Original Article

A Practical Approach to Optimize Scan Protocol for Simultaneous Whole-Body Positron Emission Tomography/Magnetic Resonance Imaging in Cancer Staging

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Abstract

Objective: The aim of the report is to present time efficient whole-body positron emission tomography/magnetic resonance imaging (PET/MRI) protocol evolved and tested for comprehensive evaluation of cancer patients. **Materials and Methods:** Whole body as well as regional simultaneous PET and MRI was performed on Biograph mMR (Siemens, Erlangen, Germany) Simultaneous PET/MRI system in 4500 clinical cases of various cancers from 2013 to 2017 with an in-house designed imaging protocol to assess its utility. **Results:** Using this protocol, the whole body is covered with optimized sequences (T1, T2, short tau inversion recovery, diffusion, and 3D volumetric interpolated breath-held) with PET which has been found adequate for complete metastatic workup in 30–45 min. With region-specific studies, it provides a comprehensive staging workup in an additional 10–15 min. The workflow offered additive advantages of effectively addressing incidentalomas besides being useful in terms of diagnostic utility. **Conclusion:** The proposed whole-body PET MRI imaging protocol used in a clinical setting is found acceptable and reasonably time efficient to optimally exploit the potentials of the technique in oncology.

Keywords: *Magnetic resonance imaging, oncology, positron emission tomography, whole-body positron emission tomography/magnetic resonance imaging*

Introduction

With the advent of simultaneous positron emission tomography/magnetic resonance imaging (PET/MRI) in clinical practice, the need of combining metabolic, functional, and anatomical information in a single frame was accomplished as a desirable step in oncologic imaging.[1] MRI operating in whole-body mode and providing the much desired anatomical landscape of high soft-tissue contrast for whole-body PET has made metastatic workup in cancer more objective. It, however, remained an unmet need to have a time efficient and clinically acceptable PET/MRI imaging protocol harnessing potential of the two techniques optimally. This can be attributed to the fact that MRI is a time-consuming technique with a wide range of image sequences providing contrast/parameters, each having weightage to influence image interpretation and clinical decision.[2] In addition, MRI can offer more options to choose the best imaging plane/s for better display of pathological anatomy impacting surgical planning but with additional imaging time.[2]

It is well documented that MRI remains the modality of choice in the local staging of primary cancer.[3,4] With simultaneous PET/MRI, both PET and MRI being acquired together, no additional time is spent on account of PET acquisition. T staging for primary tumor may require additional MR sequences such as diffusion, perfusion, and spectroscopy and quantitative PET standardized uptake values for multiparametric evaluation as per clinical need. The additional examination time spent for having the advantages of these exclusive MRI or PET attributes, not available with any other technique, can then be justified.

The challenge, however, remains in optimal whole-body metastatic workup with minimum examination time for patient comfort, throughput, and completeness of staging. No standardized imaging protocol is available till date and workers in this field have reported different approaches such

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as limiting number of MR sequences in the whole-body mode to keep the examination time short.[5-7] Well-tailored imaging protocols should include time-optimized range of MR sequences to effectively complement and supplement PET and vice versa to increase efficacy of "M" staging. Appropriate selection of tissue-specific radiotracers could also save time while enhancing utility of this combined modality in staging cancer.

In oncologic workup, detection of metastatic lesions is a vital component of the evaluation. Several groups have evaluated fluorodeoxyglucose (FDG)-PET/MRI in this context.[7-10] Early clinical evaluations of integrated whole-body PET/MRI demonstrated feasibility in a general oncology population.[7] Studies have shown that FDG-PET/MRI performs better than FDG-PET/CT in metastatic workup of most anatomical regions other than lungs.[8] Overall, even with the challenges of MRI-based attenuation correction, PET/MRI is a robust modality for the delineation of metastatic disease and quantitatively assessing tracer accumulation within different tissue types. Thus, designing imaging protocols in the detection of metastatic lesions for whole-body PET/MRI as clinical routine holds significance.

The aim of this report is to describe the utility of protocol for simultaneous PET/MRI designed at our center and applied in 4500 cancer patients since 2013. The protocol was designed keeping in view of the facts that large pool of experience is already available on PET and MRI to choose key MR sequence/s or preferred MR imaging plane or radiotracer types for lesion detection and delineation.

Materials and Methods

Brief classification of cases, various tracer used, and clinical indications are as follows. The list includes maximum number of breast studies (n = 1201). Others include: genitourinary (n = 978), craniospinal (n = 625), gastrointestinal (450), head and neck (475), lungs (210), musculoskeletal system (78), lymphomas (130), malignancies of unknown origin (78), neuroendocrine (100), hematological (73), cancer screening (82), and retroperitoneal (20). Various tracers used for the assessment of disease are: 18F-FDG (4001), 68Ga DOTANOC/DOTATATE (99), 68Ga prostate-specific membrane antigen (^{68}Ga-PSMA) (296), 18F-Fluoro ethyl tyrosine (^{18}F-FET) (97), and ^{18}F-choline (7). Among clinical indications, restaging constitutes a maximum number of cases (n = 2162), followed by staging (924), recurrence evaluation (n = 864), and diagnosis (n = 550).

Protocol and workflow considerations for the positron emission tomography/magnetic resonance imaging system

The PET/MRI system (Biograph mMR; Siemens, Germany) is equipped with fully functional PET system based on avalanche photodiode technology within 3T MRI scanner.[11] Pretest patient preparation varies according to the type of tracers to be used. Patients were fasted for at least 6 h with mean blood glucose level of 150 ± 10 mg/dl before intravenous tracer injection in case of ^{18}F-FDG, and examination is performed after a mean uptake period of 45 min from the time of tracer injection. For tracers such as ^{18}F-FET and ^{68}Ga PSMA, imaging can start immediate postinjection.

Attenuation correction

For each bed position, the attenuation data in PET/MRI are derived from the MRI scan[12,13] using 2-point Dixon MRI sequence. The Dixon fat- and water-weighted images were used to create an attenuation map (μ map) with four distinct tissue classes: background, lungs, fat, and soft tissue. Further, attenuation of the PET signal caused by instrumentation such as the patient bed and the fixed MRI coils are routinely computed into attenuation maps.[14] In case of a dedicated brain study, ultrashort echo time sequence was used to segment the skull separately.[15]

Whole-body positron emission tomography/magnetic resonance imaging acquisition

Given the relative novelty of PET/MRI, no standardized acquisition protocols exist. We have presented an imaging protocol with an innovative approach which is optimized in terms of sequence selection and application in a mixed match fashion for scanning to complete in a limited period of time. A complete PET/MRI study includes whole-body coverage from the vertex to the mid-thigh. The patient lies on special 24 channel mMR spine coil wrapped with at least 4 dedicated 6-channel mMR body matrix coils from chest to the knee (depending on the length of the patient) and a dedicated 16-channel mMR head-and-neck coil for head-and-neck regions. The diagnostic MR sequences include axial TurboFlash T1, axial T2 short tau inversion recovery (STIR) with simultaneous 3 min PET acquisition per bed position.

The whole-body protocol also included axial T2W fluid-attenuated inversion recovery (FLAIR) for brain, 4 mm high resolution T2W in axial plane for pelvis (for male patient to cover prostate gland)/T2W sagittal for pelvis (for female patients to scan the uterus and cervix in a preferred orientation), 6 mm axial DWI (multi b value diffusion-weighted imaging: b = 50, b = 800 s/mm^2 for abdomen and pelvis (to improve lesion conspicuity and lesion detection in the viscera, nodes/deposits in retroperitoneum/peritoneal cavity, respectively, and the adnexa), 4 mm sagittal (STIR T2-weighted sequences), and 4 mm sagittal T1W turbo spin echo (TSE) (to detect skeletal marrow lesions) [Figures 1 and representative case in Figure 2].

The proposed whole-body protocol also includes postcontrast (except in cases where gadolinium is contraindicated) sagittal 3D Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) for brain and 3D fat-suppressed (Volumetric Interpolated Breath-held

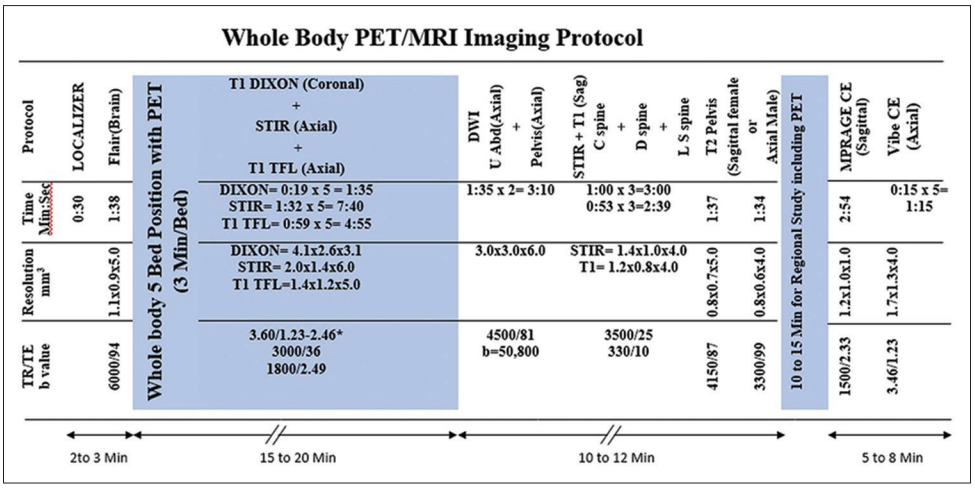

Figure 1: Representative image showing the outline of the whole-body imaging protocol with simultaneous positron emission tomography/magnetic resonance imaging

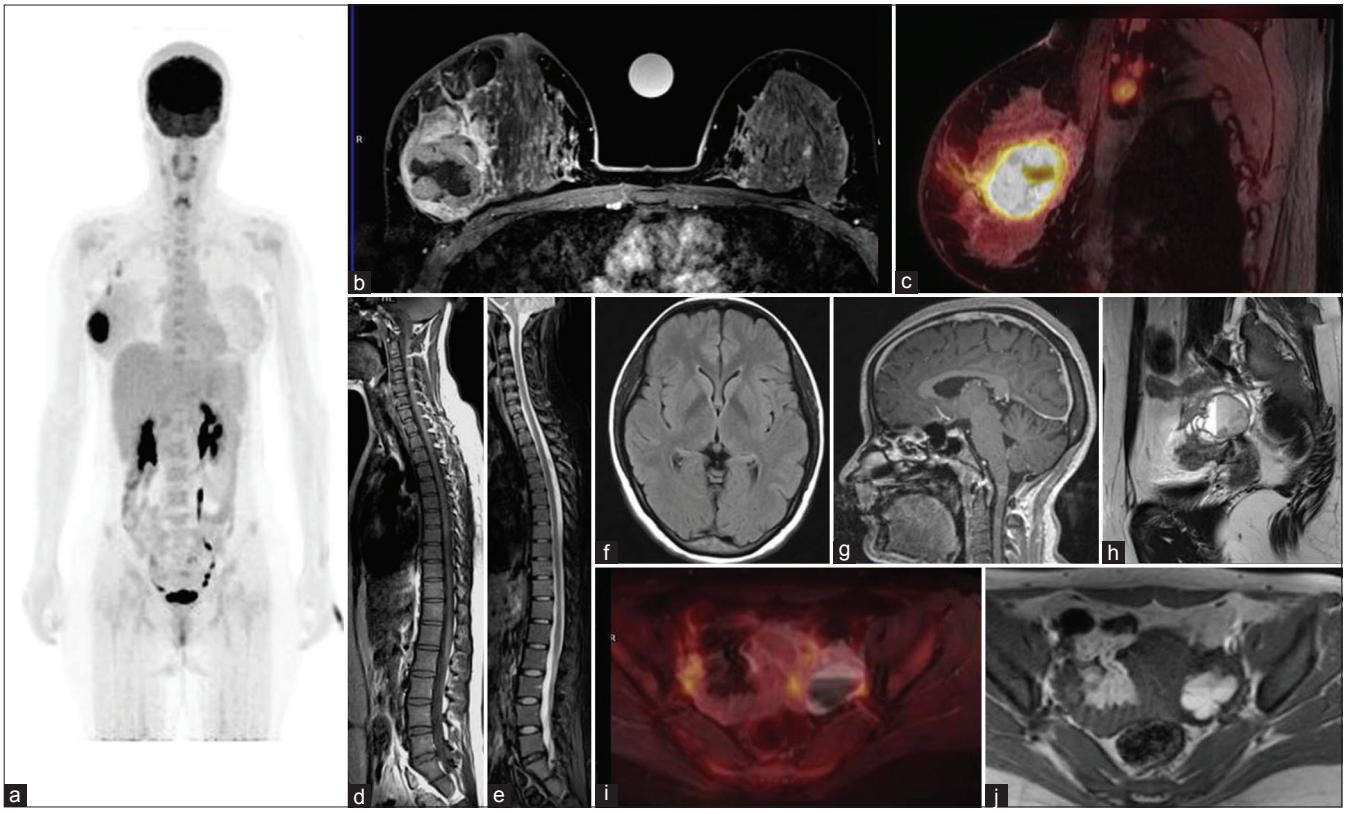

Figure 2: Positron emission tomography/magnetic resonance imaging tumor, lymph node, and metastasis staging in a 27-year-old female with invasive intraductal carcinoma right breast: solitary fluorodeoxyglucose avid T4 lesion seen in right breast: axial postcontrast (b) and with fluorodeoxyglucose avid axillary nodes in fused positron emission tomography/magnetic resonance imaging image (c). Whole-body metastatic workup shows no distant metastasis in positron emission tomography maximum intensity projection (a), 5 bed whole body axial T1 and T2 short-tau inversion recovery (not shown), sagittal turbo spin-echo T1 (d), sagittal short tau inversion recovery (e) of spine, axial T2 fluid-attenuated inversion recovery (f), and sagittal postcontrast brain images (g). The incidental complex endometriotic cyst in left ovary in sagittal T2 image of pelvis (h) correctly classified with spatially correlative multiparametric axial images as nonfluorodeoxyglucose avid lesion in fused positron emission tomography/magnetic resonance imaging (i) with T1 hyperintense blood product (j)

Examination [VIBE]) sequence for the whole-body examination after completing the regional study that further adds MR capabilities in localizing small lesions in brain and body organs. To make the overall imaging time short, however, these MR sequences use acquired whole-body PET for correlative reading.

Image analysis and positron emission tomography/magnetic resonance imaging reading

An important step in the PET/MRI reading is the mode of image display for quick and correlative review of different

series types with multiparametric information. Image analysis was performed using Syngovia workstation and software (Siemens, Germany) by consensus agreement of two readers (one radiologist and one nuclear medicine physician). We prefer to look spatially correlated axial sections for image evaluation and use axial STIR and T1 MRI data to get an overview of suspected lesions in whole-body mode for metastatic workup. Correlates of the suspected areas in these images are assessed for PET uptake, diffusion behavior and contrast enhancement of lesions for characterization. On relook, we localize area of abnormal PET uptake like physiological brown fat or hot clot artifacts in lungs by assessing structural correlate in the spatially matched MR images. This approach helped to avoid bias induced by subjective selection of PET avid areas as lesions. Inputs from any special MR sequences in case of regional studies are available for evaluation of lesions from tailored sequences regarding status of biliary tree with magnetic resonance cholangiopancreatography (MRCP), hypervascular metastatic deposits/primary liver lesions (such as hepatocellular carcinoma [HCC]) with triple phase contrast study, etc., in the same examination.

Limitations

Patient compliance

The present protocol with an imaging time of ~1 h though could effectively address in most oncology cases, further optimization with faster and newer MR sequences will remain an area of research toward reducing imaging time and to improve patient comfort. Gradient noise remains a cause of discomfort with MRI examination. Reduction of noise across sequences is a work in progress to achieve silent MRI in future in routine.

Image degradation

Besides metallic artifacts, large ascites/pleural effusion or respiratory motion in uncooperative/sick patients remains a major cause of image degradation and loss of information.

Results and Discussion

The present protocol acquires images in axial orientation to cover the whole body in matching slices with optimized T1 TFL sequence for T1 contrast, STIR for T2 contrast, diffusion (with different b values), and fat-suppressed postcontrast (VIBE) images in addition to PET for spatial correlation of tissue parameters to assess the nature of a lesion which is distinct from reported by others.[5,6] Such an approach greatly helps in the correct classification of a nonmetastatic marrow lesion from a true metastatic one as seen in Figure 3, thus improving staging accuracy impacting clinical management. Acquiring in the axial plane through optimized sequences avoided bias induced in the localization of lesions when images are read in rather different planes with an objective to reduce imaging time. T2W TSE sequence in coronal and axial plane for whole abdomen (acquired during regional mode of operation)

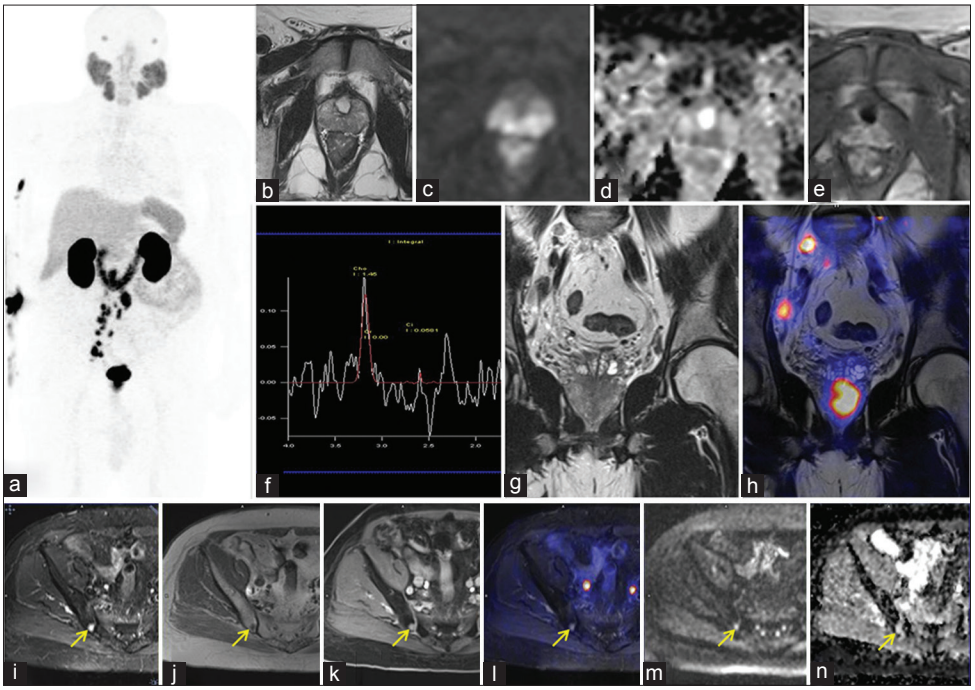

Figure 3: PET/MRI TNM staging: in a 56 year male of carcinoma of prostate: PET MIP (a) shows PSMA avid prostate lesion with nodal metastasis. Regional PET/MRI with multiparametric MRI (mpMRI) shows a PIRADS 4 lesion in bilateral peripheral gland appearing hypointense in axial T2 (b) with diffusion restriction (c), hypointense in ADC map (d), enhancing in post contrast VIBE (e) with increased Choline in MRS (f). Spatially correlative coronal T2 (h) and fused PSMA PET/MRI images (h) show organ confined PSMA avid prostatic lesion and chain of iliac and retroperitoneal nodes. Note: Multiparametric assessment of a marrow lesion in right ilium using the protocol; axial STIR, T1 TFL, post contrast VIBE image (i-k) with no PSMA uptake in PET/MRI Fused image (l) and showing no diffusion restriction in Axial DWI and ADC map (m & n): non metastatic

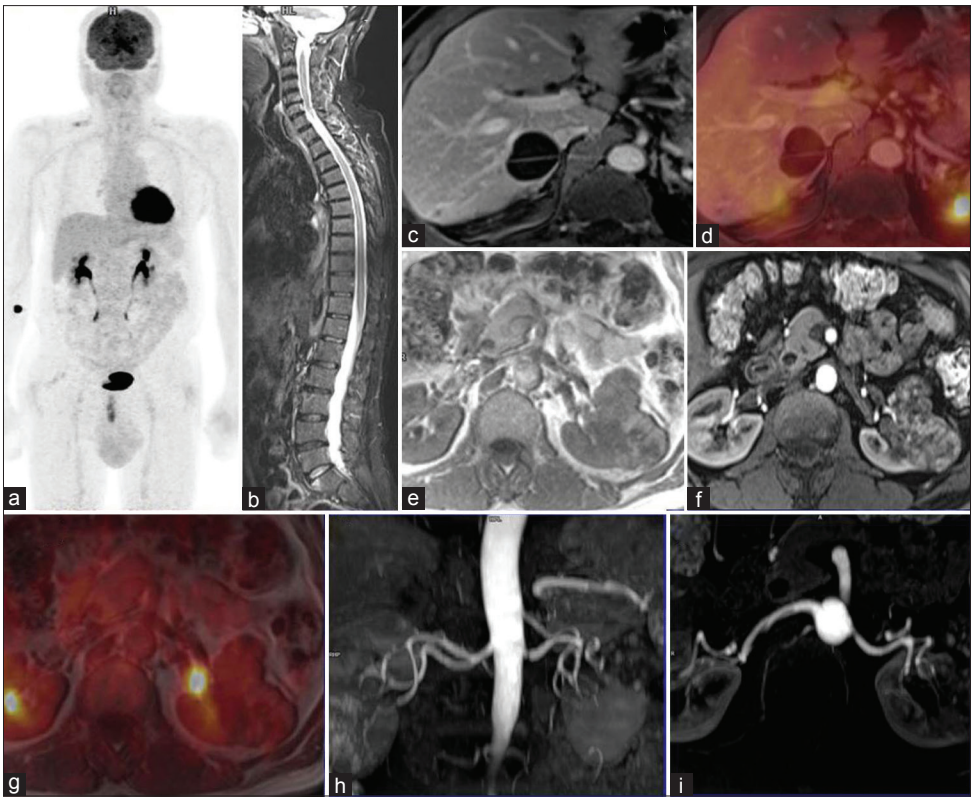

Figure 4: Whole-body tumor, lymph node, and metastasis staging: a case renal cell carcinoma in a 62-year-old male. Coronal positron emission tomography maximum intensity projection (a), correlative axial whole body magnetic resonance imaging (not shown), L5 end plate change inT2 short-tau inversion recovery sagittal spine (b) and no distant metastasis. A simple cyst in segment VI of liver shows no enhancement (axial postcontrast volumetric interpolated breath-held: (c) and no fluorodeoxyglucose uptake (axial positron emission tomography/magnetic resonance imaging: (d). Regional positron emission tomography/magnetic resonance imaging shows a heterogeneous T1 hyperintensity hemorrhagic left renal mass (axial T1 image: e) showing arterial phase enhancement (volumetric interpolated breath-held: f) and no fluorodeoxyglucose uptake (axial positron emission tomography/magnetic resonance imaging: g). Triple-phase angiography (maximum intensity projection coronal: h and axial: i) showing two left renal arteries, the second left renal artery arising cranial to the main artery between the origin of celiac and specific membrane antigen

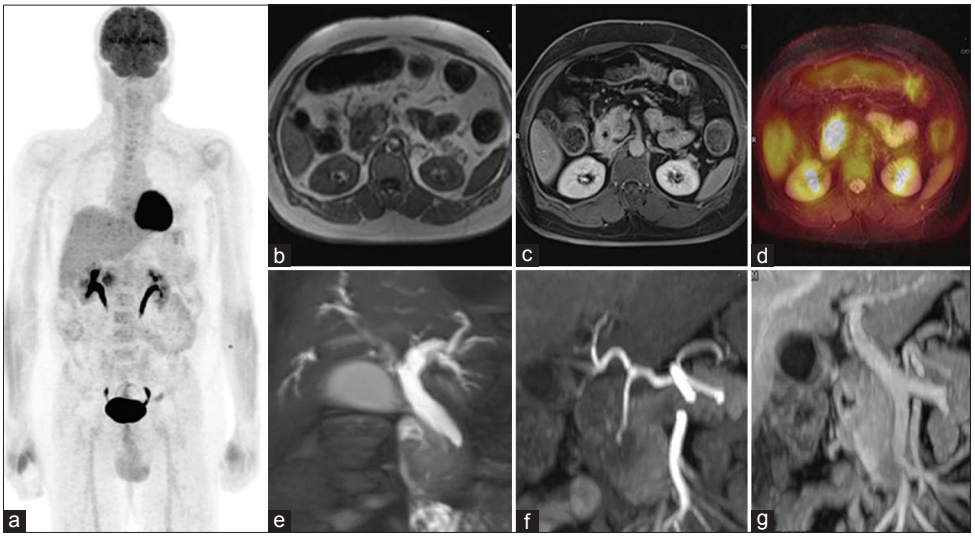

Figure 5: Whole-body tumor, lymph node, and metastasis staging: in a case of a 68-year-old male with cholangiocarcinoma. Positron emission tomography maximum intensity projection image (a) along with spatially correlated magnetic resonance images of whole body (not shown) excluded any distant metastasis. Regional positron emission tomography/magnetic resonance imaging shows eccentric thickening of the medial wall of duodenum in axial T1 turbo spin-echo (b) enhancing in postcontrast volumetric interpolated breath-held (c) with increased fluorodeoxyglucose uptake and no active regional nodes in axial fused positron emission tomography/magnetic resonance imaging image (d). Coronal maximum intensity projection magnetic resonance cholangiopancreatography images (e) showing abrupt cutoff of bile signal. Triple phase contrast-enhanced angiography: arterial (f) and venous (g) anatomy maximum intensity projection images shows no tumor infiltration of vessels and normal flow in specific membrane antigen and the portal vein

provides image contrast for evaluation of bowels and in the detection of cysts, cystic lesions, or free fluid spaces besides displaying organ-anatomy/lesions in additional orientation. As reported earlier in MR imaging,[16] diffusion images with multiple b values in our protocol also enhanced conspicuity of lesion detection with low b value while aiding in the characterization with high b value with inputs from postprocessed apparent diffusion coefficient (ADC) map. Furthermore, selection of preferred imaging planes in our case was directed to have quick evaluation of certain regions such as a sagittal view in spine and pelvis.

The duration required for covering the whole body with TFL T1 and STIR with PET takes a mean time of only 18 min which was found adequate to have a whole-body imaging with somewhat similar time taken for a whole body PET/CT. Supplementary sequences that are optimized for time as well as preferred orientations for brain, spine, whole abdomen, and pelvis could be completed in a mean time of 35 min found adequate for whole-body metastatic workup. For patients having normal renal function and no contraindication for Gadolinium administration, another mean time of 8 min was spent to acquire postcontrast MPRAGE for brain and fat-suppressed VIBE for whole body for completeness of staging workup. Further, having PET uptake and multiple MR parameters: T1, T2, diffusion, ADC, contrast behavior of a lesion together for same voxel position is the hallmark in the present protocol that helps better lesion definition along with tackling incidentalomas such as cysts, angiolipomas, dermoid, hemangiomas, endometriotic cysts, etc., that are encountered during whole-body MRI examinations. Furthermore, it aids in adequately resolving the limitations of localizing PET nonavid lesion like renal cell carcinoma [Figure 4] shown in this report.

Keeping in view of poor sensitivity of MRI in detecting small nonavid lung nodules, in cases where PET/MRI is the first examination to be performed for whole-body metastatic evaluation, if not available already, an additional high-resolution computed tomography of the chest is usually included to assess the lungs.

Regional positron emission tomography/magnetic resonance imaging

With this protocol, whole-body acquisition is followed by regional examination for evaluation of primary disease before contrast administration to avoid blurring of tissue (fat) planes. The regional imaging protocol [Supplementary Tables 1 and 2] includes coronal and axial T2 HASTE in abdomen, additional sequences such as T2 STIR and TI TSE with and without contrast in axial and coronal planes for head and neck. Special sequences are included such as dynamic contrast enhanced MRI for breast [Figure 2], Multiparametric MRI for prostate [Figure 3], MRCP for evaluation of hepatobiliary cancers [Figure 5], and renal cancer [Figure 4]. Triple phase contrast examination for the abdomen in cases such as HCC, cancer of bowel (small/large intestine),

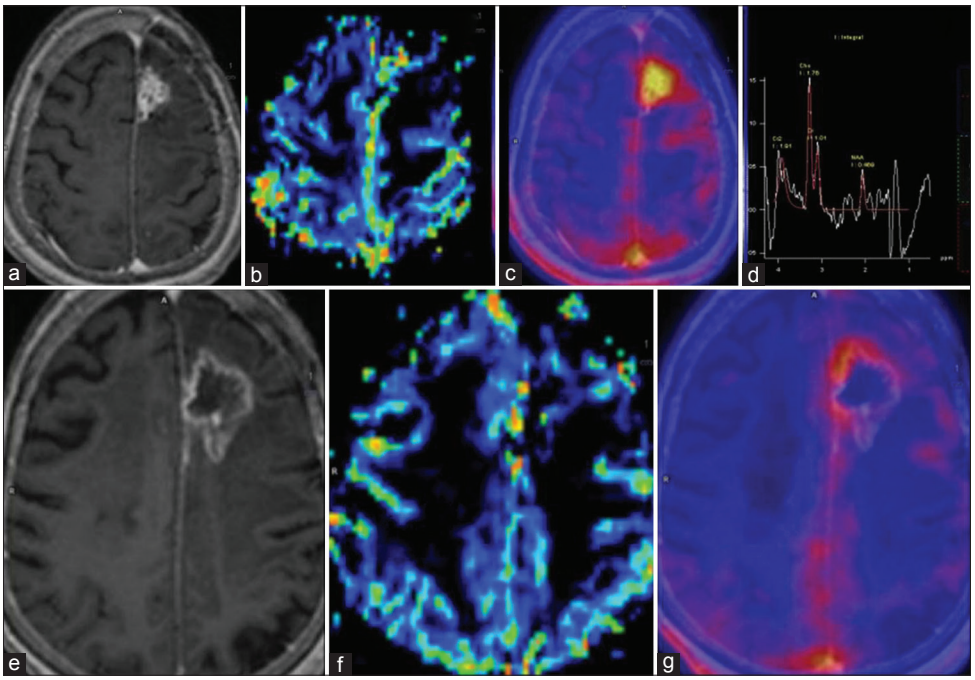

Figure 6: A case of a 63-year-old female of left frontoparietal gliosarcoma (Gr IV), 18-month postsurgery and radiotherapy. Regional positron emission tomography/magnetic resonance imaging shows: postopeerative cavity with heterogeneously enhancing lesion in the tumor bed with nodular component in its anterosuperior part: axial contrast-enhanced image (a) showing increased perfusion: axial regional cerebral blood volume map (b), increased 18F-Fluoro ethyl tyrosine tracer uptake: axial positron emission tomography/magnetic resonance imaging image (c) and increased choline in the proton magnetic resonance spectroscopy (d) suggesting recurrence. The diffusely enhancing inferior component: axial postcontrast image (e) with no increased perfusion: axial regional cerebral blood volume map (f) or tracer uptake: axial positron emission tomography/magnetic resonance imaging image (g) suggesting posttreatment radiation effect: proved on histology

gallbladder, pancreas, urinary bladder, rectum, and lungs routinely included within the imaging time as standard to have regional vascular anatomy and detection of hypervascular metastasis. Brain evaluation includes T2 FLAIR, DWI, susceptibility weighted image, perfusion weighted image, 3D MPRAGE (pre and postcontrast), and proton magnetic resonance spectroscopy (in glioma) as routine along with FDG PET facilitating multiparametric evaluation [Figure 6]. MR angiography, diffusion tensor imaging, and functional MRI were included in selected cases with additional time as per clinical need. The details of whole-body imaging as well as specific regional protocols vary in different clinical situations and have been outlined in Figure 1 and Supplementary Tables 1, 2.

This adopted time efficient PET/MRI whole-body protocol and regional study as per clinical need is similar to reported earlier[5,6] but were different in terms of MR sequence type along with selective imaging planes.

Conclusion

Diagnostic quality imaging for whole-body metastatic workup along with a well-tailored regional T staging within an acceptable examination time is possible by appropriately sorting PET and chosen MR sequences while fully utilizing the potential of the hybrid modality. While this customized protocol presented may be a guide, it will be an ongoing pursuit to improve further with continuing clinical development of PET and MRI techniques individually using simultaneous PET/MRI.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Technical aspects of the regional protocols for simultaneous positron emission tomography/ magnetic resonance imaging of breast, prostate, and Abdomen

Region	Sequences	Image plane	Gap percentage	Slice	Acquisition time (min: s)	TR/TE	Resolution (mm^3)	Remarks
AC	**3D T1 VIBE Dixon**	**Coronal**	**0**	**128**	**0:19**	**3.60/1.23-2.46**	**4.1×2.6**	
Diagnostic sequences for breast	STIR	Axial	10	67	2.13	6570/61	1.3×1.0×3	
	Diffusion	Axial	10	32	2:33	7300/82	1.8×1.8×4	b=50,800
	T1 non fs	Axial	0	288	2:27	6.02/2.46	1.2×0.08×1	
	PRE, DCE 1 min, 6 min	Axial	0	160	1:09	4.58/1.65	0.9×0.07×1.0	
	InterView	Axial	0	192	3:01	8.80/4.37	0.9×0.7×0.0.9	Between 1 and 6 min
AC	**3D T1 VIBE Dixon**	**Coronal**	**0**	**128**	**0:19**	**3.60/1.23-2.46**	**4.1×2.6**	
Diagnostic sequences for Prostate	T2W	Sagittal	10	27	1:37	4150/87	0.8×0.7×5.0	
	T2W	Coronal	10	25	1:14	4000/97	0.9×0.7×4.0	
	T2W	Axial	10	40	2:47	3300/99	0.8×0.6×4.0	
	Diffusion	Axial	10	40	2:38	7500/81	3.0×3.0×4	b=50,800,1400
	VIBE 2 and 15 Deg	Axial	0	20	0.23	5.18/1.78	1.9×1.4×3.6	DCE VIBE 15 Deg Temporal resolution 7.6 s×25
	T1 VIBE	Axial	0	224	1:13	3.87/1.45	1.0×0.8×1.0	
	Spectroscopy	3D			3.40	720/145	8.4×8.4×8.8	Optional
AC	**3D T1 VIBE Dixon**	**Coronal**	**0**	**128**	**0:19**	**3.60/1.23-2.46**	**4.1×2.6**	
Diagnostic sequences for abdomen	T2 HASTE	Coronal	10	40	1:20	1400/97	1.5×1.5×4	U.Abd+pelvis
	T2 HASTE	Axial	10	45	1:14	1600/95	1.5×1.2×5	U.Abd+pelvis
	*T2 cholangiogram	Coronal	0	96	3:55	1500/719	1×1×1.2	Optional
	T1 VIBE triple phase for liver	Axial	0	112	0:14	3.13/1.43	2×1.2×2	Optional

STIR: Short-tau inversion recovery, VIBE: Volumetric Interpolated Breath-held Examination, DCE: Dynamic contrast enhancement, 3D: Three-dimensional, AC: Attenuation correction, TR/TE: Repetition time/Echo time

Supplementary Table 2: Technical aspects of the regional protocols for simultaneous positron emission tomography/magnetic resonance imaging of neck and brain

Region	Sequences	Image plane	Gap percentage	Slice	Acquisition time (min: s)	TR/TE	Resolution (mm^3)	Remarks
AC	**3DT1 VIBE Dixon**	**Coronal**	**0**	**128**	**0:19**	**3.60/1.23-2.46**	**4.1×2.6**	
Diagnostic sequences for neck	T2_STIR	Coronal	10	20	1:04	3300/37	1.3×0.9×5	
	T1W	Coronal	10	20	1:03	400/9.4	1.2×0.09×5	+ Postcontrast
	T2_STIR	Axial	10	40	2:04	3070/27	1×0.8×5	
	T1W	Axial	10	40	1:30	400/9.8	1.1×0.8×5.0	+ Postcontrast
	T2W	Axial	10	40	1:43	3900/156	0.8×0.6×5.0	
	CE VIBE	Axial	0	224	1.13	3.87/1.45	1.0×0.8×1	
AC brain	**3D UTE**	**Axial**	**0**	**192**	**1:40**	**11.94/0.07-2.46**	**1.6×1.6×1.6**	
	3D T1 VIBE Dixon	**Coronal**	**0**	**128**	**0:19**	**3.60/1.23-2.46**	**4.1×2.6**	
Diagnostic sequences for brain	Flair	Axial	10	25	1:36	7000/94	1.0×0.9×5.0	
	SWI	Axial	0	32	1:37	26/20	0.8×0.7×4.0	
	Diffusion	Axial	10	25	1:52	4600/101	1.4×1.4×5.0	b=400,1000
	T2W	Axial	10	25	1:00	4300/100	0.7×0.4×5.0	
	Perfusion	Axial	10	25	2:40	2550/31	1.8×1.8×5	
	MPRAGE+PC	Sagittal	0	160	2:40	1410/2.33	1.2×1×1	
	Spectroscopy	Axial			5:41	1510/135	12×12×15	

UTE: Ultrashort echo time, VIBE: Volumetric Interpolated Breath-held Examination, 3D: Three-dimensional, STIR: Short-tau inversion recovery, SWI: Susceptibility weighted image, PC: Post contrast, AC: Attenuation correction, TR/TE: Repetition time/Echo time