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COMPUTED TOMOGRAPHY

Could new reconstruction CT techniques challenge MRI for the detection of brain metastases in the context of initial lung cancer staging?

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Abstract

Objectives To evaluate the diagnostic performance of brain CT images reconstructed with a model-based iterative algorithm performed at usual and reduced dose.

Methods 115 patients with histologically proven lung cancer were prospectively included over 15 months. Patients underwent two CT acquisitions at the initial staging, performed on a 256-slice MDCT, at standard (CTDIvol: 41.4 mGy) and half dose (CTDIvol: 20.7 mGy). Both image datasets were reconstructed with filtered back projection (FBP) and iterative model-based reconstruction (IMR) algorithms. Brain MRI was considered as the reference. Two blinded independent readers analysed the images.

Results Ninety-three patients underwent all examinations. At the standard dose, eight patients presented 17 and 15 lesions on IMR and FBP CT images, respectively. At half-dose, seven patients presented 15 and 13 lesions on IMR and FBP CT images, respectively. The test could not highlight any significant difference between the standard dose IMR and the half-dose FBP techniques (p-value = 0.12). MRI showed 46 metastases on 11 patients. Specificity, negative and positive predictive values were calculated (98.9–100 %, 93.6–94.6 %, 75–100 %, respectively, for all CT techniques).

Conclusion No significant difference could be demonstrated between the two CT reconstruction techniques.

Key points

- *No significant difference between IMR100 and FBP50 was shown.*
- *Compared to FBP, IMR increased the image quality without diagnostic impairment.*
- *A 50 % dose reduction combined with IMR reconstructions could be achieved.*
- *Brain MRI remains the best tool in lung cancer staging.*

Keywords Brain CT with dose reduction · Model-Based Iterative Reconstruction · Diagnostic performance · Brain metastases · Lung cancer staging

Introduction

MultiDetector computed tomography (CT) is part of clinical routine, and its indications continue to grow, as does the radiation exposure [1]. Concurrently, manufacturers have been working on new techniques of image reconstruction [2]. Introduction and implementation of iterative reconstruction (IR) algorithms in a daily practice could enable significant dose reductions [2–6].

Many studies have evaluated the image quality (IQ) of CT IR images obtained after dose reduction on phantom, but only few papers analysed the diagnostic value of these new reconstructions per anatomical region (brain, lung, abdomen, bones and temporal bone) [7, 8].

Consequently, the radiological community has to evaluate the effect of these new techniques on IQ and diagnostic performance per organ after dose reduction.

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Brain metastases are the most common brain tumours in the adult population. Lung cancer causes up to 40 % of them. In addition, brain metastases are the most frequent secondary localisation in lung cancer [9–11]. Following international guidelines, brain imaging with magnetic resonance imaging (MRI) as first choice is part of the initial staging workup when a lung cancer has been histologically confirmed [12, 13]. For several reasons including price, accessibility and contraindications, MRI is not considered as an easy routine-access examination and therefore brain CT could also be performed.

Good quality head CT images require a high level of x-ray dose [14, 15]. IR images maintaining IQ with radiation dose reduction could play an important role in challenging the traditional filtered back projection (FBP) in diagnostic performance.

Several papers have already shown that IR algorithms enable significant dose reduction while maintaining IQ [3, 4, 16].

To our knowledge, there is no previous study comparing brain CT with two different reconstruction techniques (FBP and model-based iterative reconstruction) at two different dose levels (standard dose (SD-CT) and half dose (HD-CT)) on the same patient. This study was designed to evaluate the diagnostic performance in the detection of brain metastases in the staging workup of lung cancer of brain CT images reconstructed with an IR algorithm compared to those obtained with FBP reconstruction algorithm at two levels of dose, while brain MRI was used as the reference.

Table 1 Patient selection (demography, histology and TNM classification)

		Total N=115
Gender	Female	38 (33.0 %)
	Male	77 (67 .0 %)
Age at diagnosis	Mean (years)	66.3
	Standard deviation	10.68
	Median	65
	Min-max	40-84
Histological type	Non-small cell lung carcinoma (NSCLC)	102 (88.7 %)
	- NSCLC adenocarcinoma	- 76 (74.5 %)
	- NSCLC epidermoid	- 20 (19.6 %)
	- Large cell carcinoma	- 4 (3.9 %)
	- Unknown	- 2 (2 %)
	Small cell lung carcinoma (SCLC)	8 (7 %)
	Unknown	5 (4.3 %)
TNM 7th edition stage NSLC (n=102)	Ia	18 (17.6 %)
	Ib	7 (6.9 %)
	IIa	6 (5.9 %)
	IIb	5 (4.9 %)
	IIIa	11 (10.8 %)
	IIIb	8 (7.8 %)
	IV	42 (41.2 %)
	Unknown	5 (4.9 %)

Materials and methods

This prospective single-institution study was approved by our institutional review board. Written informed consent was obtained from all patients.

Patient selection

Between 1 July 2014 and 31 September 2015, 115 consecutive patients (38 women and 77 men; mean age, 66.3 years; range, 40–87 years) with histologically proven lung cancer were prospectively included in this study (Table 1). Exclusion criteria were: age under 18 years, pregnant, compromised renal function (glomerular filtration rate less than 30 ml/min/1.73 m^2), severe allergy to iodinated contrast material and contraindication to MRI. Sample size was determined by patient availability. As no similar study has been done before, there is no known effect size comparing the IMR versus FBP and IMR or FBP versus MRI.

MDCT protocol

All examinations were performed using a 256-slice MDCT (ICT, Philips Healthcare, Cleveland, OH, USA) after intravenous injection of contrast media (Iobitridol 350, Guerbet, Aulnay sous bois, France; 350 mg of iodine/ml or Iomeprol 400; Bracco Imaging, Milan, Italy; 400 mg of iodine/ml). Those two contrast media were randomly used following the daily practice procedure of our institution. All examinations were part of the clinical management of the patients. Therefore, in a case of a single head CT acquisition, 60 ml of contrast media was injected at an injection rate of 3.5 ml/s (62 patients). When the cranial CT was performed as part of a whole body examination, up to 120 ml was injected (rate of 2.5 m/s) (53 patients). In both cases, delayed CT acquisitions were performed during the same session, 5 min after the injection. Patients were positioned supine, with head first on the table. After obtaining CT scout views, data were acquired in a spiral mode from the foramen magnum to the vertex at SD and HD with the following parameters: collimation 64x0.625 mm; pitch 0.390; rotation time 0.4 s. Standard dose (SD-CT) used in our institution was obtained with a tube voltage at 120 kVp and 300 mAs (CTDIvol: 41.4 mGy). Half dose (HD-CT) was obtained with 120 kVp and 150 mAs (CTDIvol: 20,7 mGy) (Table 2). Total CTDIvol received by each patient was 61.1 mGy [14]. The first 57 patients received the SD-CT first, the remaining 58 were given the HD-CT first.

Table 2 MDCT and MRI protocols: acquisitions, post-processing and image reconstruction parameters

CT protocol acquisition parameters		MRI protocols	
Standard dose (SD-CT)	Half dose CT (HD-CT)	3T Philips (Achieva, Ingenia)	3T Siemens (Skyra)
Collimation : 64 × 0.625 mm Pitch : 0.390			
Rotation Time : 0.4 s			
120 kVp			
300 mAs	150 mAs		
CDTIvol : 41.4 mGy.cm	CDTIvol : 20.7 mGy.cm		
Post-processing and image reconstruction		Axial diffusion DWI 4 mm	
Iterative model-based reconstruction (IMR)		Axial T1 TSE 4 mm	
Filtered back projection (FBP)		Axial T2* 4 mm	
FOV : 250 mm		Coronal T2 FSE 4 mm	
Matrix : 512 × 512		Axial FLAIR post injection	
Soft tissue kernels (1 and 3-mm slice thickness) Brain routine L3 (IMR)		Axial 3D T1 post injection	
Brain standard UB (FBP)			
Detail kernels (1-mm slice thickness)			
SharpPlus L3 (IMR)			
Detail D (FBP)			
Images labels			
	SD-CT	HD-CT	MRI
IMR	IMR100	IMR50	
FBP	FBP100	FB50	

Post-processing and image reconstruction

The raw data were reconstructed using both model-based iterative reconstruction (IMR, Philips HealthCare, OH, USA) and traditional filtered back projection (FBP) algorithms. The image reconstruction parameters were as follows: field-of-view 250 mm, reconstruction matrix 512 x 512.

Soft tissue (Brain Routine L3 and brain standard UB for IMR and FBP, respectively) wase used to get 1-mm thick and 3-mm thick parenchymal series (used for high quality MPR analysis with reduced partial volume averaging and parenchymal analysis respectively) and detail kernels (SharpPlus L3 and Detail D for IMR and FBP, respectively) were used to get 1-mm thick bone series (Table 2).

MRI protocol

Brain MRI was performed within 7 days on a 3-T Achieva and Ingenia Philips units (Philips, Cleveland, OH, USA) or a 3-T Skyra Siemens unit (Siemens, Erlangen, Germany). MRI images were considered as the reference due to higher MRI sensitivity in brain lesion detections [12, 13]. MRI protocol parameters are given in Table 2 and were the same as the usual brain MRI performed in our institution for oncological staging.

Image analysis

Four sets of images were generated for each patient: SD-CT and HD-CT images were labelled, IMR100, FBP100 and IMR50, FBP50 respectively (Table 2). Blinded to the dose, the reconstruction technique and the MRI results to ensure reading concordance, the 372 sets of images were independently and randomly reviewed by two neuroradiologists (1 and 7 years of experience, respectively; DB and DM) on a Picture Archiving and Communication System (PACS) workstation (Carestream Client version 11.4.0.1253, Carestream Health, Rochester, NY, USA). The study statistician was also blinded to the images. To ensure the blindness, an independent statistician attributed a key number to each dataset before the radiological reading. All details about the key attribution of the blinding process were provided in the randomisation plan specific to the study.

As in daily practice, readers analysed the images in axial and MultiPlanarReformation (MPR) mode and were free to change the windowing parameters. They had to detect any brain parenchymal metastasis. If such a lesion was diagnosed, measurements (three orthogonal diameters) and location were reported. Bone lesions, the detection of which were not the primary goal of this study, were recorded in a separate file.

Brain MRI images were independently and blindly analysed, following the same method, in a separate session,

7–14 days after a CT reading session. Consensual MRI results were recorded and used in case of discordant results.

Overall diagnostic image quality was assessed with a 5-point scale (Fig. 1a) according to the European Guidelines on Quality Criteria for CT [15]. Additional noise measurements were performed in two regions of interest (ROIs) of 200 mm^2, in the parenchyma (basal ganglia) and in the lateral ventricles (LV) by one reader (DM) (Fig. 1c).

Statistical analysis

A Statistical Analysis Plan (SAP) was built by two members of our institution's Statistical Unit (SC and AVM).

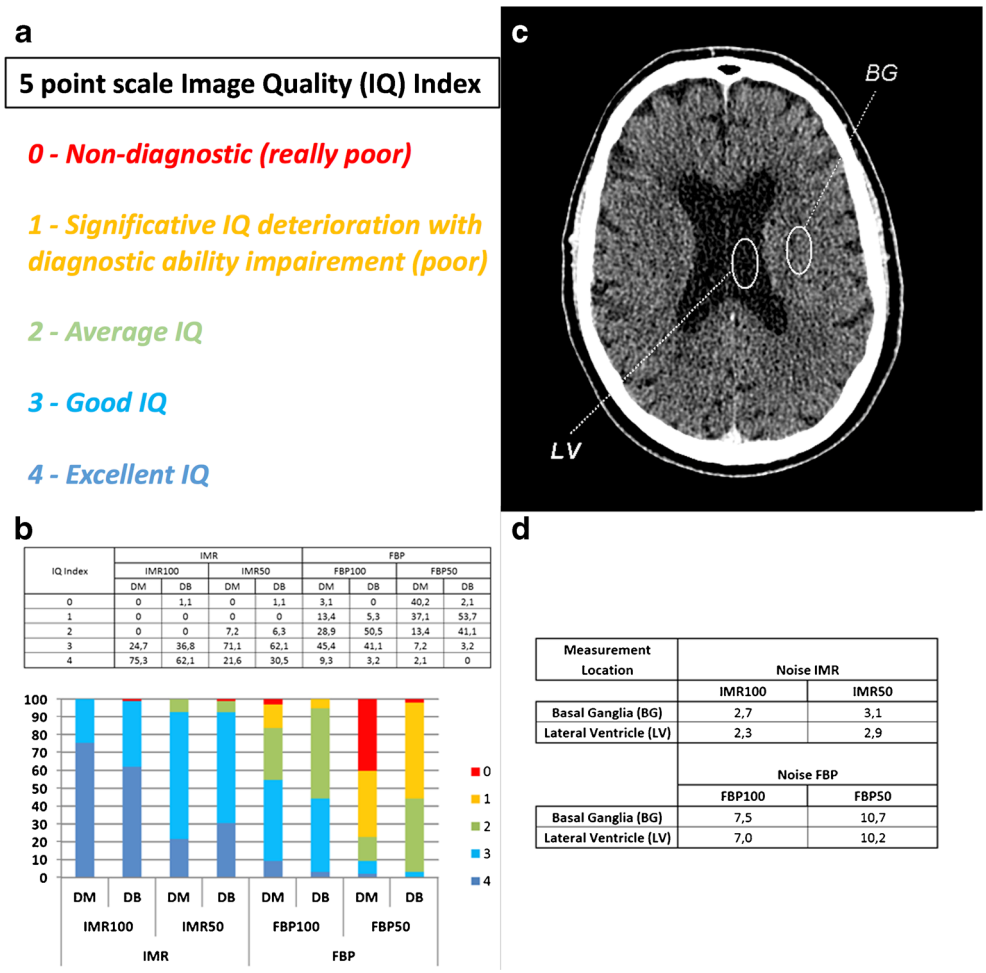
Primary analysis: inter-CT comparison

For technical reasons, eight CT data sets and four additional MRI data sets were missing. Therefore, analysis was performed on the 93 remaining patients. Before comparing the performance of the two imaging techniques with their respective dose levels, concordance and homogeneity between readers were checked. As the normality assumptions were not met, the Wilcoxon signed rank sum test was used and showed that there was no heterogeneity between readers, implying that the mean of their observations could be used.

The effect of the technique (IMR, FBP) and dose (SD-CT, HD-CT) on the number of lesions detected was analysed using the Wilcoxon signed rank sum test following a hierarchical methodology to avoid adjustment of the type I error for multiplicity: step 1 IMR100 versus FBP50; step 2 IMR100 versus FBP100; step 3 IMR50 versus FBP50. The null hypothesis was: there is no difference between the detection efficiency of the techniques (H_0: $\Delta=0$; H_A: $\Delta\neq0$). The last test of this hierarchical process (step 4) was a non-inferiority test, based on the null hypothesis that the number of lesions detected by IMR50 is worse than that detected by the FBP100 technique, with a non-inferiority margin set to 1 (one lesion difference).

Secondary analysis: CT versus MRI comparison

The secondary analysis aimed to compare the diagnostic performance of CT images (IMR100, IM50, FBP100 and FBP50) to the MRI (gold standard).



IQ Index	IMR				FBP			
	IMR100		IMR50		FBP100		FBP50	
	DM	DB	DM	DB	DM	DB	DM	DB
0	0	1,1	0	1,1	3,1	0	40,2	2,1
1	0	0	0	0	13,4	5,3	37,1	53,7
2	0	0	7,2	6,3	28,9	50,5	13,4	41,1
3	24,7	36,8	71,1	62,1	45,4	41,1	7,2	3,2
4	75,3	62,1	21,6	30,5	9,3	3,2	2,1	0

Measurement Location	Noise IMR	
	IMR100	IMR50
Basal Ganglia (BG)	2,7	3,1
Lateral Ventricle (LV)	2,3	2,9
	Noise FBP	
	FBP100	FBP50
Basal Ganglia (BG)	7,5	10,7
Lateral Ventricle (LV)	7,0	10,2

Fig. 1 Image quality: methods and results. a: Image quality score. b: Image quality score/techniques. c: Region of interest position. d: Noise measurements: quadratic average

Results

Brain metastases detection

Primary analysis

The Wilcoxon signed rank sum test could not highlight any significant difference between images provided by IMR100 and FBP50 (p-value 0.12) (Table 3).

Following the hierarchical process, the analysis was stopped at this stage and it was concluded that we failed to show any superiority of IMR100 versus FBP50.

Secondary analysis

11/93 (11.8 %) MRIs detected a total amount of 46 parenchymal lesions, sized from 1 to 28.7 mm; 8/93 (8.6 %) IMR100 and 7/93 (7.5 %) IMR50 were positive detecting 17 and 15 lesions, respectively, from 2.1 mm to 30 mm. In eight and seven cases (8.6 and 7.5 %, respectively), FBP100 and FBP50 were positive, detecting 15 and 13 lesions, respectively, from 5 mm to 29.4 mm. Negative predictive value (NPV), positive predictive value (PPV) and accuracy were calculated and are reported in Table 3.

Eighty-two of 93 (88.2 %) MRIs were considered negative (MRI-). Eleven of 93 (11.8 %) MRIs were considered positive (MRI+) (detecting at least one lesion). In 3/11 cases (27.3 %), all CT techniques concluded the same diagnosis as MRI images (Fig. 2). All lesions were correctly detected by the four CT techniques. All CT techniques led to a correct staging. In eight cases (72.7 %), MRI and CT images findings were different. We report and detail those cases in Table 4 and they are illustrated in Figs. 4 and 5.

In four cases, none of the four CT series was able to detect any lesion, while MRI diagnosed at least one lesion. CT series would have understaged the tumour (Fig. 3). With regard to the four remaining cases, we had four different situations. Discordance between MRI and CT, between CT series themselves and concerning the number of lesions (n) to detect.

Skull metastases detection

In 3/93 cases (3.2 %), MRI detected bone lesions. In two cases, these were reported correctly by all CT techniques (Fig. 6). In the remaining case, all CT techniques missed the bone lesion.

Image quality

Image Quality (IQ) results are reported in Fig. 1b. IMR100 and IMR50 images were considered as excellent and good, from 98.9 to 100 % and 92.6 to 92.7 %, respectively. FBP100 and FBP50 images were considered as excellent and good,

Table 3 Results. Diagnostic performance

		IMR				FBP				MRI
Techniques/dose		IMR100		IMR50		FBP100		FBP50		
Readers		DM (N=93)	DB (N=93)	DM (N=93)	DB (N=93)	DM (N=93)	DB (N=93)	DM (N=93)	DB (N=93)	(N=93)
Any tumour observed?	NO	85 (91.4 %)	82 (88.2 %)	86 (92.8 %)	83 (89.7 %)	85 (91.4 %)	85 (91.4 %)	86 (92.8 %)	83 (89.7 %)	82 (88.2 %)
	YES	8 (8.6 %)	11 (11.3 %)	7 (7.2 %)	10 (10.3 %)	8 (8.6 %)	8 (8.6 %)	7 (7.2 %)	10 (10.3 %)	11 (11,8 %)
PPV		75		100		80.0		100		
NPV		94.6		94.6		94.6		93.6		
Sensitivity		37.5		44.4		44.4		33.3		
Specificity		98.9		100		98.9		100		
Accuracy		94		94.8		93.8		93.8		

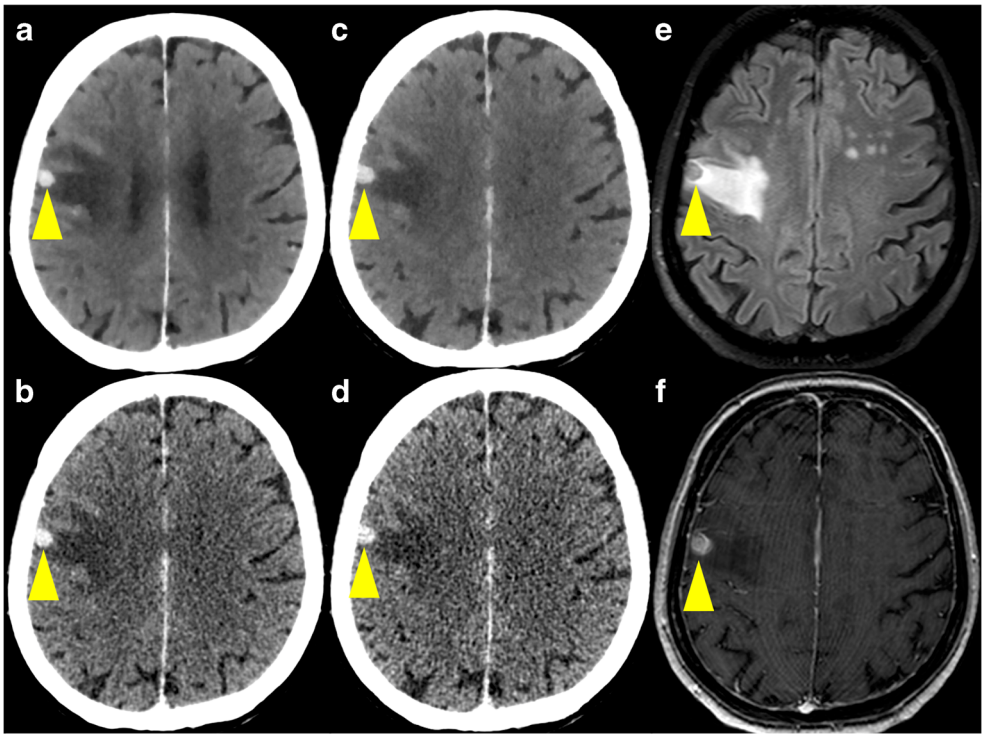


Fig. 2 Concordant case. All CT techniques correctly detected all parenchymal brain lesions. Right frontal lobe cortical-enhanced lesion with peripheral oedema (arrow head)

from 44.3 to 54.7 % and 3.2 to 9.3 %, respectively. The IMR100 and IMR50 images were considered poor and really poor, from 0 to 1.1 %. FBP100 and FBP50 images were considered as poor and really poor from 5.3 to 16.5 % and 55.8 to 77.3 %, respectively.

Root mean square (RMS) of the noise measurements is given in Fig. 1d.

Discussion

First, our study could not highlight any significant difference between IMR and CT images in terms of brain metastases detection in the context of lung cancer staging. Next, our study showed that IQ scores were higher for IMR CT images than FBP CT images, without diagnostic performance impairment. Even IMR50 IQ score was still higher than FBP100 IQ score. Finally, our study showed that MRI was still the best tool to detect brain metastases in the context of lung cancer staging.

Without any significant difference between the two techniques, we could not prove any superiority or inferiority of IMR images or FBP images. No diagnostic impairment would be observed while using IMR images instead of traditional FBP images.

While using iterative reconstruction techniques, X-ray dose reduction could also be achieved.

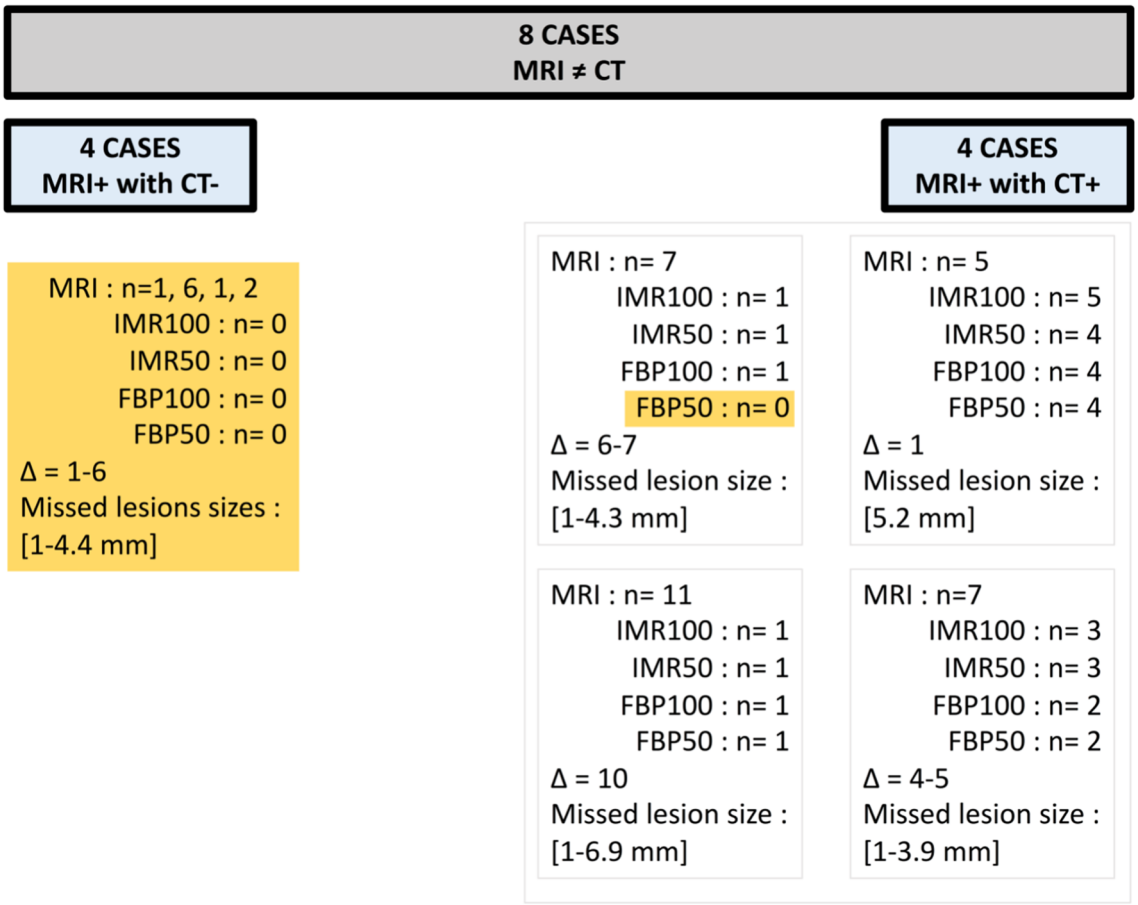
Figure 1b showed that both readers scored the IMR50 images good to excellent in more than 90 % of the studies, and with an average image quality score superior to the one of the FBP100. Notohamiprodjo et al. have already obtained similar results [17]. This meant that a 50 % dose reduction could be applied with IMR, leading to an extremely low CTDI around 20 mGy, without diagnostic impairment and with an average image quality superior to the one obtained with the traditional FBP reconstruction technique at 41 mGy, thus providing a large diagnostic confidence to the radiologist reading the images.

Therefore, the $CTDI_{vol}$ of 41 mGy that was used at our institution with FBP100, seemed to be well adapted to generate images of sufficient quality to provide diagnostic confidence to the radiologists. Considering the diagnostic reference dose levels, our SD-CT dose was already lower than recommendations. In 2004, the European Commission had published their guidelines which recommended a 60 mGy $CDTI_{vol}$ for a basic head CT examination. In our study, the total dose of our double CT (SD and HD-CT) was around 60 mGy [14].

The results of our study also suggested that 50 % did not seem to be the lower limit and that an additional dose reduction could be applied. This should be verified in future studies.

As expected and with a larger amount of metastases detected, MRI remained the most accurate examination to perform in the context of lung cancer staging. However, our study was designed to compare CT techniques themselves. MRI being the reference in neuroimaging, it seemed mandatory to compare results of the four sets of CT images to MRI results. Such a comparison showed that both CT techniques at both X-ray dose levels would have led to the same diagnosis. In case of non-accessibility of MRI, using IMR combined with a 50 % X-ray dose reduction did not mean a loss of benefit for the patient with a higher IQ score leading to a higher diagnostic confidence.

Table 4 MRI and CT discordant results. Details of eight cases where MRI and CT results were discordant



MRI+ magnetic resonance Imaging positive, *CT-/CT+* computed tomography negative/positive

n = number of detected lesions

Δ = Difference in number of lesions detected

On the left side of the figure, four cases with MRI considered positive, while all CT techniques were negative

On the right side of the figure, four cases with four different scenarios

Highlighted in yellow, CT series would have understaged the tumour

Considering the four cases where CT did not detect the correct amount of lesions, an additional MRI would have been required to provide an exact answer (and decide the most appropriate treatment).

In the four cases leading to a wrong diagnosis (while CT did not show any lesion, and MRI showed at least one) thus could have led to a 'wrong diagnosis', understaging the oncological pathology. However, for these four patients, extracranial metastases had already been reported as a stage IV, and no additional treatment would have been performed.

We also reported the number of detected bone lesions because skull analysis is part of head imaging analysis in daily routine and also in oncological practice. Concerning the detection of those lesions, both IMR and FBP images gave good results but we noticed many more difficulties in characterising those lesions (benign or malignant). In such cases, we either needed to know the extracranial bone status or to perform an additional MRI.

So far, MRI is the best tool to provide an accurate evaluation of both the bone and parenchymal structures.

The main limitation of our study was obviously the small size of our sample. Another study with a larger sample would be required to confirm the trend of our primary analysis.

In case of extracranial stage IV, no further cerebral examination was required during the multidisciplinary weekly meetings, excluding de facto many patients with high probability of brain metastases. We also missed patients who revealed their thoracic pathology through a neurological syndrome. In such cases, brain examinations were performed in the emergency room and we could not include them retrospectively.

A second limitation was that we analysed only one single model-based iterative reconstruction algorithm. Another study comparing the algorithms provided by different manufacturers would be required to confirm these conclusions.

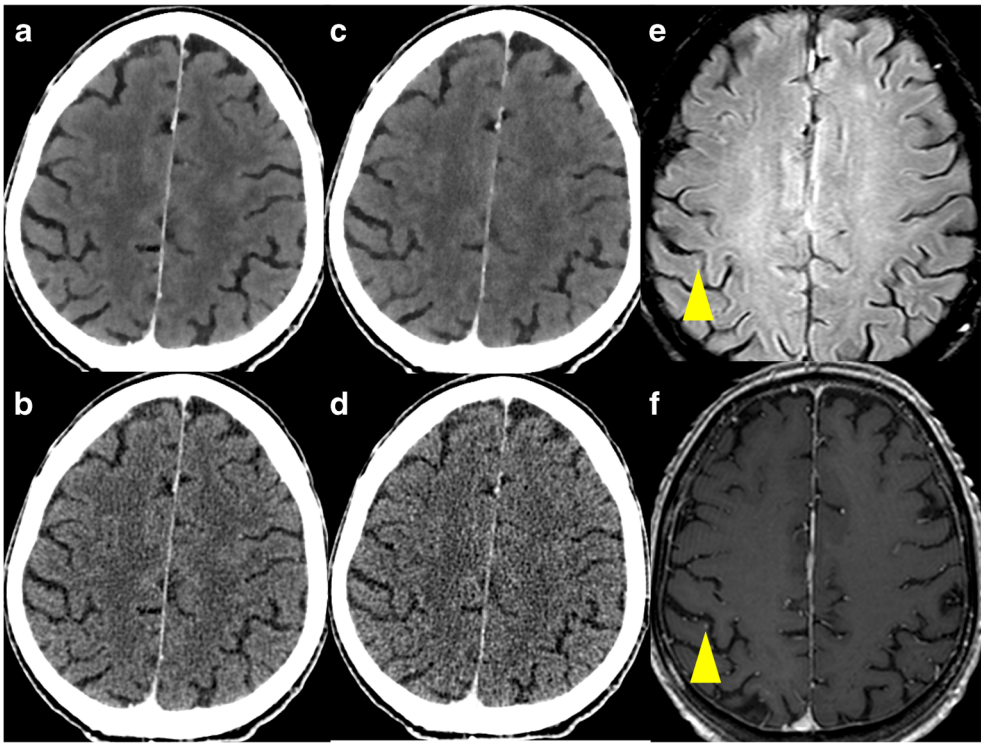


Fig. 3 Concordant case (2). All CT techniques missed this millimetric cortical left post central lesion (arrow head)

Even if the two readers had to analyse 372 sets of images, a recall bias has to be mentioned, also for the positive cases. When a lesion was detected, with additional clues from the topography, the reader would easily look for another one in an already known area.

In conclusion, MRI remained the best tool to detect brain metastases, but in case of non-accessibility, CT could be an excellent alternative. In addition, 50 % X-ray dose reduction with iterative reconstructions could apparently be applied without loss of diagnostic confidence.

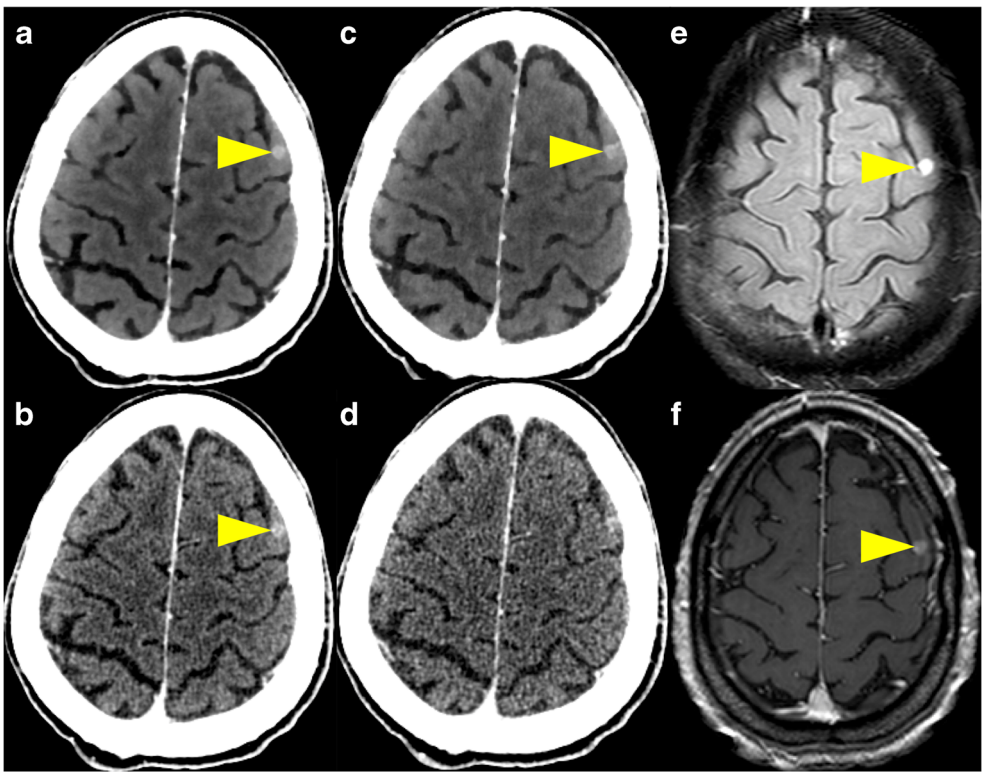


Fig. 4 Discordant case. FBP50 missed the left frontal lobe cortical enhanced lesion (arrow head)

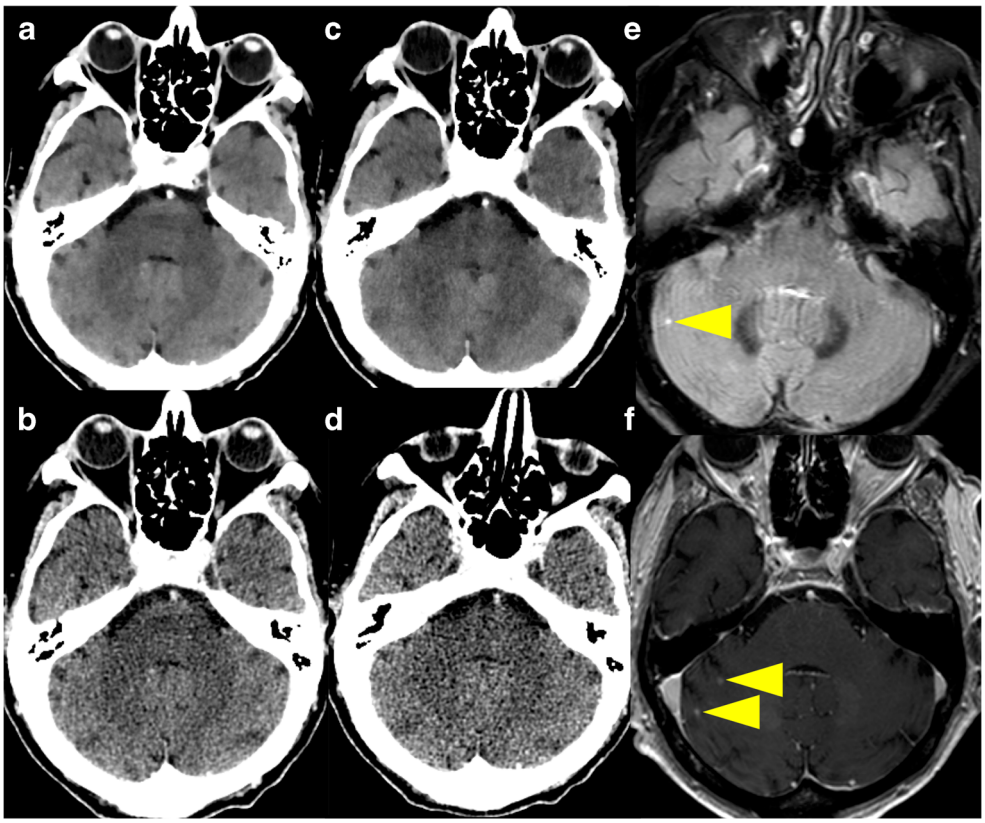


Fig. 5 Discordant case (2). All CT techniques missed those posterior fossa lesions (arrow heads), while they detected supra tentorial lesion (Δ=5 lesions)

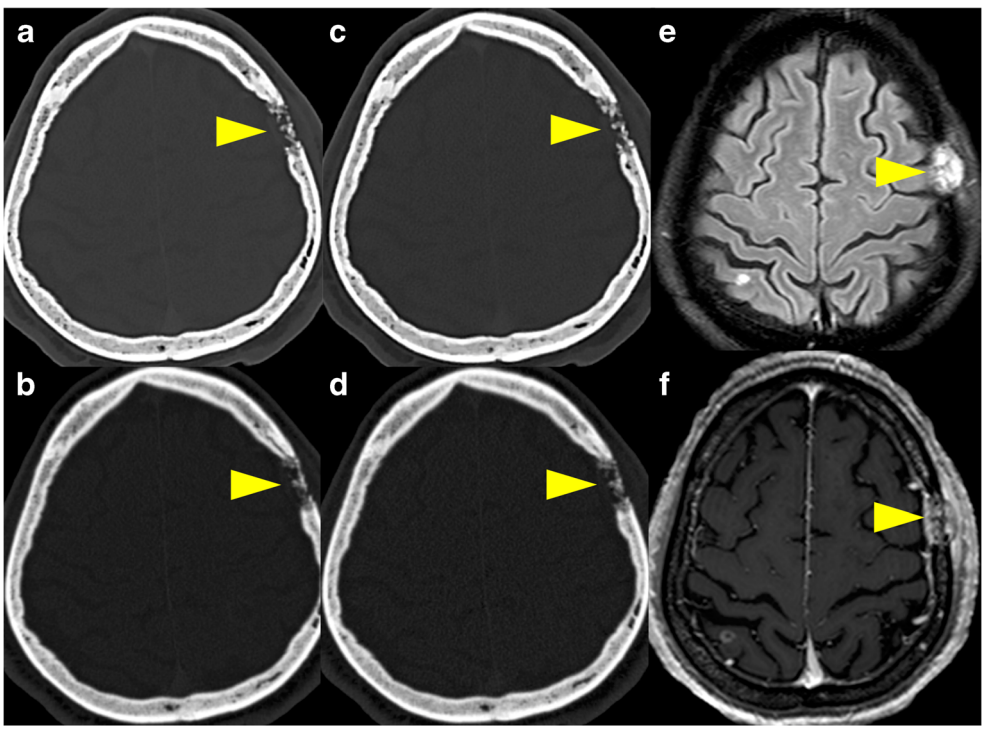


Fig. 6 Bone lesion. Left frontal bone lesion correctly detected by all CT techniques (arrow head)

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Compliance with ethical standards

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Conflict of interest One author (Alain Vassenbroek) of this manuscript declares relationships with the following companies: Philips Healthcare.

Statistics and biometry Two of the authors have significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
• prospective
• experimental
• performed at one institution

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