

# Reduction of effective dose and organ dose to the eye lens in head MDCT using iterative image reconstruction and automatic tube current modulation

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**Aims.** To compare the effective and eye lens radiation dose in helical MDCT brain examinations using automatic tube current modulation in conjunction with either standard filtered back projection (FBP) technique or iterative reconstruction in image space (IRIS).

**Methods.** Of 400 adult brain MDCT examinations, 200 were performed using FBP and 200 using IRIS with the following parameters: tube voltage 120 kV, rotation period 1 second, pitch factor 0.55, automatic tube current modulation in both transverse and longitudinal planes with reference mAs 300 (FBP) and 200 (IRIS). Doses were calculated from CT dose index and dose length product values utilising ImPACT software; the organ dose to the lens was derived from the actual tube current-time product value applied to the lens. Image quality was assessed by two independent readers blinded to the type of image reconstruction technique.

**Results.** The average effective scan dose was  $1.47 \pm 0.26$  mSv (FBP) and  $0.98 \pm 0.15$  mSv (IRIS), respectively (33.3% decrease). The average organ dose to the eye lens decreased from  $40.0 \pm 3.3$  mGy (FBP) to  $26.6 \pm 2.0$  mGy (IRIS, 33.5% decrease). No significant change in diagnostic image quality was noted between IRIS and FBP scans ( $P=0.17$ ).

**Conclusion.** Iterative reconstruction of cerebral MDCT examinations enables reduction of both effective and organ eye lens dose by one third without significant loss of image quality.

**Key words:** multidetector computed tomography, image reconstruction, radiation effects, eye lens, cataract

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## INTRODUCTION

Radiation doses resulting from medical exposure are steadily increasing in the population. In the United States, the medical radiation dose has already reached the average level of natural radiation background<sup>1</sup>. Although computed tomography (CT) accounts for only about 15% of radiologic examinations in the United States, it delivers two thirds of the entire cumulative exposure from all radiologic studies<sup>1,2</sup>. Diagnostic use of computed tomography may be responsible for up to 2% of all incident cancer cases in the United States nowadays<sup>3</sup>.

In order to change this unfavourable trend resulting from the continuously increasing number of CT procedures performed worldwide, adoption of adequate precautions aimed at radiation dose reduction is of great importance. Among the most promising approaches seems to be the technique of iterative reconstruction (IR) of CT image. Interestingly, IR was already used on first generation CT scanners in the early 1970s. However, it was rapidly replaced by filtered back projection (FBP) which offered incomparably shorter reconstruction times. For the next three decades, IR continued to develop solely in the field of nuclear medicine. As emission tomography methods (SPECT, PET) deal with much less projection data but with increased proportion of noise than CT, image noise suppression emerged as the most desirable feature and long reconstruction times of IR were subsidiary<sup>4</sup>.

Eventually, recent advancement in computer hardware and implementation of multi-core processors led to dramatic increase in computational power enabling reintroduction of IR to computed tomography in the very late 2000s. Despite still longer yet acceptable reconstruction times, IR proved its ability to significantly reduce image noise thus enabling radiation exposure reduction by tens of percent compared to standard FBP (ref.<sup>5,6</sup>).

The purpose of the study was to compare image characteristics, effective dose and organ dose to the eye lens in cerebral multidetector computed tomography (MDCT) using either standard FBP or iterative reconstruction in image space (IRIS). As all studies published have dealt with fixed tube current head MDCT protocols, this is, to our knowledge, the first study which evaluates the potential benefit of iterative reconstruction protocol combined with automatic tube current modulation. A brief review of the pertinent literature is included.

## MATERIALS AND METHODS

A total of 400 non-emergency adult brain MDCT examinations were prospectively included in the study. Of these, 200 were reconstructed using standard FBP and, after image reconstruction software upgrade, 200 using IRIS. All scans were performed in accordance with local protocol on a single source MDCT scanner (Somatom

Definition AS+, Siemens Healthcare, Forchheim, Germany) with the following parameters: collimation 2 x 64 x 0.6 mm with z-flying focal spot, tube voltage of 120 kV, pitch factor of 0.55, rotation time of 1 s and quality reference mAs value set to 300 for FBP protocols. In order to take advantage of radiation dose saving capabilities of the iterative reconstruction technique, the reference mAs value for IRIS protocols was, after consulting the vendor and according to the available literature at the time of implementation, lowered by one third to 200 mAs. Scans were acquired in helical mode with no gantry tilt, from the level of occipital condyles to the vertex. Image quality and image noise were evaluated on 5 mm axial slices with reconstruction kernel H31s (FBP) and J30s (IRIS). Automatic 4D dose modulation adjusting tube current in both transverse and longitudinal planes (CareDose4D, Siemens) was switched on in all FBP and IRIS acquisitions in order to further decrease the radiation dose.

Effective radiation dose was calculated from CT dose index (CTDI<sub>vol</sub>, mGy) and dose length product (DLP, mGy.cm) values utilising ImPACT software (Impact, London); the organ dose to the eye lens was derived from the actual tube current-time product value applied to the lens.

In order to calibrate and validate the organ dose to the eye lens calculated by a computer model, ten subjects in each category were scanned with a thermoluminescent dosimeter (TLD) placed in front of closed eyelids. The personal body dosimeter (TLD-CSOD, Czech Dosimetry Service, Prague, Czech Republic) was equipped with aluminiumphosphate glass 8.0 x 0.9 mm.

For purposes of quantitative image analysis, image noise was measured as standard deviation of attenuation values in a 1.5 cm<sup>2</sup> circular region of interest placed into homogeneously appearing white matter at frontal centrum semiovale (avoiding focal white matter abnormalities when possible).

Qualitative visual scan assessment was independently performed by two radiologists with 17 and 10 years of cross-sectional imaging experience who were blinded to the type of CT image reconstruction, using a visual analogue scale: 1 = very low noise, optimal diagnostic quality; 2 = standard noise, good diagnostic quality; 3 = increased noise, diagnostic quality; 4 = high level noise, limited diagnostic quality; 5 = unacceptable noise, non-diagnostic scan.

Descriptive parameters of the study population and image reconstruction techniques were statistically compared using t-test or non-parametric tests (Kolmogorov-Smirnov). Quantitative items are reported as mean  $\pm$  standard deviation for normally distributed variables or median with 95% confidence interval (CI) for non-normally distributed variables, as stated. Qualitative parameters were compared using Fisher's exact test for contingency tables. Interobserver agreement between subjective image quality ratings was calculated by kappa reliability test with kappa > 0.75 indicating substantial agreement. Statistical analysis was performed using NCSS 2007 programme (NCSS, Kaysville, Utah, USA) with p-values < 0.05 considered as significant.

The institutional ethics committee waived the need for individual informed patient consent for this study as all examinations were performed as standard of care.

## RESULTS

In terms of radiation dose, IRIS based protocols showed significant ( $P < 0.001$ ) radiation dose reduction when compared to standard FBP protocols. The average effective dose was  $1.47 \pm 0.26$  mSv (FBP) and  $0.98 \pm 0.15$  mSv (IRIS), respectively (33.3% decrease). The average organ dose to the eye lens decreased from  $40.0 \pm 3.3$  mGy (FBP) to  $26.6 \pm 2.0$  mGy (IRIS, 33.5% decrease). An overview of all evaluated radiation exposure parameters is summarized in Table 1.

Compared to numeric modelling of the organ dose by dedicated software, the results of direct thermoluminescent dosimetry showed lower organ dose values in both scan categories. The mean organ dose to the eye lens in FBP category was 40.0 mGy (calculated by ImPACT software) and 33.9 mGy (measured by TLD, i.e. 15% less). Respective results for IRIS category were 26.6 mGy (ImPACT) and 23.0 mGy (TLD, i.e. 14% less).

Quantitative analysis of image noise revealed slightly increased noise levels in the IRIS group. The median value of image noise was 3.9 for FBP (95% CI 3.9 – 4.0) and 4.2 for IRIS (95% CI 4.1 – 4.3), respectively. The difference was statistically significant ( $P < 0.01$ ).

Analysis of subjective image quality perception showed no significant difference ( $P = 0.17$ ) between groups of FBP scans (mean quality score = 2.12; median = 2) and IRIS scans (mean quality score of 2.17; median = 2). The vast majority of scans were rated with score 2 (standard noise, good diagnostic quality) in both FBP (88%) and IRIS (83%) categories. Of 400 scans, only one scan in FBP and one scan in IRIS group were rated with score 4 (high level noise, limited diagnostic quality). No scans rated with score 5 (unacceptable noise, non-diagnostic scan) were noted in either FBP or IRIS category. Kappa reliability test showed substantial interobserver agreement with kappa = 0.76. For details see Table 2.

## DISCUSSION

It is an unfavourable fact that despite unprecedented progress in medical technologies within the last few decades, medical radiation exposure continuously and progressively rises. Worldwide, there are an estimated 3.1 billion radiologic procedures, 0.5 billion dental exposures, and close to 40 million nuclear medicine procedures performed annually. The global average annual per-capita effective dose from medicine is about 0.6 mSv (of the total 3.0 mSv received from all natural sources) and has approximately doubled in the past 10–15 years<sup>1</sup>.

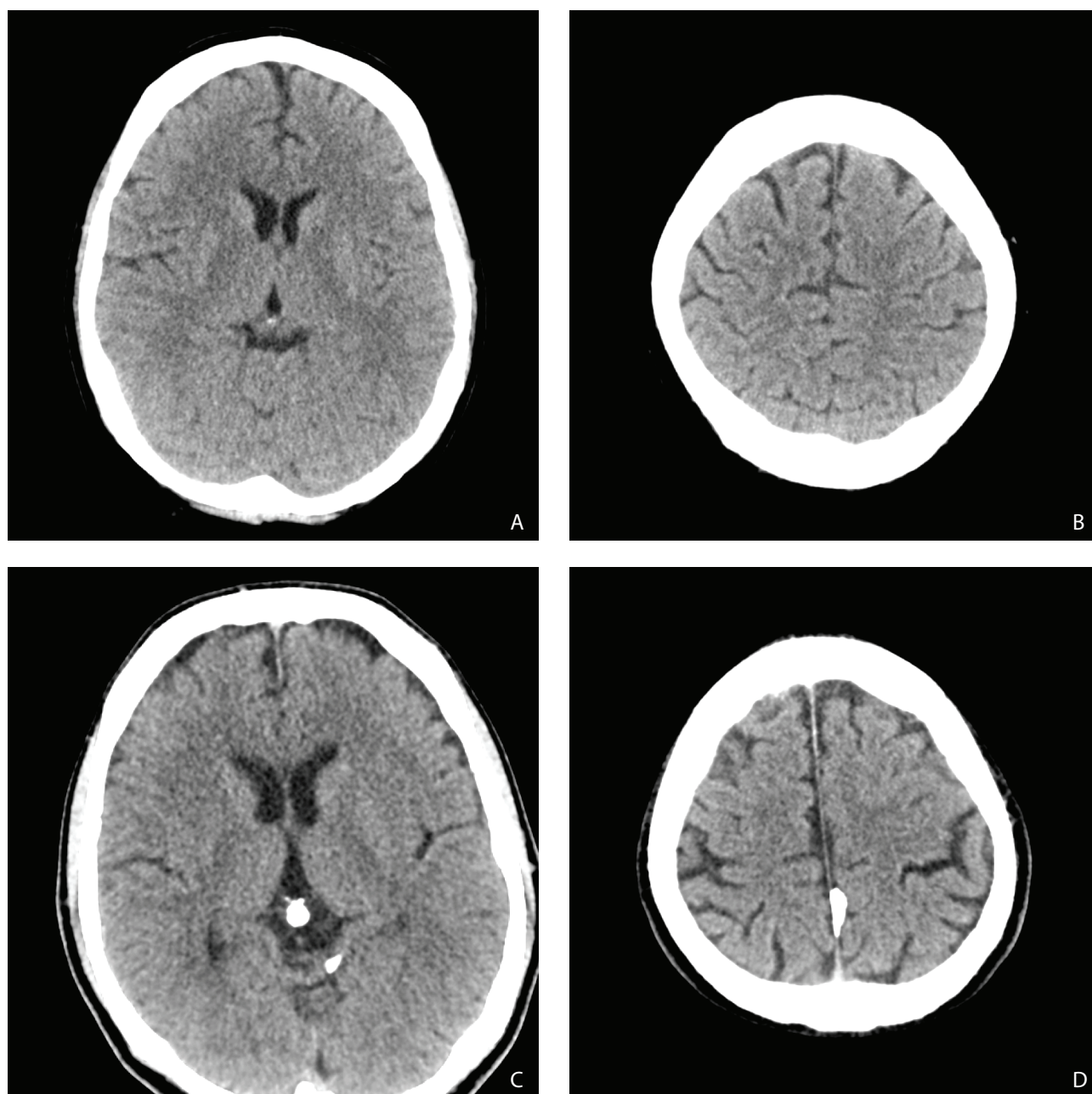
Due to high availability of medical imaging and standards of medical care, the situation in well developed countries is – from the point of view of radiation safety – paradoxically worse. The average medical radiation ef-

fective dose to the U.S. population showed an increase of 600% in a single generation, reaching the annual per capita value of 3.0 mSv in 2006, i.e. exceeding the average annual exposure from natural background of 2.4 mSv (ref.<sup>7</sup>). From 1995 to 2007, the number of visits to U.S. emergency departments that included a CT examination increased from 2.7 million to 16.2 million, constituting an almost six-fold increase with an exponential growth rate of 16% per annum<sup>8</sup>.

It should be stressed that CT is by far the most significant contributor to the collective dose among all medical diagnostic procedures in developed countries. In the

United States, CT accounts for one half (1.47 mSv) and nuclear medicine for one quarter (0.77 mSv) of the annual per capita effective dose received from all medical procedures (3.01 mSv). If the contribution of nuclear medicine studies is omitted, CT accounts for two thirds of the per capita effective dose from all radiologic procedures, including interventional ones (2.24 mSv annually) (ref.<sup>1,7</sup>).

Available data from other well developed (Level I) countries show that CT (0.87 mSv) accounts for approximately 44% of the effective dose from all medical procedures (2.00 mSv per person annually)(ref.<sup>9</sup>).



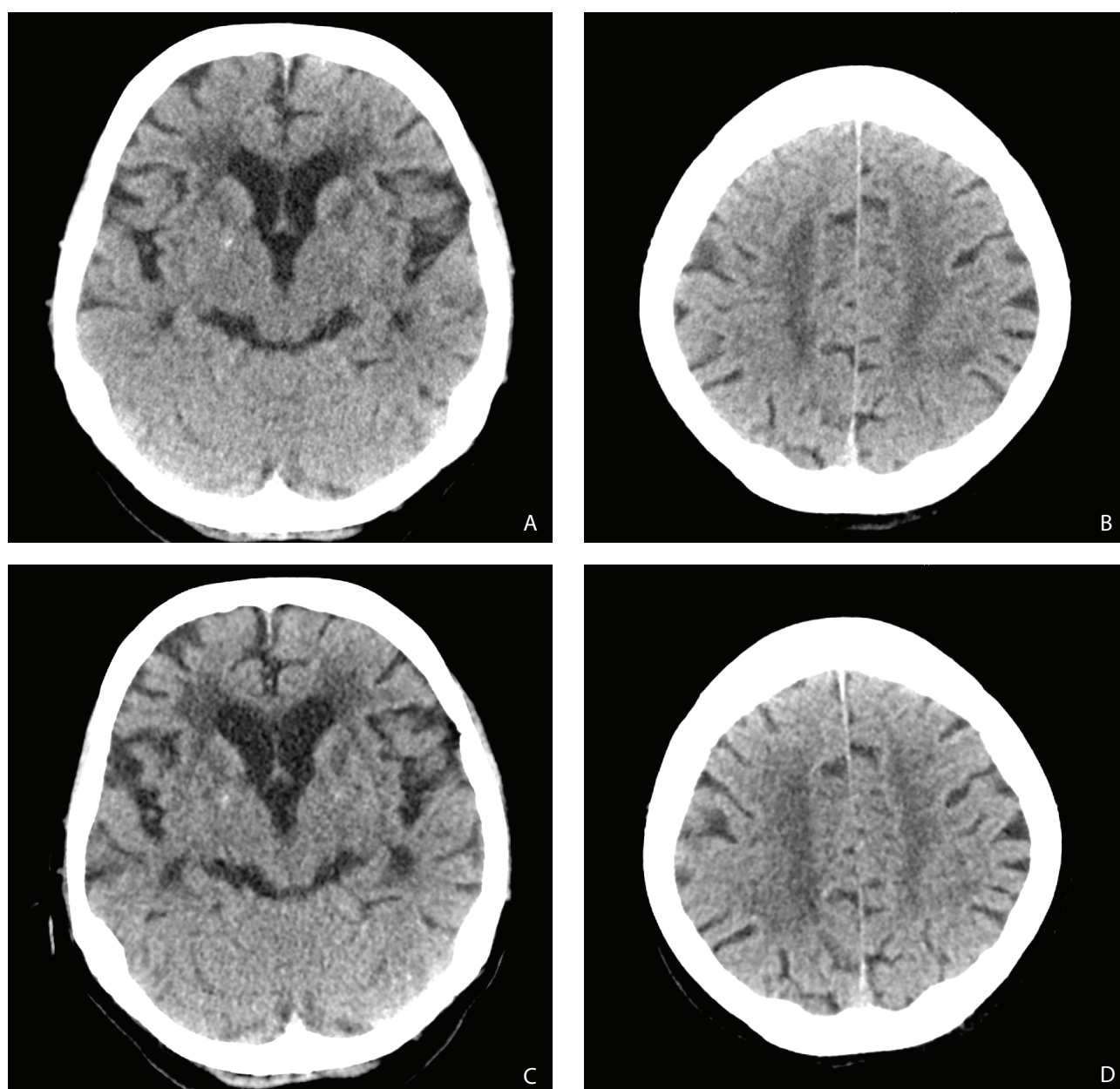
**Fig. 1.** Comparison of normal head MDCT scans reconstructed with FBP in a 35-year-old male (A and B; CTDIvol = 34.03 mGy) and IRIS in a 46-year-old male (C and D; CTDIvol = 22.73 mGy). The differentiation between gray and white matter, sharpness of contours, and image noise are comparable. The image texture of IRIS scans (C and D) is slightly different, also known as “blotchy” appearance, however, the diagnostic value is fully comparable. The image quality was rated with score 2 in both cases by both reviewers.



Although quantification of estimated cancer risk from CT scans is a controversial way of expressing the CT dose concerns, it has been estimated that between 0.7% and 2.0% of new cancer cases in the United States may be solely attributable to CT scanning<sup>3,10</sup>. Based on the fact that there are approximately 1.5 million new cancer cases in the United States each year, CT might be the cause of 10 000 to 30 000 new cancers annually. Thus, the need for standardization, optimization, and stringent adherence to ALARA (“as low as reasonably achievable”) principles is of utmost importance. Nonetheless, even recent publications indicate that there is substantial variance of doses applied for the same types of CT procedures on different

scanners and at different institutions as well as significant potential for reducing radiation dose in routine CT examinations<sup>11,12</sup>. A multicentric study from California showed a great deal of variance with a 20-fold difference across effective doses applied at routine head MDCT scans among four institutions: median of 2 mSv with absolute range of 0.3 – 6 mSv (ref.<sup>11</sup>).

In the past three decades, various dose reduction strategies have been implemented by CT scanner manufacturers such as automated tube current modulation, peak kilovoltage optimization, x-ray shutters for over-ranging, high pitch scanning, adaptive noise filtering, increasing detector efficiency and so forth<sup>13-15</sup>. Although some of



**Fig. 2.** Scans of suboptimal / limited diagnostic quality acquired in the same 88-year-old female who entered the study twice. Both FBP (A and B; CTDIvol = 33.70 mGy) and IRIS scans (C and D; CTDIvol = 21.69 mGy) show increased image noise level, indistinct delineation between normal and altered white matter, and arteficially increased attenuation at the interface between the skull and cerebral surface. In terms of image quality, the FBP scans (A and B) were rated 3 by both reviewers and IRIS scans (C and D) were rated 3 and 4 by respective reviewers. Still, the extent of chronic ischaemic changes including the lesion within the left anterior limb internal capsule can be appreciated in both scans.

**Table 1.** Comparison of radiation exposure parameters between groups of FBP and IRIS scans.

	FBP (n=200)	IRIS (n=200)	% reduction
CTDIvol [mGy]	33.3 ± 2.1	22.4 ± 1.6	- 32.7%
DLP [mGy.cm]	589.7 ± 64.2	396.2 ± 41.4	- 32.8%
Effective dose [mSv]	1.47 ± 0.26	0.98 ± 0.15	- 33.3%
Organ dose to the lens [mGy]	40.0 ± 3.3	26.6 ± 2.0	- 33.5%

Values are expressed as mean ± standard deviation. FBP = filtered back projection; IRIS = iterative reconstruction in image space; CTDIvol = volume computed tomography dose index; DLP = dose length product

**Table 2.** Results of qualitative image analysis for readers 1 and 2.

Visual score	FBP (n=200)		IRIS (n=200)	
	Reader 1	Reader 2	Reader 1	Reader 2
1	0	0	0	0
2	180	177	165	168
3	20	22	34	32
4	0	1	1	0
5	0	0	0	0

FBP = filtered back projection; IRIS = iterative reconstruction in image space. Visual scores: 1 = very low noise, optimal diagnostic quality; 2 = standard noise, good diagnostic quality; 3 = increased noise, diagnostic quality; 4 = high level noise, limited diagnostic quality; 5 = unacceptable noise, non-diagnostic scan.

these tools enabled dose savings of the order of tens of percent, the overall radiation load to the population has not begun to taper<sup>1,3</sup>. This can be easily explained by the fact that all those radiation dose reduction measures still do not outweigh the rapidly growing number of CT procedures.

The most straightforward approach to lowering CT dose is an overall reduction of tube current and, if possible, of tube kilovoltage. Recently introduced techniques of iterative CT image reconstruction benefit from inherent low image noise levels and have already proved their ability to decrease radiation exposure by tens of percent compared to standard FBP (ref.<sup>5,6</sup>). Since 2009, multiple studies have confirmed the ability of IR to achieve robust image quality with up to 60% dose reduction in abdominal, chest, cardiac, vascular, and colon MDCT studies<sup>5,6,16-24</sup>.

Head CT examinations are of the most common of CT indications. In the United States, CT head scans represent the second most common indication for CT and constitute 28.4% of all CT examinations, surpassed by only abdominal/pelvic CT studies with 31.7% of the total<sup>1,7</sup>. It is therefore surprising that much less attention has been attracted to the dose reducing potential of IR in head CT rather than in body CT examinations, notwithstanding the considerable radiosensitivity of the eye lens. This was also one of the major reasons why we decided to perform this study.

Only recently, first few papers on the use of IR in head MDCT have been published<sup>25-28</sup>. Three of the four studies dealt with the use of adaptive statistical iterative reconstruction (ASIR). ASIR is not a pure iterative reconstruction technique as it utilizes FBP for calculating an initial image data set in order to speed up the reconstruction process. Then, iterative algorithms are applied to this data set in order to reduce image noise. In clinical practice, one

can use variably blended images with individually adjusted ratios of FBP and ASIR techniques.

In the study of Ren et al.<sup>25</sup>, forty patients received two complete non-helical brain MDCT studies in a single session, one using 300 mAs and one 200 mAs of fixed tube current – time product. No significant differences in image qualities were found between the FBP reconstruction technique with 300 mAs and 50% ASIR blending with 200 mAs. Except for CTDIvol and DLP, no radiation dose parameters were evaluated. The major disadvantage of this study is the fact that all subjects underwent two complete CT head scans in one session thus contradicting the ALARA principles.

Kilic et al.<sup>26</sup> retrospectively evaluated 149 adult non-helical head MDCT scans divided into two groups, standard (FBP) and low (ASIR) dose. They used a fixed blend of 70% FBP and 30% ASIR in the low dose group and achieved effective dose reduction of 31% (1.6 mSv with ASIR) compared to standard dose group (2.3 mSv with FBP). The effective dose was estimated by multiplying DLP by a conversion factor of 0.0021. No significant difference in diagnostic acceptability and artifacts was noted between groups. For posterior fossa scanning, 140 kVp tube voltage was used which lead to high CTDIvol values in both standard dose (93.49 mGy) and low dose (69.14 mGy) groups, thus increasing the radiation load near/in the area of the eye lens. However, no eye lens dose calculations or measurements were provided.

Rapalino et al.<sup>27</sup> compared 50 helical head MDCT scans reconstructed with FBP (120 kV; 175 mAs with fixed tube current, CTDIvol of 66.51 mGy) and 100 reduced-dose scans (120 kV; 140 mAs with fixed tube current; CTDIvol of 49.70 mGy) reconstructed at six predefined levels of ASIR blended with FBP. The effective dose was estimated by multiplying DLP by a conversion factor of 0.0021 and yielded 2.66 mSv for higher dose

scans and 1.95 mSv for lower dose scans, respectively. Signal-to-noise ratios of the reduced-dose scans were significantly higher at ASIR levels of  $\geq 60\%$  compared to routine-dose FBP scans. Also, contrast-to-noise ratios were significantly higher at ASIR levels of  $\geq 40\%$ . Significant improvements in perceived image noise, artifacts, and grey-white matter differentiation were noted at ASIR levels  $\geq 60\%$ .

All three studies dealt with blended FBP and IR techniques (ASIR). The only head MDCT study using a reconstruction algorithm based purely on IR techniques is the study of Korn et al.<sup>28</sup>, utilizing iterative reconstruction in image space (IRIS). Ninety consecutive patients were randomly assigned to undergo helical brain MDCT reconstructed with both FBP and IRIS, using either standard dose (320 mAs; CTDIvol 60.1 mGy), 15% (275 mAs; CTDIvol 51.8 mGy), or 30% dose reduction (225 mAs; CTDIvol 42.3 mGy). The effective dose which was estimated by multiplying DLP by a conversion factor of 0.0023 yielded 2.2 mSv, 1.8 mSv, and 1.5 mSv in respective categories. IR resulted in lower image noise and higher contrast-to-noise levels at all dose levels. Image quality and overall diagnostic acceptability were considered significantly lower at 30% dose reduction. Based on linear regression analysis, the authors state that standard contrast-to-noise levels may be obtained at about 20% dose reduction when IR is used.

None of these four IR based MDCT head studies utilized automatic tube current modulation or provided measurements of organ dose to the eye lens. But in fact, it is the eye lens which is the most endangered organ in terms of radiation damage in adult CT head scans. Compared to sequential (non-helical) CT acquisitions aligned with orbito-meatal line where the eye lens might be excluded from direct irradiation due to proper gantry tilt, helical CT acquisitions expose the lens to the primary beam much more frequently since gantry tilt is often limited or even not allowed in many helical MDCT systems. Moreover, based on recent epidemiological evidence, the International Commission on Radiological Protection (ICRP) issued a new statement in April 2011 lowering the threshold in absorbed dose for the lens of the eye from 2.0 Gy to 0.5 Gy in order to reduce the risk of radiation induced cataract development<sup>29</sup>.

The potential of dose savings in head MDCT utilizing just iterative reconstruction has recently been shown in the aforementioned studies<sup>25-28</sup> where the researchers reached effective dose reduction ranging from approximately 20 to 33% compared to standard protocols. None of these studies included more than 150 subjects or dealt with eye lens dose measurements.

The results of our clinical study with a total of 400 subjects included offer the first clinical observations of combining iterative reconstruction algorithm with automatic tube current modulation in order to further reduce both the effective and particularly organ dose to the eye lens in helical head MDCT scans. Our routine institutional FBP protocols utilize carefully reduced reference mAs settings together with automatic tube current modulation in order

to fulfill ALARA objectives while maintaining acceptable image quality. Compared to European Commission Quality Criteria for MDCT (ref.<sup>30</sup>) which set CTDIvol of 60 mGy as a reference standard for head scans, our FBP protocols alone offer 44% dose reduction against the standard of reference (CTDIvol of 60 versus 33.3 mGy). Further, if we add the synergic effect of the iterative reconstruction in image space, the resulting dose reduction yields 63% against the reference standard (CTDIvol of 60 versus 22.4 mGy).

Despite the fact that the eye lens was exposed to the primary beam virtually in all subjects of our study, the average organ dose to the eye lens (26.6 mGy) remained 19 times lower than the new strict threshold of 500 mGy for absorbed dose as stated by ICRP standards<sup>29</sup>. These results are already comparable to average eye lens dose achieved in non-helical CT scans performed in tilted axial mode:  $18.1 \pm 7.6$  mGy with automatic tube current modulation switched off and  $15.6 \pm 4.2$  mGy with automatic tube current modulation switched on<sup>12</sup>.

This is also the first study on patients in routine clinical settings, based on eye lens dose calculations in head MDCT protocols utilizing IR algorithms. Both effective and eye lens doses were calculated by a numerical model (ImpACT software). In a limited number of subjects, we attempted to calibrate the data acquired from a mathematical model using direct thermoluminescent dosimetry. The results of direct eye lens dose measurements were even 15% (FBP) or 14% (IRIS) lower than numerical simulations provided by the dedicated software. Considering the remarkably different ways of obtaining organ dose values between these two methods, the difference of the order of 15% seems rather low if we take into account the methodological disparity of the two approaches. The observed difference might be attributed to the fact that the eye lens exposure dramatically changes during the x-ray tube rotation: the eye lens is exposed to maximum dose input in a range of anteroposterior projections whereas in posteroanterior directions the x-ray beam is markedly attenuated by calvarium and skull base before it reaches the eye lens. This effect may show a great deal of interindividual variability due to unequal calvarium thickness, actual cut plane orientation (e.g. whether the plane containing the lens also includes the pyramids) and so forth. Therefore, it is virtually impossible to build a precise mathematical model for eye lens dose estimations. Nevertheless, our calculated and measured organ doses did not differ remarkably, thus suggesting clinically acceptable accuracy of the numerical model.

The achieved effective and organ doses in our study population are at the very low end of published ranges<sup>1,11-12,25-28</sup>. Albeit undoubtedly beneficial from the radiation safety point of view, the study might have limitations, namely decreased image quality and the inferior diagnostic performance of such scans. Due to inherently unfavorable intracranial signal-to-noise ratios, minor attenuation differences between grey and white matter, and shielding of brain tissue by the skull bones, head CT scans generally require high-dose protocols set up for boosting contrast-to-noise ratios. For example, a classic neuroradiologic issue



of acute ischaemia detection requires exceptional image quality in order to identify subtle differences in grey matter attenuation. On the contrary, the vast majority of non-urgent head CT scans are for much less demanding issues in terms of contrast-to-noise ratios, such as detection of space occupying lesions, lacunar infarctions, calcifications, acute haemorrhage, or assessment of ventricles/subarachnoid CSF spaces. The same applies to almost all follow-up CT studies. The protocols presented in our study were set up and used in non-emergency cases only. It should be mentioned that our institutional emergency head CT protocols are based on higher mAs settings and solely on FBP algorithms in order to reduce the reconstruction time to minimum.

Although there was a slight, yet statistically significant decrease in signal-to-noise ratios in IRIS scans, the analysis of subjective image quality perception showed no significant differences between FBP and IRIS groups. Of 400 scans, only two scans (0.5%) were rated as of limited diagnostic quality. It is debatable whether such degree of dose reduction might theoretically result in impaired diagnostic performance, however, this problem is beyond the scope of our study and will require future intraindividual comparative studies in large cohorts of patients. Nevertheless, 99.5% of scans were considered to be of adequate image quality and our reduced dose IRIS protocol became a routine non-emergency head CT protocol. Also, we have not encountered a clinical case of incorrect or incomplete CT diagnosis which might have been attributable to insufficient diagnostic value of these low dose head CT scans.

In conclusion, our results show that combination of dose reducing strategies, namely iterative image reconstruction and automatic tube current modulation, is capable of significant radiation dose reduction, particularly in terms of organ dose delivered to the eye lens which is several times more radiosensitive than previously thought. The synergic effect of both techniques allowed us to routinely obtain non-emergency helical head MDCT scans with only 37% of the radiation dose set as a reference standard for head scans. The average organ dose to the eye lens achieved with our protocol is already comparable to organ dose achieved in standard non-helical MDCT scans performed in tilted axial mode where the eye lens is not exposed to the primary beam.

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## CONFLICT OF INTEREST STATEMENT

The authors state that there are no conflicts of interest regarding the publication of this article.

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