Significant reduction of radiation dose and DNA damage in ¹⁸F- FDG whole-body PET/CT study without compromising diagnostic image quality

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ABSTRACT
Reduction of radiation dose from medical investigations still remains an important strategy. The combined effect of the reduced injected activity of ¹⁸F – FDG, low tube voltage & iodine concentration with iterative reconstruction on image quality, radiation dose, and DNA damage in patients undergoing PET/CT examination were examined. The study includes 16 patients who underwent PET/CT investigation twice using two different protocols; standard & new. A new protocol was followed during follow-up after 4–6 months. All acquisition and reconstruction parameters were the same in both protocols, except administered activity, iodine concentration and CT tube voltage which was reduced. Image quality was assessed using various parameters. Effective dose from PET/CT was assessed using CTDivol and ICRP coefficients. DNA damage analysis was performed using comet and γ-H2AX assay. No significant difference was noted in quality parameters between two protocols (p > 0.05) except CT noise level (p < 0.05). Mean iodine dose, total radiation dose, mean foci and TM in the new protocol were found significantly lower than standard PET/CT (p < 0.05). There were 26.68% reduction in radiation dose, 10% reduction in contrast load, 20.31% reduction in the number of foci and 17.67% reduction in TM was noted with optimized protocol.

1. Introduction
Positron emission tomography/computed tomography (PET/CT) has evolved as a noninvasive and powerful hybrid imaging tool in the diagnosis, management and follow-up of various diseases and cancers based on functional information. The combination of CT with PET increases the diagnostic information with the additional advantage of anatomical localization in a single image (Griffeth, 2005). Because of dual imaging modality, it leads to increased radiation dose burden to the patients in comparison to individual CT or PET (Brix et al., 2014). The increased radiation dose ultimately enhances DNA (deoxyribonucleic acid) damages and associated risks in the patients (Prasad et al., 2019). These risks are more in patients visiting for multiple follow-up PET/CT or other radiological investigations.

Many tools and strategies have been adopted in PET/CT to minimize the radiation dose to patients (Delbeke et al., 2006; Kanematsu et al., 2014; Nakamoto et al., 2018; Sánchez-Jurado et al., 2014). In CT, resulted dose to patient depend upon tube voltage (kVp) & tube current (mA) (Nakaura et al., 2012; Prieto et al., 2018). Previous studies have reported that kVp and mA have a direct influence on effective dose and image quality (Lira et al., 2015). Since PET scan has substantially low spatial resolution and higher noise, therefore it is important to get CT images without compromising diagnostic quality to maintain the efficacy of integrated PET/CT (Townsend et al., 2004). The additional contributing factor of radiation dose is the use of iodinated contrast media (ICM) during the PET/ CT procedure. The high-density contrast media increases the attenuation of radiation inside the body resulting in enhanced image quality (Aschoff et al., 2012). However, increased x-ray absorption by contrast material further increases the radiation dose to the patient (Sahbaee et al., 2017).

The most significant agent that induces double-strand break (DSBs) is ionizing radiation. The direct effect of diagnostic dose of radiation and induction of DNA damage in patients have been studied by many authors (Mondal et al., 2019; Shi & Tashiro, 2018). Gamma H2AX foci and comet assay have been used as a potential biomarker to estimate DSB caused by ionizing radiation and contrast media in medical applications (Piekowiak et al., 2015; Santivasi & Xia, 2014).
The use of ionizing radiation in the routine practice of PET/CT is a major concern because of the increased risk of genetic disorders or cancer development (Huang et al., 2009). The total effective radiation dose received by patients from whole body $^{18}$F FDG PET/CT examination was found in a range of 15–30 mSv (Huang et al., 2009; Nautiyal et al., 2019). Although, out of the total combined dose, the majority of radiation dose contributed by CT alone (Huang et al., 2009). Therefore, lowering the CT tube voltage and iodinated contrast media concentration along with the reduction of total administered $^{18}$F-FDG activity to the patients seems a promising strategy to minimize total radiation dose, total iodine load, and DNA damage while maintaining imaging quality.

The study purpose was to investigate the combined effect of the optimized weight-based injected dose of $^{18}$F-FDG in PET and the use of low CT tube voltage & iodine concentration with iterative reconstruction ASiR (adaptive statistical iterative reconstruction) 100% on image quality, total radiation dose, and DNA damage in patients undergoing whole-body PET/CT examination, and compare it with the routine standard protocol of PET/CT.

2. Materials and methods

This prospective study includes 16 (10 females & 6 males, mean age 54.62 ± 7.83) patients with various oncology histories who visited PET/CT department twice for the investigation. The study was conducted between Jun 2017 and December 2018. The study was duly approved by the institutional ethics board and written informed consent was obtained from all participants. A detailed flow chart of the study design is mentioned in Figure 1.

2.1. Patient selection

Eligibility criteria for participation were decided to generate consistent and reliable results of image quality, total radiation dose, and DNA damage in a patient population. Inclusion criteria were (a) patients stick to routine follow-up for the last one year; (b) patients with body weight (40–65 kg); and (c) patients of different cancers except for liver metastasis. The exclusion criteria were (a) patients with a minimum interval of 4–6 weeks from last chemotherapy, radiation therapy, or another contrast-enhanced radiological investigation; (b) patients with raised serum creatinine level; (c) patients with a previous history of iodine contrast media allergy; (d) liver metastasis; and (e) unable to give consent.

2.2. Patient preparation

All patients were well prepared before the WB PET/CT procedure. The patients were asked for overnight fasting. Any intravenous fluid with dextrose content was stopped 24 h before the investigation. Patients were asked to remain well hydrated before the study. Patients were asked for a previous history of allergy or any renal diseases. The patients were explicitly asked for the date of their last chemotherapy, radiotherapy, or any other radiological investigation.

2.3. Acquisition protocols

Whole-body PET/CT (WB PET/CT) was performed using GE Discovery 690 system with a 64-slice light speed VCT (GE Healthcare, Israel). All participants underwent $^{18}$F-FDG WB PET/CT investigation twice using different protocols; standard & new. PET/CT using new protocol was performed 4–6 months after standard WB PET/CT.

2.3.1. Standard protocol

$^{18}$F-FDG was administered intravenously with 8MBq/kg (430.5 ± 49 MBq). Following injection, patients were asked to sit comfortably in an isolation room for 60 min. The patients were asked to drink 1 liter of plain water as negative contrast. Before taking the patients for scanning, CT tube warmup, fast calibration, and daily PET quality control test were performed in the morning using a $^{60}$Ge rod source. After 60 min of post-injection, patients were asked to void. Thereafter, patients were asked to lie down on the table in a supine position with their hands in a resting position. Following the positioning low-dose CT scout view, WB contrast-enhanced computed tomography (CECT) and PET was acquired over 7–8
Table 1. Acquisition and reconstruction parameters of PET/CT examination.

| Parameter                        | Standard protocol | New protocol |
|----------------------------------|-------------------|--------------|
| Administered activity (MBq/kg)   | 8                 | 5            |
| Contrast media concentration (mgI/mL) | 300             | 270          |
| Tube voltage (kVp)               | 120               | 100          |
| Tube current time product (mAs)  | Auto (150–250)    |              |
| Slice thickness/interval (mm)    | 5/5               |              |
| Helical pitch (mm)               | 1.37              |              |
| Rotation time (s)                | 0.5               |              |
| Scan field of view (mm)          | 500               |              |
| Reconstruction algorithm (CT)    | 100% ASiR         |              |
| Matrix (CT)                      | 512               |              |
| Matrix (PET)                     | 192               |              |
| Reconstruction algorithm (PET)   | OSEM              |              |
| Iterations & subsets             | 2 & 24            |              |
| Time per bed (min)               | 2                 |              |

OSEM = Ordered subset expectation maximization, ASiR = adaptive statistical iterative reconstruction

bed positions. Before starting the transmission scan, an intravenous injection of non-ionic contrast media (Omnipaque, GE Healthcare) with a concentration of 300 mgI/mL was administered based on patient body weight (1.4 mL/kg) using a pressure injector having a digital display system (Perrin et al., 2018). The total administered volume of contrast medium was 75.33 ± 8.85 mL with a flow rate of 2–3 mL/s. Detailed acquisition and reconstruction parameters are mentioned in Table 1.

2.3.2. New protocol
All techniques & acquisition parameters were the same as standard protocol, except 18F-FDG injected activity which reduced to 5MBq/kg (269.06 ± 31.63 MBq), iodine concentration, which reduced to 270 mgI/mL (Visipaque, GE Healthcare), and CT tube voltage, which reduced to 100 kVp.

2.4. Image analysis
Patient images were transferred to Advanced work station 1 (ADW1) for processing and evaluation. The liver was selected as a reference site for image quality assessment in PET/CT images.

2.4.1. Assessment of CT quantitative parameters
Quantitative measurements were performed by drawing circular regions of interest (ROIs) within the liver (target) and muscle (background). The diameter of ROI was 150 mm². From all ROIs average, CT values were measured in the unit of Hounsfield units (HU). All measurements were performed at the same anatomic levels (Figure 2a, b). The quantitative parameters used were:

(i) Image noise, which was calculated by mean SD of HU measured in different ROIs placed over the liver.

(ii) SNR (Signal to noise ratio) was estimated using formula 1.

\[
SNR = \frac{MeanHU_{\text{Liver}}}{\text{ImageNoise}}
\]

Where mean HU is mean Hounsfield unit

(i) CNR (contrast to noise ratio) was estimated using the following formula 2.

\[
CNR = \frac{MeanHU(\text{liver}) - MeanHU(Bkg)}{\text{Noise}(\text{liver}) + \text{Noise}(Bkg)}
\]

Here, paravertebral muscle was selected as background. CNR was estimated on the four images of two different protocols. On each image, measurement was repeated three times and a mean CNR was calculated for each protocol.

(ii) Uniformity comparison between two different protocols was done using integral non uniformity (IU), which was calculated as follows (Bissonnette et al., 2008)

\[
IU = \frac{MeanHU_{\text{max}} - MeanHU_{\text{min}}}{MeanHU_{\text{max}} + MeanHU_{\text{min}} + 2000}
\]

Where mean HUmax is the maximum mean Hounsfield unit and mean HUmin is the minimum mean Hounsfield unit in multiple ROIs placed over the liver.

2.4.2. Assessment of PET quantitative parameters
The quantitative parameters we assessed were:

(i) % COV (coefficient of variation) was used to see the variability of counts in all patients. A 20 mm sphere volume of interest (VOI) was drawn in the center of the right lobe of liver (Figure 2c). Here, % COV was calculated using the following formula
\[
\%COV = \frac{SD\text{counts in ROI}}{Mean\text{counts in ROI} \times 100}
\]  

Where SD is the standard deviation

(i) M/B (maximum to background) ratio calculated by defining 10 mm VOI over center of right lobe of the liver and in descending aorta (Figure 2c, d). Thereafter, M/B ratio was estimated using following formula

\[
\frac{M}{B} \text{ratio} = \frac{SUV\text{max in Liver}}{SUV\text{max Descending aorta}}
\]

Where SUVmax is the maximum Standard Uptake Value

2.4.3. Assessment of qualitative parameters

Visual assessment of both set of PET/CT images was done by two independent PET/CT consultants and 1 radiologist (9, 3, and 8 years of experience in PET/CT) using a 9-point grading score. Image quality was assessed in terms of image noise, image sharpness, and overall quality of images. All images with average grading scores of 8–9, 6–8, and 4–6 were marked as excellent, good, and average, respectively. Whereas grading scores of less than 4 were considered as not reportable.

2.5. Radiation dose assessment

2.5.1. Estimation of external dose (CT)

Effective dose (ED) from transmission scan was assessed using CT Dose Index volume (CTDIvol) and Dose Length Product (DLP).

2.6. CTDIvol = CTDIw/pitch (6)

Where, CTDIw is weighted computed tomography Dose Index.

2.7. CTDIw = 1/3×CTDI\text{f enter} \text{100} + 2/3×CTDI\text{periphery} \text{100} \times 100

Pitch = table movement in 360-degree tube rotation/beam collimation

2.8. DLP = CTDIvol × L (mGy·cm) (7)

Where, L is scan length

Thereafter, total ED from the CT scan was estimated using the gender-specific conversion factor k (mSv/mGy·cm) (Inoue et al., 2015)

\[ ED = DLP \times \text{conversion factor} \]

2.8.1. Estimation of internal dose PET

Absorbed dose (DT) to different internal organs (T) from an intravenous injection of \(^{18}\text{F}-\text{FDG}\) was estimated by using fixed-dose coefficients recommended by the International Commission on Radiological Protection (ICRP) in Publication 106 (ICRP 2007) (International Commission on Radiological Protection ICRP, 2008)

\[
DT = A \cdot \Gamma_T^{FDG}
\]

Where \(\Gamma_T^{FDG}\) is the dose coefficient recommended by ICRP in publication 106 for different organs and tissue. Thereafter, ED from \(^{18}\text{F}-\text{FDG}\) WB PET scans was calculated by using the following formula

\[
ED = \sum_T w_T \cdot DT = A \cdot \sum_T w_T \cdot \Gamma_T^{FDG} = A \cdot \Gamma_E^{FDG}
\]

where \(w_T\) is Tissue weighting factor provided by ICRP Publication 103 and \(\Gamma_E^{FDG}\) is dose coefficient recommended by ICRP in publication 106 for the whole body.

2.9. DNA damage analysis

The magnitude of DNA damage was also assessed during the WB PET/CT study. The DNA damage analysis was performed for all patients who underwent WB PET-CT twice using different protocols. Immediately after completion of WB CECT imaging, 1 mL of blood sample was collected from each patient in a heparinized tube, diluted (1:1) with phosphate buffer saline (PBS) and processed for lymphocytes separation using Histopaque 1077 (Boyum, 1974). Further, these isolated cells suspended in buffer solution were processed for DNA damage analysis using single gel electrophoresis technique and Gamma H2AX assay. A blood sample before injecting \(^{18}\text{F}-\text{FDG}\) was kept as a control during all experimental procedures.

2.9.1. Single gel electrophoresis technique

The isolated lymphocytes were analyzed for DNA damage with a comet assay (Mondal et al., 2017). Briefing the procedure here, 1% of low melting agarose at 37°C, dissolved in PBS were mixed with the suspension of cells. Microscopic slides were prepared by coating melting agarose (1%) and the mixture was placed on the prepared slides. Further, the cell lysis, i.e., removing cell membrane and histones from DNA was done for 2 h at 4°C using cell lysis buffer solution (100 Mm EDTS, 2.5 NaCl, 1% Triton and 10 Mm Tris buffer of pH 10) were processed for the electrophoresis. An electrophoresis buffer was prepared (1 Mm EDTA and 300 Mm NaOH of pH 13–14) for keeping DNA to be unwrapped and denatured. For examination, the staining was done with intercalating dye and was visualized by the
epifluorescence microscope (Carl Zeiss Fluorescence) followed by the electrophoresis, which revealed the DNA break. Images were analyzed with the help of open comet (Boston) software. This software was used to estimate tail moment (TM) by computing the tail length.

2.9.2. Gamma H2AX assay
The isolated lymphocytes were first incubated at 37°C and 5% CO₂ for 30 min. Freshly prepared 4% paraformaldehyde was added to each slide and incubated at room temperature for 15 min. Thereafter, cells were washed three times with PBS. These cells were permeabilized on ice using Triton X-100: PBS (0.1% v/v) at room temperature for 15 min and washed again with PBS. These cells were blocked in PBS and phosphate buffer saline tween-20 (PBST) for 30 min and incubated with Primary mouse monoclonal anti-phospho histone-H2AX antibody (100 μl) kept for 2-h incubation at room temperature and washed with PBST. These cells were again incubated with 100 μl of secondary antibody (Alexa Fluor 488 goat anti-mouse IgG, 1:500) in dark conditions at room temperature for 60 min and washed four times with PBST. Further, these cells were evaluated using a fluorescent microscope (Leica DM300, Leica Microsystems, Wetzlar, Germany). Moreover, the number of foci counting and analysis were performed using imageJ software (Hernández et al., 2013).

2.10. Statistical analysis
Statistical analysis was performed using Origin Pro 2019 (OriginLab Corp., Northampton, MA, USA). All quantitative variables were denoted as mean ± SD. Paired sample t-test was used to compare the difference of quantitative image parameters, total effective dose (CT + PET), total iodine dose and DNA damage parameters between the two protocols. Mann-Whitney test was used to compare the qualitative image assessment results between both study protocols. For both tests, a p-values < 0.05 were perceived as statistically significant. Moreover, the Pearson correlation coefficient was used to estimate the relationship of patient age and weight with image parameters, total effective dose and DNA damage parameters during each protocol. Furthermore, a correlation was also observed between iodine dose, total effective dose and DNA damage parameters. Box and whisker plots were used to display and compare the distribution of image parameters, total effective dose, iodine dose, and DNA damage parameters between protocols. A line in the box was indicated as median value, whereas a rectangular marker inside the box was indicated as mean value. The end of whiskers described the minimum and maximum value of data, while the top and bottom parts of boxes represented the interquartile range (IQR).

3. Results
3.1. Patient demographics
Total 16 patients were included in the study (6 males, 10 females). All patients underwent WB PET/CT imaging twice using two different protocols (standard and new). Mean age and weight of patients was 54.62 ± 7.83 years (range 39–65 years) and 53.81 ± 6.32 kg (range 42–64 kg), respectively. Mean Capillary blood glucose (CBG) and creatinine of participants in two protocol was 108.25 ± 16.21 mg/dL (83–140 mg/dL), 109.87 ± 10.20 mg/dL (91–133 mg/dL) and 0.82 ± 0.17 mg/dL, 0.83 ± 0.15 mg/dL, respectively. Detailed patient demographics are mentioned in Table 2.

3.2. Image quality assessment
Mean results for image noise, SNR, CNR, IU, %COV and M/B ratio in the quantitative analysis are mentioned in Table 3 and 4. CT quantitative parameters do not show any significant difference in mean SNR, CNR, IU between the two study protocols (p >0.05) (Figure 3). In addition, the noise level in the new protocol was found significantly higher than the standard protocol (p < 0.05). Similarly, PET qualitative parameters also show no significant difference in % COV and M/B ratio between the two protocols (p >0.05) (Figure 4). There was a weak correlation observed in two imaging protocols between image quality parameters and age of patients except for IU and COV in both study protocols, which shows a moderate correlation with age (Table 5 and 6). Moreover, M/B ratio also shows moderate relation (r =0.48) with age in the new protocol. Weak and no significant correlation observed in both imaging protocol between image quality parameters and weight of patient except IU in standard protocols, which shows moderate negative correlation with weight (Table 7).

Mean scores of experts for quality assessment in terms of image noise, image sharpen, overall quality of CT and fused PET/CT images are summarized in Table 5. All qualitative parameters do not show any significant difference between the two protocols (p >0.05) (Figure 5).

3.3. Iodine load and total effective dose assessment
Detailed comparison of mean administered iodine dose, total effective dose received by patients in two different PET/CT protocols are mentioned in Table 3.

| Parameter          | Standard protocol | New protocol |
|--------------------|-------------------|--------------|
| Age (y)            | 54.62 ± 7.83 (39–65) | 53.81 ± 6.32 (42–64) |
| Male/female        | 6/10              |              |
| Body weight (kg)   | 53.81 ± 6.32 (42–64) | 108.25 ± 16.21 (83–140) |
| CBG (mg/dL)        | 109.87 ± 10.20 (91–133) | 109.87 ± 10.20 (91–133) |
| Creatinine (mg/dL) | 0.82 ± 0.17       | 0.83 ± 0.15   |

*Results displayed as mean ± SEM
The total administered volume of contrast media was the same in both study protocols (75.33 ± 8.85 mL). However, the mean iodine load in new protocol was reduced by 10% compared to the standard protocol.

**Table 3.** Comparison of mean iodine dose, total effective dose (CT + PET) & DNA damage in two PET/CT protocols.

|                        | Standard protocol | New protocol | P value |
|------------------------|-------------------|--------------|---------|
| Iodine dose (gm)       | 22.6 ± 2.65       | 20.33 ± 2.39 | < 0.05  |
| ED (mSv)               | 19.56 ± 2.53      | 14.34 ± 1.80 | < 0.05  |
| γH2AX-foci per cell    | 0.64 ± 0.13       | 0.51 ± 0.13  | > 0.05  |
| TM                     | 56.93 ± 16.84     | 46.87 ± 16.11| < 0.05  |

ED = Effective dose, TM = Tail moment
*Results displayed as mean ± SEM
**p value

The mean iodine dose (gm) received by patients in new protocol was significantly lower than the standard protocol (p < 0.05) (Figure 6).

The mean total effective dose received by patients in new protocol was reduced by 26.68% compared to standard protocol. The total effective dose (mSv) received by patients from new protocol was found significantly lower than the standard PET/CT procedure (p < 0.05) (Figure 7). A moderate negative correlation was observed between radiation dose and age of

**Table 4.** Mean Image noise, SNR, CNR, IU, % COV, M/B ratio measurements in two PET/CT protocols.

|                        | Standard protocol | New protocol | P value |
|------------------------|-------------------|--------------|---------|
| CT Noise               | 16.56 ± 2.69      | 17.32 ± 2.78 | < 0.05  |
| SNR                    | 7.33 ± 1.57       | 7.32 ± 1.52  | > 0.05  |
| CNR                    | 3.99 ± 1.56       | 3.99 ± 1.53  | > 0.05  |
| IU                     | 2095.04 ± 48.62   | 2092.76 ± 31.37| > 0.05 |
| PET % COV              | 4.19 ± 1.47       | 4.18 ± 1.34  | > 0.05  |
| M/B ratio              | 1.32 ± 0.15       | 1.30 ± 0.16  | > 0.05  |

SNR = signal to noise ratio, CNR = contrast to noise ratio, IU = Integral non-uniformity, COV = Coefficient of variation, M/B = maximum to background
*Results displayed as mean ± SEM
**p value

**Table 5.** Qualitative image quality assessment in two PET/CT protocols.

|                        | Standard protocol | New protocol | P value |
|------------------------|-------------------|--------------|---------|
| CT Image noise         | 8.12 ± 0.80       | 7.73 ± 1.03  | > 0.05  |
| CT Image sharpness     | 8.18 ± 0.75       | 8.06 ± 0.68  | > 0.05  |
| Overall quality        | 8.12 ± 0.71       | 8.07 ± 0.73  | > 0.05  |
| Fused PET/CT           | 8.62 ± 0.5        | 8.37 ± 0.61  | > 0.05  |

*Results displayed as mean ± SEM
**p value

**Table 6.** Association of age with quantitative image parameters, radiation dose and DNA damage parameters.

|                        | Standard protocol | New protocol |
|------------------------|-------------------|--------------|
| SNR                    | 0.3               | 0.21         |
| CNR                    | 0.2               | 0.2          |
| IU                     | 0.47              | 0.34         |
| COV                    | −0.44             | −0.32        |
| M/B ratio              | 0.12              | 0.48         |
| Total dose (mSv)       | −0.45             | −0.39        |
| Excess γH2AX-foci      | −0.39             | −0.41        |
| TM                     | −0.23             | −0.31        |

SNR = signal to noise ratio, CNR = contrast to noise ratio, IU = Integral non-uniformity
COV = Coefficient of variation, M/B = maximum to background, TM = Tail moment

*Results displayed as mean ± SEM
**p value
patient in both study protocols (Table 6). However, strong positive association was noted in both study protocols between radiation dose and weight of the patient (Table 7).

### 3.4. DNA damage analysis

Mean estimates of DNA damage parameters ie. γH2AX-foci and TM are summarized in Table 3. Mean γH2AX-foci and TM in new protocol reduced by 20.31%, 17.67%, respectively, compared to standard protocol. The mean number of foci and TM observed in patients from the new imaging protocol was found significantly lower than standard PET/CT protocol (p < 0.05) (Figures 8, 9). There was a moderate negative correlation observed in both study protocols between DNA damage parameters and age of the patient (Table 6). Similarly, a moderate positive correlation was observed in both study protocols between DNA damage parameters and weight of the patient (Table 7).

### 4. Discussion

Reduction of radiation dose from medical investigations still remains an important strategy for minimizing radiation-associated risk. In the present study, we have evaluated and compared the image quality, total effective dose and percentage of DNA damage for WB PET/CT protocol consist of optimized administered 18F-FDG activity, optimized tube voltage and iodine concentration of contrast medium with standard WB PET/CT protocol.

In the present study, we observed 26.68% reduction of total radiation dose by optimization of PET/CT protocol. Feng et al. also demonstrated that a combination of lower tube voltage and a lower concentration of contrast agent reduces effective doses in diagnostic CT scan by 25.7% (Feng et al., 2018). Our findings are in accordance with previous CT studies that showed effective reduction of radiation dose by the combination of low tube voltage and amount of contrast media (Kanematsu et al., 2014; Nakamoto et al., 2018; Nakaura et al., 2012).

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**Table 7.** Association of weight with quantitative image parameters, radiation dose and DNA damage parameters.

| Parameter         | Standard protocol | New protocol |
|-------------------|-------------------|--------------|
| SNR               | -0.002            | 0.09         |
| CNR               | 0.08              | 0.1          |
| IU                | -0.35             | -0.26        |
| COV               | 0.17              | 0.002        |
| M/B ratio         | 0.23              | 0.13         |
| Total dose (mSv)  | 0.71              | 0.72         |
| Excess γH2AX-foci | 0.62              | 0.67         |
| TM                | 0.65              | 0.62         |

SNR = signal to noise ratio, CNR = contrast to noise ratio, IU = Integral non-uniformity
COV = Coefficient of variation, M/B = maximum to background, TM = Tail moment

**Figure 7.** Comparison of total effective dose (CT + PET) between two study protocol. Significant reduction of total radiation dose (p-value < 0.05) is noted in new protocol as compared to standard study protocol.

**Figure 8.** Comparison of DNA parameters between two study protocol. Significant reduction of mean γH2AX-foci (a) p-value < 0.05 and mean TM (b) p-value < 0.05 is noted in new study protocol as compared to standard protocol.
Studies with the objective to minimize contrast media concentration during PET/CT investigation are less evident in the literature. As reported in many kinds of literature, minimizing the total load of ICM has several advantages in minimizing radiation dose, DNA damage and contrast-induced nephropathy compared to use of high concentration contrast material (Huang et al., 2009; Sahbaee et al., 2017). In the present study, the total load was reduced by the use of weight-adapted administration along with a lower concentration of ICM. The weight-adapted contrast protocol uses less volume than the fixed-dose protocol (George et al., 2016). We found that changing the iodine concentration of contrast media from 300 mg I/mL to 270 mgI/mL, significantly reduces total iodine load. The iodine concentration and volume used for tissue & organ enhancement in previous WB PET/CT studies were found relatively higher compared to our study (Barai et al., 2020; Beyer et al., 2005). In a cerebral CT angiography procedure, the concentration of contrast medium was reduced along with optimized tube voltage (Luo et al., 2014). In the present study too, we effectively reduced the concentration of contrast media along with CT tube voltage. The use of 100 kVp tube voltage considerably increases x-ray absorption voltage because of the attenuation coefficient of iodine, which increases while photon energy decreases (McCollough, 2002; Nakaura et al., 2011).

In the present study, following the optimization of protocol, the quality of CT and PET images of the liver have been extensively investigated and compared with the standard study protocol. Because of Poisson statics of positron emission in PET, the SNR of PET images rely on the administered activity and total acquisition time. Besides, CT exposure factors and ICM administration are essential for maintaining the image quality of organs and intravascular structures. In the present study, we did not observe any significant difference in qualitative and quantitative image quality parameters between both protocols except image noise in CT. Similar results have been seen in previous studies as well (Bernstine et al., 2014; Luo et al., 2014; Managing patient dose in computed tomography, 2000; Nakayama et al., 2005; Van Cauteren et al., 2017). Some studies demonstrated that image noise is a limiting factor for low tube voltage (Bushberg et al., 2011; Sigal-Cinquabre et al., 2004). However, this problem may be overcome by the use of ASIR reconstruction algorithms (Van Cauteren et al., 2017).

Because of dual imaging modality, the radiation risk is more in PET/CT compared to other diagnostics modalities. The γ-H2AX and TM are sensitive and rapid parameters for measuring DNA DSBs in PET/CT (Huang et al., 2009; Mondal et al., 2019). There are several studies revealed that radiation dose and contrast media both enhance the DNA damage in patients (Grudzinski et al., 2009; Piechowiak et al., 2015; Santivasi & Xia, 2014; Schumann et al., 2020). These high-density iodine molecules in contrast media absorb more radiation than human tissues and eject photoelectron, which causes further ionization and excitation in tissue. In the present study, we observed a considerable reduction of γ-H2AX foci and TM along by optimizing PET/CT protocol. Similar to our results, Popp et al also observed a significant reduction of γ-H2AX foci by optimization of tube current in a diagnostic investigation (Popp et al., 2016).

Meanwhile, we noted that the total effective radiation dose decreased as the age of patients increased in both study groups. Furthermore, it was noted that the total effective radiation dose increased as the weight of patients increased in both study groups. Similar findings were also revealed by previous authors (Kharbanda et al., 2015; Miglioretti et al., 2013; Vargas et al., 2012). Moreover, weak and no relationship noted between image quality and patient parameters, i.e., age and weight in both study protocols except for IU, %COV and M/B ratio. In the new study protocol, a moderate positive correlation was noted between M/B ratio and the age of the patient. A study performed with 120 kVp tube voltage revealed a significant positive correlation between image quality and patient age and a significant negative correlation with weight (Kalra et al., 2003; Roggenland et al., 2008). In both study
protocols, DNA damage decreases with patient age and increases with patient weight. Heavier patients receive more radiation doses due to automatically modulated mA, more administered activity and contrast media, which enhance DNA damage (Huang et al., 2009). We also noticed a significant increase in DNA damage with iodine load and radiation dose after taking all parameters together from both imaging protocol. Our results were in line with previous studies that demonstrated similar results (Nautiyal et al., 2019; Wang et al., 2013).

Our study has certain limitations, which need to be considered. First, the total number of patients was comparatively less because of the availability of the same patient in routine follow-up. The mean body weight of PET/CT patients in our study was relatively less than the European and American populations. Third, we measured only the combination of 100kVp, 270 mg/mL, and ASIR in CT. Future studies can be performed with the further reduction of tube voltage and contrast density with the use of interactive reconstruction techniques. Fourth, we didn’t measure the time for DSB repair in patients. Future studies can be executed to assess the DNA DSB induction and repair mechanisms.

5. Conclusion
We concluded that optimization of WB PET/CT protocol is feasible with reduced weight-based administration of $^{18}$F-FDG activity (5MBq/kg), combined use of 100 kVp tube voltage, 270 mg/mL concentration, and ASIR 100% in patients with normal body weight. This protocol able to maintain diagnostic image quality with a 26.68% reduction in total radiation dose, 10% reduction in contrast load, 20.31% reduction in numbers of γ-H2AX foci, and 17.67% reduction in TM compared to standard WB PET/CT protocol. The outcomes of this study may be of significance particularly in patients undergoing repeated follow-up studies in a short period.

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Disclosure statement
No potential conflict of interest was reported by the author(s).

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