity signal. Marrow infiltration by tumor replaces normal marrow fat, which shows up as areas of altered signal on various MRI sequences. Tumor, because of its long T1, is easily detected as a low-intensity defect in the marrow. STIR suppresses the signal from fat and shows the normal vertebral bodies as low intensity. Tumor has high intensity and is easily detected against the low-intensity surroundings [9].

Bone scan is presently the method of choice in the evaluation of skeletal metastases because of its accessibility, reasonable cost & ability to show the entire skeletal system [10]. When a tumor invades bone, it produces two changes, which are seen to varying degrees with all types of metastases. The first is bone destruction and the second is reactive bone formation or repair. It is in the repair stage where radioisotopes are significant. In new bone formation, hydroxyapatite crystals are deposited in the osteoid matrix by the osteoblasts. If sufficient radioactive atoms are available for incorporation into the hydroxyapatite crystals, the new bone can be visualized by the scintillation scanning. The bone scan is primarily an index of osteoblastic activity [11].

New imaging technologies have been developed for the detection of advanced cancer. PET-CT would be the ideal imaging modality as it allows for whole-body imaging and for the combination of physiologic and anatomic evaluation of disease. With PET-CT, the PET examination captures the physiologic aspects of disease that can be shown by the type of radiopharmaceutical administered, and the CT examination provides attenuation correction and activity localization, and allows for morphologic assessment of disease.

Sodium Fluoride (NaF) is excellent bone seeking agent.[12]. Mechanism of uptake is based on ion exchange which is similar to the 99m Technetium –Methyl diphosphonate (99mTc-MDP). 18F-NaF demonstrated promising results when used with PET-CT.

In 2012, the Medical Imaging & Technology Alliance conference convened a group of experts and stakeholders to discuss possible research endpoints that might be used to demonstrate that new PET procedures and radiopharmaceuticals lead to improved outcomes. The attendees agreed that intermediate endpoints should be used to generate data to support coverage decisions by the Centers for Medicare and Medicaid Services (CMS) [13].

18F-NaF was first approved by the US Food and Drug Administration (FDA) in

1972. We have seen resurgent interest in it over the past decade, in part due to the increasing availability of PET-CT scanners across the country. The use of PET-CT in bone imaging presents several technical advantages over traditional bone scanning, but costs remain a significant concern.

18F-NaF is rapidly cleared from the blood, which allows for a shorter time interval between injection and imaging.[14]. This in turn allows for a much shorter overall imaging time compared with conventional 99mTc-based bone scans, which makes the procedure more convenient for patients. Radiation exposure from the radiopharmaceutical alone is similar to that from 99mTc-based bone scan agents[15]. However, the total radiation dose is greater than that from traditional bone scanning because of the CT portion of the PET-CT examination. The National Oncologic PET Registry (NOPR) began accrual of 18F-NaF PET/CT data in January 2011. NOPR was created in consultation with the Centers for Medicare and Medicaid Services (CMS) to evaluate PET's impact on intended management, using prospective questionnaire data before and after PET studies.

This study was conducted to recognize best imaging modality among 18-F NaF PET-CT and MRI scan to detect vertebral metastasis which will help in staging and reducing the morbidity associated with advanced malignancy.

Materials and Methods

This prospective study was done in the Department of Radio diagnosis in collaboration with Department of nuclear medicine, in one of the service hospitals in the period between Jan 2014 and August 2015 with a study population of 32 patients who were suffering from biopsy-proven malignancy. All patients underwent MRI of the spine and whole-body 18F NaF PET-CT scan in the same day. Pregnant patient, patients having metal implant/cardiac pace maker, having severe claustrophobia and unwilling for the study were excluded.

MRI Scanning: MRI studies were performed at 1Tesla (Simens magnetom) along sagittal and axial planes. MRI sequences included T1, T2 weighted turbo-spin-echo images and Short Tau Inversion Recovery (STIR). Contrast was not given and so no special precaution or preparation was required.

18F NaF PET/CT Scanning: Combined PET-CT scan was performed using Discovery 690 Lyso (Lutetium-Yttrium-Orthosilicate) with a 64 multi-slice CT scanner F-18 NaF-PET-CT scan was performed according to SNM (Society of Nuclear Medicine) guideline [16]. Patients was hydrated by giving plenty (224 mL) of water within 1 hour prior to the examination, and another two or more glasses of water after administration of 18F NaF. Patients were asked to evacuate their bladder immediately before imaging. There was no need to fast and patients were instructed to take all their usual medications. Patient was in an elevated position when the axial skeleton was scanned.

185-370 MBq (Millibecquerel) [5-10 mCi (millicurie)] 18F-NaF was injected intravenously by intravenous catheter.

CT imaging was done first and then PET emission imaging was carried out after 30-45 minutes of administration of the radiopharmaceutical in patients with normal renal function. Images was acquired in 2D or 3D mode.

Image interpretation: The MR images and 18-F NaF PET-CT scans was read independently by an experienced Radiologist and an experienced Nuclear Physician respectively, who were blind to the results of the other study.

18-F NaF PET-CT scan were read positive using the accepted subjective criteria such as the intensity of uptake, focality, number, location and pattern of distribution. An area

is considered abnormal when its uptake of tracer is increased compared to adjacent structures.

Standardized Uptake Value (SUV) is defined as the tissue concentration of tracer as measured by a PET scanner divided by whole body concentration of injected radio activity. SUV values can be different between the normal bones and bones with tumour or metabolic bone disease. SUV can be used to quantify NaF-18 PET-CT studies. If the SUV values of the normal skeleton are known, they can be used in the characterization of bone lesions and in the assessment of treatment response to bone diseases. MR images were read positive if a well-defined focus of low signal intensity is seen on T1-weighted images and high signal Intensity on STIR or T2-weighted images.

The spine was divided into cervical, upper dorsal (T1-4), middle dorsal (T5-8), lower dorsal (T9-12), lumbar(L1-5), sacral and coccyx regions. In each region the reading was scored as positive or negative for metastatic involvement.

Subsequently images were reread with PET- CT scan and MRI side by side to ensure that concordant lesions are truly concordant. Corresponding Magnetic Resonance Imaging and PET CT scan interpretations were considered concordant in a region if both readings were positive or negative for metastases and discordant if the readings differed. Confirmation of findings was sought in discordant cases using correlative modalities. Subsequent progression on repeat bone scans and MRI was considered confirmatory. The presumption made was that all focal lesions on PET-CT or MR images were metastases unless proved otherwise.

Calculation of the outcome was done with the help of Microsoft Excel 2007.

Results

The current study included 32 histopathologically proven cancer patients. There were 18 male and 14 female patients with a mean age of 55.65 years. The case distribution of the study population is given in Table 1.

Table 1: Age distribution of the study population

Sl. No.	Age group	No. of cases	Percentage
1	21-30	2	6.25
2	31-40	1	3.12
3	41-50	6	18.75
4	51-60	14	43.75
5	61-70	6	18.75
6	71-80	3	9.37
	Total	32	100

Table 2: Histopathological case distribution of the study population

Sl. no	Primary	No of Cases	Percentage
1	Ca Breast	12	37.5
2	Ca Prostate	6	18.75
3	Ca Lungs	6	18.75
4	Ca bladder	1	3.12
5	RCC	1	3.12
6	Rectal Ca	2	6.25
7	Multiple myeloma	2	6.25
8	Ca ovary	1	3.12
9	HCC	1	3.12
	Total	32	100

Metastatic lesion detection: A total of 1056 vertebrae of 32 patients were examined. In the PET CT scan 199 vertebral lesions were detected and most common region involved is Lumber vertebra. PET_CT scan readings as per region are given in Table 3

Table 3: PET CT scan readings as per vertebral region

Sl No.	Region	No of lesions	Percentage
1	Cervical	43	21.61
2	Upper Dorsal	39	19.60
3	Lower Dorsal	48	24.12
4	Lumber Vertebra	54	27.14
5	Sacral	15	7.54
	Total	199	100.00

In MRI total 148 lesions were picked up and most common region involved is lower dorsal vertebra. MRI readings as per region are given in Table 4.

Table 4: MRI readings as per vertebral region

Sl No.	Region	No of lesions	Percentage
1	Cervical	19	12.84
2	Upper Dorsal	32	21.62
3	Lower Dorsal	48	32.43
4	Lumber Vertebra	39	26.35
5	Sacral	10	6.76
	Total	148	100

Comparison of detectibility of lesions in MRI and PET-CT scan:
As this study is comparison between the two diagnostic tests, the detectibility of the lesions are made by calculating Mc Nemar's chi^2 test assuming PET CT as case and MRI as control. Comparison of regions read positive and negative is given as table 5.

Table 5: Comparison of regions read positive and negative by PET CT and MRI.

	MRI SCAN (Control)		
PET CT(Case)	**POSITIVE**	**NEGATIVE**	**TOTAL**
Positive	141	58	199
Negative	07	850	857
Total	148	908	1056

Odds ratio 8.286 with 95% confidence interval extending from 3.776 to 21.518
Among the 1056 vertebrae, 141 lesions were read positive on both PET and MRI. 850 vertebrae were read negative on both. 58 lesions were read positive on PET CT scan and negative on MRI and 7 lesions only were read positive on MRI and negative on PET CT scan [Table 6].

Table 6: PET * MRI Cross tabulation

Count		MRI		Total
		1	2	
PET	1	141	58	199
	2	7	850	857
Total		148	908	1056

In Mc Nemar's chi^2 test the p value calculated is 0.000 which is significant and 95% confidence does not encompasses zero that means there is statistically 'highly significant difference' seen in detection of vertebral metastasis by PET- CT than MRI, as PET -CT picked up more number of lesions [Table 7].

Table 7: Chi-Square Test

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	657.372(b)	1	0.000		
Continuity Correction(a)	651.573	1	0.000		
Likelihood Ratio	534.442	1	0.000		
Fisher's Exact Test				0.000	0.000
Linear-by-Linear Association	656.749	1	0.000		
N of Valid Cases	1056				

Discussion

Spinal metastasis is a commonly encountered problem in oncology practice. The primary challenge involved is early detection of the metastatic lesions and the distribution of the lesions as it has got a tremendous impact in selecting the treatment protocol and assessing prognosis. There is no consensus regarding the use of the imaging modality for the early detection of spinal metastasis as studies are limited. Different institutions advocate different protocol for imaging depending on the availability of machines, cost and expertise.

The two most commonly used imaging modality in detection of spinal metastasis are MRI and bone scintigraphy.

MRI is highly sensitive to skeletal metastasis because of its ability to demonstrate abnormalities in bone marrow. Bone marrow (hematopoietic or red marrow) contains a high percentage of fat and readily imaged with T1 weighted spin echo technique. Tumour due to its long T1, easily detected as a low intensity defect in the marrow. On fat suppressed T1 weighted images metastasis demonstrate mixed to high signal intensities whereas non neoplastic lesion show low signal intensity. Radiation therapy results in replacement of marrow by yellow marrow & consequently shows uniform hyper intense signal. On T2 weighted images metastatic lesions are brighter than bone marrow due to their high water content. STIR suppresses the signal from fat and shows the normal vertebral bodies as low intensities. Tumour has high intensity and is easily detected against the low intensity surroundings.

Bone scanning is based on the uptake of a nuclide or tracer by the crystal lattice of bone and not upon uptake by cancer cells. The degree of nuclide uptake by a particular bone is related to bone blood flow [17]. Positron Emission Tomography (PET) is a nuclear medicine imaging system used to create a three dimensional image of the emitted positron within the human body. One of the major concerns about PET imaging is its relatively low spatial resolution. PET can provide a functional or metabolic assessment of normal tissues or neoplasms by imaging the concentration and distribution of specific chemical compound labelled by positron-emitting radionuclides in the body [18]. The common labelling radionuclides are Carbon-11, Fluorine-18, Oxygen-15, and Nitrogen-13. 18F labelled FDG (18F-fluoro-deoxyglucose) is the most widely used radiotracer in clinical PET application and the only oncologic PET tracer approved by FDA for routine clinical use. More than 90% of PET examinations is based on 18F-FDG which can be produced in on-site cyclotrons [19].

Sodium fluoride F 18 decays by positron emission. The mechanism of skeletal uptake of 18F-NaF is based on ion exchange, which is similar to that of 99mTc-MDP. 18F-Fluoride is a highly sensitive bone-seeking PET tracer used for detection of skeletal abnormalities. The

uptake mechanism of 18F-Fluoride resembles that of 99mTc-MDP with better pharmacokinetic characteristics including faster blood clearance and two-fold higher uptake in bone. Uptake of 18F -Fluoride reflects blood flow and bone remodelling.

The use of novel hybrid PET-CT systems, has significantly improved the specificity of 18F- Fluoride imaging as the CT component of the study allows morphologic characterization of the functional lesion and more accurate differentiation between benign lesions and metastases.

18F is a diagnostic molecular imaging agent used for identification of new bone formation.

Our study was undertaken with the aim to recognize best imaging modality among 18-F NaF PET-CT and MRI scan to detect vertebral metastasis which will help in staging and reducing the morbidity associated with advanced malignancy.

In our study, 32 patients (18 males & 14 females) with a proven malignancy and clinical as well as laboratorial suspicion of vertebral metastases were included. The age was between 26 to 75 years. The commonest age group of patients with vertebral metastases was 51-60 years with mean age 55.65 years.

The commonest primary tumor in our study was carcinoma breast with 12 cases (37.5%). The second commonest tumor in our study was carcinoma prostrate with 6 cases (18.75%). Carcinoma lung also have similar cases.

We have examined total 1056 vertebrae of 32 patients, PET CT scan was positive in 199 regions (18.82%). The commonest region positive for metastatic involvement, in PET scan was lumbar region with 33 (55%) positive lesions and the second commonest was lower dorsal region with 48 positive lesions (24.12 %).

Out of the total 1056 regions, MRI was positive in 148 regions (14%), here most common regions involved is lower dorsal (32%). The lumbar regions were the second commonest with 39 (26.35%) positive lesions in our study.

Among the 1056 vertebrae, 141 lesions were read positive on both PET and MRI. 851 vertebrae were read negative on both. 58 lesions were read positive on PET CT scan and negative on MRI and 7 lesions only were read positive on MRI and negative on bone scan.

The similar detectability of metastasis to lumbar spine by both modalities is shown in Fig 1.

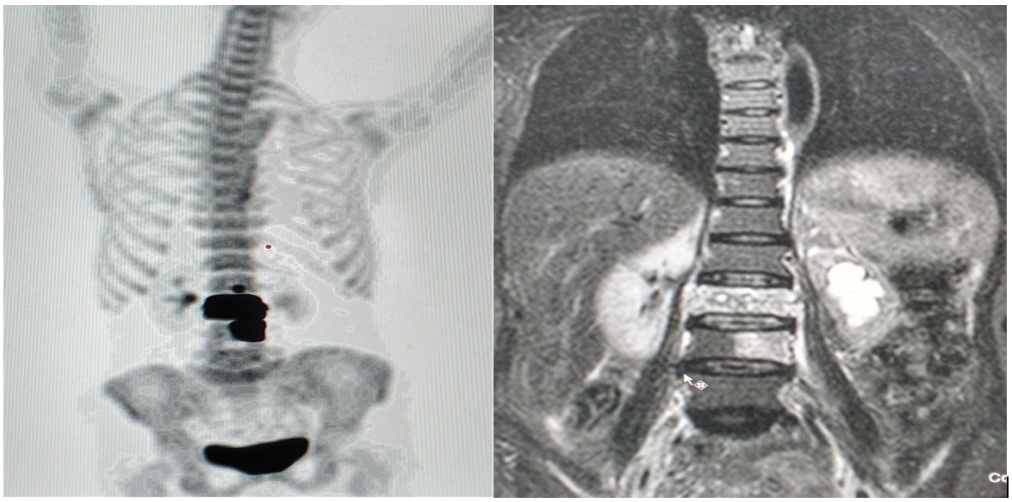

Figure 1: 62 year old patient with CA prostate. PET scan showing increased uptake in L1, L2 and L3 vertebra. MRI STIR sequence of the same patient shows a hyper intensity in the L2 and L3 vertebra. Note the left sided hydronephrosis

The increased sensitivity of picking up of lesions by PET scan is shown in **fig 2 & 3.**

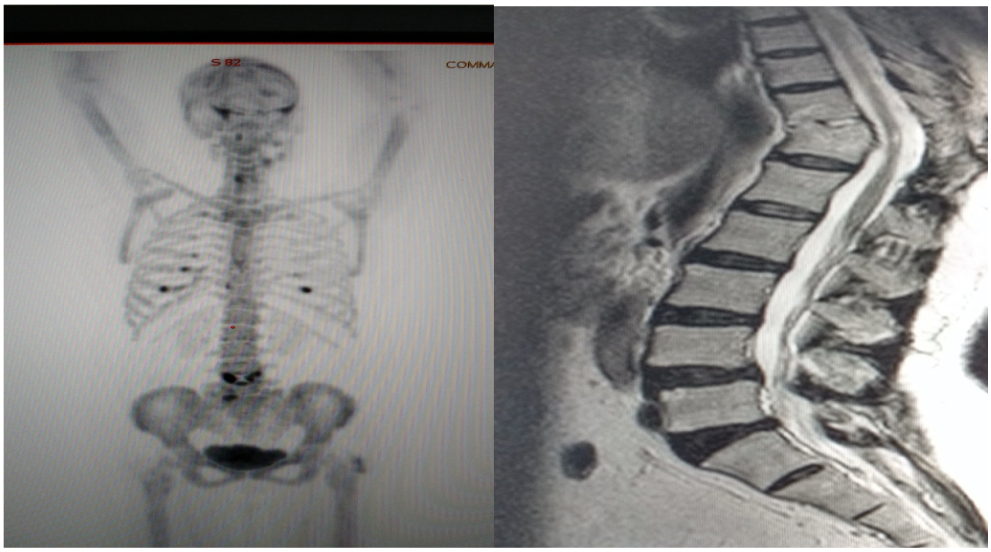

Figure 2: 53 years old female patient of breast cancer. PET scan showed increase uptake in LV4. MRI revealed only compression fracture of DV12 and reduced IV disc space between D11-12.

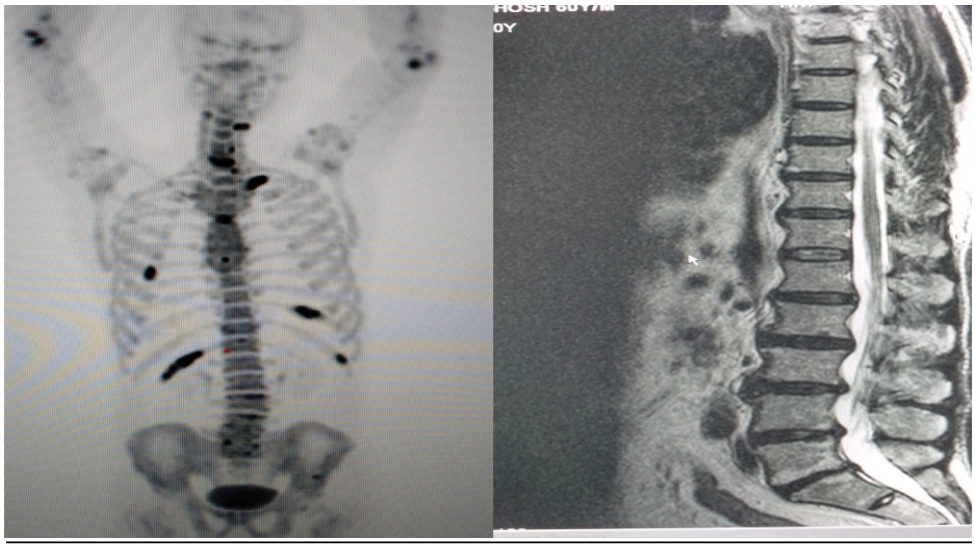

Figure 3: Case of Ca Lung. PET CT Scan shows increased uptake in C3, C6, D1 and D7. MRI sequences showed only degenerative changes.

This type of study between PET CT and MRI is limited. So the direct comparison with previous study is not possible. According to the study of Heike E. Daldrup et al sensitivities for the detection of bone metastases were 90% for FDG PET, 82% for whole-body MR imaging, and 71% for skeletal scintigraphy [20]. Schirrmeister et al compared 18F-NaF PET and planar 99mTc-MDP scintigraphy for metastases detection [21]. 18F-NaF PET identified a significantly higher number of vertebral metastases.

Our study also showed statistically significant difference in detecting the vertebral metastasis in PET CT & MRI and PET CT is picking up more lesions. The 18F-NaF PET CT scan detects more number of lesions and it is due to small lesions with rapid bone turnover very early in the metastatic process, before the onset of lytic or blastic process, would have

higher detectibility with 18F-NaF PET. Specificity has increased by combining the PET with CT scan.

The present study has the limitation of having a small study population. That is partly due to high cost and non-availability of the radiopharmaceuticals. Though our study has shown 18F-NaF PET CT having an edge over MRI in detecting spinal metastasis, MRI will continue to enjoy its status as an important imaging tool. PET-CT is a relatively new imaging technique and the availability of the scanners and expertise are limited. As on date, PET-CT and MRI should be considered as prime modalities for assessment of spinal metastasis, rather than considering them as competing diagnostic tools. There is a need to exercise caution in declaring one of them as superior than the other. In future, large controlled studies designed to study the relative accuracy of detectability of spinal metastasis by PET-CT and MRI is mandated before making any concrete recommendations.

Conclusions

Spinal metastasis is a commonly encountered problem in management of common malignancies and selection of imaging modality play a crucial role in early detection of disease burden which has a tremendous impact in the final outcome. Our study showed

F-18 NaF PET-CT has statistically significant higher detection rate of spinal metastatic lesions as compared to MRI. The combined F-18 NaF PET-CT showed both functional and anatomical details which gives diagnostic confidence in detection & assessment of spinal metastases. Thus, F-18 NaF PET-CT as a primary imaging modality for assessing spinal metastasis merit consideration. Further work in this field with larger study population is needed before establishing the claim.

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