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IMAGE QUALITY IN ABDOMINAL CT: A COMPARISON OF TWO RECONSTRUCTION ALGORITHMS IN FILTERED BACK PROJECTION (FBP)

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The articles are professional and scientific: results of research, technological assessments, descriptions of cases, etc.

Dear colleagues,

We present the issue of Medical Imaging and Radiotherapy journal, Volume 39 (2022). From this year on, the journal will be published annually. The editorial board of the journal is proud and happy that word has spread about our journal and that we are receiving manuscripts from different countries and on different topics. We would be very grateful if you could help us spread the word about our journal and invite your colleagues to submit their manuscripts to our international journal.

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Nejc Mekis
Editor-in-chief of MIRTJ

Spoštovane kolegice in kolegi!

Pred Vami je nova številka revije Medical imaging and Radiotherapy journal, letnik 39 (leto izdaje 2022). Od letošnjega leta naprej revija izhaja enkrat letno. V uredništvu nam je v veliko veselje, da se je dobro ime o naši reviji razširilo in da redno pridobivamo članke iz različnih držav na različne tematike. Prav tako bi bili zelo hvaležni za vašo pomoč pri informiranju kolegov o reviji in vabilu za oddajo člankov.

Revija še vedno ostaja brezplačna in prosto dostopna vsem bralcem na spletni strani revije in v bazah, ki revijo indeksirajo. Vabimo vas, da si ogledate spletno stran revije, ki je dostopna na povezavi http://mirtjournal.net/index.php/home. Na omenjeni spletni strani najdete vse potrebne informacije za pripravo in oddajo člankov.

Nejc Mekiš
Glavni urednik MIRTJ

Original article

IMAGE QUALITY IN ABDOMINAL CT: A COMPARISON OF TWO RECONSTRUCTION ALGORITHMS IN FILTERED BACK PROJECTION (FBP)

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ABSTRACT

Objectives: The aim of this study was to evaluate the effect of the choice of kernel on the image quality in abdominal CT images with a focus on liver lesion visibility.

Methods: In this comparative study, 84 abdominal CT examinations of patients with liver lesions that included parallel series reconstructed with two different kernels (B30 and B45) were analysed. A subjective assessment of image quality was performed using visual grading analysis based on anatomical criteria, liver lesion visibility and perceived image quality. Objective image quality was assessed using measurements of Hounsfield unit (HU) values (average and standard deviation) in abdominal organs and calculations of contrast-to-noise ratios (CNR).

Results: B30 kernel performed significantly better than B45 in all criteria except for sharpness. The most considerable improvement of the image quality was in terms of subjective experienced image noise, overall diagnostic image quality and visually sharp reproduction of liver lesions. The physical measurements showed that CNR increased by up to 46% when using B30.

Conclusions: Using a B30 kernel algorithm for image reconstruction reduces noise and thus improves image quality and diagnostic accuracy significantly relative to B45.

Key words: kernel, image quality, CT, noise reduction, liver lesions

Introduction

In computer tomography (CT) examinations, image quality depends on scanning parameters, reconstruction technique and parameters, together with scanners particularities. One of the factors that affect image quality and particularly image noise is the image reconstruction algorithm, also referred to as kernel. In filtered back projection (FBP)-based image reconstruction, images are obtained by filtering the projection data using a reconstruction kernel and then back projecting the filtered data to the image space (1). The kernels incorporate noise reduction, spatial resolution- and edge-increasing techniques that are applied to the raw data resulting from CT scanning. The choice of kernel always implies a trade-off between image noise and sharpness (spatial resolution) (2). CT images can be reconstructed multiple times with no additional radiation dose to the patient.

Different manufacturers operate with different designations for the kernels available on their CT-scanners. For example, GE uses more descriptive denominations (with kernels names like soft, detail, standard, bone, etc.) while others use codes (Phillips uses alphabetic denominations, Siemens uses codes, such as B30, B40, B45, B80, etc., while Toshiba uses FC08, FC12, FC30, etc.).

The detection and characterization of small focal lesions in parenchymal organs represent a challenge for the diagnostic radiologist and can have significant importance for a patient's further treatment. Reconstruction algorithms have an impact on image quality, i.e. to determine if adjustments in kernel reconstructions can improve the detection of parenchymal lesions.

Although iterative reconstruction (IR) is increasingly used as a result of its radiation dose reduction potential, FBP is still widely applied internationally due to some potential disadvantages of IR. These include increased implementation cost due to necessary purchases for every scanner or the inability to adopt this method at all because of older, incompatible scanners (1). Another disadvantage of IR is the usual change in noise texture compared to FBP images with which radiologists are more familiar, which may alter the radiologist satisfaction with the images and diagnostic confidence (3). Another reason FBP is still used is that applying the same reconstruction technique makes it is easier to compare with previous images. The purpose of this study was to evaluate the effect of the choice of kernel on the image quality in abdominal CT images with a focus on liver lesion visibility.

Material and methods

The CT scanners used in this study were Somatom Definition AS+ (128 slice), Somatom Definition Flash (2 x 128) and Somatom Sensation 64 (Siemens Medical Solutions, Forchheim, Germany). For a period of one year, all abdominal CT examinations included parallel series reconstructed with two different kernels (B30 and B45) in order to make it easier to compare the images with previous examinations. All examinations that showed liver lesions were included in the study (n=84). A post-hoc power analysis confirmed that the sample size was appropriate for detecting differences in image quality with a power of 80%.

Only the portal venous phases were evaluated. Scan timing was individualized using bolus-tracking with a threshold of 150 Hounsfield units (HU) in a region of interest (ROI) in the abdominal aorta on an axial image through the middle of the liver. The arterial phase was acquired using a delay of 25 seconds after reaching the threshold, and portal venous phase was acquired 30 seconds after the arterial phase. Iohexol (Omnipaque 350 mgI/ml, GE Healthcare) followed by 30 ml of saline was administered through an 18-gauge cannula placed in an antecubital vein. The contrast agent amount and flow were tailored to patient weight (<50 kg 120 ml and 3.2ml/s; 50–79 kg 150 ml and 4 ml/s; and >80 kg 180 ml and 4.8ml/s). The injection time was 37.5 s for all patients.

All examinations were performed at 120 kVp using automated tube current modulation (CareDose4D, Siemens) with 240 reference mAs. Pitch was set to 0,6 and the rotation time was 0.5 s/rotation. Both subjective and objective assessments of image quality were performed on images from the portal venous phase.

Patients' gender and age were retrieved from Picture Archiving and Communicating System (PACS) and, in order to compensate for the lack of information about patients' height and weight, effective diameter (eq 1) was used as an indicator for body habitus.

$$\text{Effective diameter} = \sqrt{anteroposterior\ diameter \times lateral\ diameter} \quad \text{(eq 1)}$$

Subjective assessment of image quality

The images were evaluated by two radiologists (with 5 and 12 years of experience) using relative visual grading analysis (VGA). The two image series were randomly displayed on the left and right monitor in PACS. A Sectra IDS7 (Linkoping, Sweden) PACS workstation with two diagnostic Eizo Radiforce MX241W monitors (Cypress, CA, USA) was used for image evaluation. The monitors' luminance was 320 cd/m^2, and the measurements were performed at a distance of 50–60cm from the monitor in an ambient lightning of 40–50lux. The radiologists evaluated the images independently, blinded to reconstruction kernel and without knowledge of the results of the physical measurements performed on the images. Radiologists were free to use all the tools available in PACS that are commonly used for clinical images (adjustment of window/level, magnification, etc.).

Table 1: Quality criteria used for visual image assessment

C1: visually sharp reproduction of the liver parenchyma
C2: visually sharp reproduction of the intrahepatic vessels
C3: visually sharp reproduction of liver lesions
C4: visually sharp reproduction of the spleen parenchyma
C5: visually sharp reproduction of the pancreas
C6: visually sharp reproduction of the kidneys and proximal ureters
C7: visually sharp reproduction of lymph nodes smaller than 15 mm in diameter
C8: image noise
C9: overall sharpness
C10: total assessment of diagnostic image quality

The criteria used in VGA (Table 1) were visualization of liver lesions (C3), perceived image quality (C8–C10) and a selection of anatomical criteria (C1–C2, C4–C7) from the European Guidelines on quality criteria for computed tomography (4). The '2 / -2' rating (Table 2) was used when the radiologists thought it could have diagnostic consequences, for example that one could overlook or not completely evaluate something seen on one of the images when looking at the corresponding image reconstructed with the other kernel.

Table 2: Scoring

–2: Images on left monitor are much better than images on right monitor
–1: Images on left monitor are better than images on right monitor
0: Images on left and right monitor are equivalent
+1: Images on right monitor are better than images on left monitor
+2: Images on right monitor are much better than images on left monitor

The results from the VGA were summarized using VGA scores (VGAS) (5) for every criterion calculated using equation 2.

$$\mathrm{VGAS}=\frac{\sum_{o,i} S_c}{N_i N_0} \qquad \text{(equation 2)}$$

where Sc represents the given individual scores for observer (o) and image (i), Ni represents the total number of images, and No represents the total number of observers.

Objective assessment of image quality

Attenuation (quantified as average HU) and noise (quantified as standard deviation HU) were measured in ROIs of approximately 12 mm in diameter placed on axial slices in paravertebral muscle, liver parenchyma, liver lesions, spleen, pancreas, aorta and fat tissue (Figure 1). To standardize measurements, ROIs were then copied and pasted on corresponding images reconstructed with the other kernel. CNR values were calculated using the following equation (6):

where CNR represents $(HU_{Organ} - HU_{Muscle}) / SD_{Muscle}$,

CNR for liver lesions were calculated using the following equation (6):

where CNR represents $(HU_{liver} - HU_{Lesion}) / SD_{Muscle}$

Noise difference was calculated using the equation (6):

$$\text{Noise difference} = \frac{noise\ 45 – noise\ 30}{noise\ 45} \times 100$$

where noise 45 and noise 30 is the SD measured in the liver on the images reconstructed with B45 kernel and B30 kernel, respectively.

Statistical analysis

Statistical analyses were conducted using SPSS for Windows version 27 (IBM Inc., Armonk, NY). The highlighted factors related to the distribution of data were: average, standard deviation, and lowest and highest value. The Shapiro–Wilk test was used to determine whether the data were normally distributed. Differences in physical image quality parameters between the groups were evaluated using a paired t-test. Differences in scores for subjective image quality were assessed using the Wilcoxon signed-rank test, while correlations between measured image quality parameters and criteria-based evaluations were analysed using Spearman's rank order. Inter-rater agreement was assessed using the weighted Cohen's kappa test with the following interpretation of agreement: 0.00–0.20 slight; 0.21–0.40 fair; 0.41–0.60 moderate; 0.61–0.80 substantial; and 0.81–1.00 almost perfect (7). Detailed analyses of percentage agreement were also used.

Ethical considerations

Institutional ethics review board approval was obtained (Research Committee of the Department of Medical Imaging at St. Olavs Hospital nr. 202012/21.04.2020). Written informed consent was waived due to the study's retrospective design. No personally identifiable information was recorded.

Results

A total of 84 examinations were assessed. Patient characteristics are presented in Table 3.

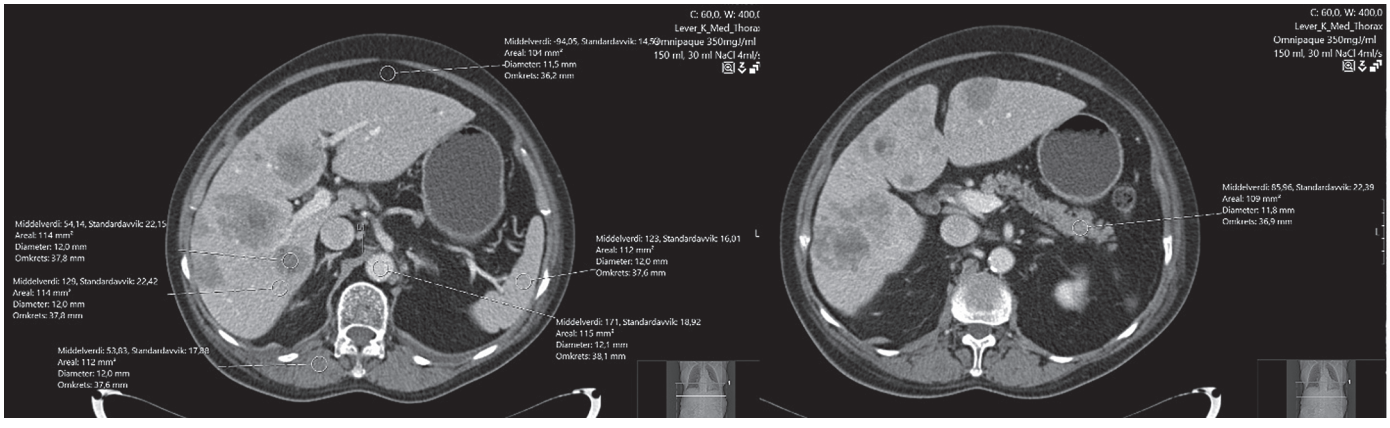

Figure 1: ROIs for the objective measurements of attenuation (quantified as average HU) and noise (quantified as standard deviation HU)

Table 3: Patient characteristics presented as average ± standard deviation (minimum – maximum)

Age	Gender (male/female ratio)	Effective diameter
64.47 ± 13.3 (35-89)	41/43	294 ± 38.3 (205-399)

Subjective assessment of image quality

The image quality differences made B30 the most preferred kernel option, and that kernel performed significantly better than B45 in all criteria except for overall sharpness (C9). These results are in line with the VGAS for each criterion that show the magnitude of the difference between kernels (Table 4) and the percentual distribution of difference evaluation scores (ure 2). The difference in favour of B30 is consistent and statistically significant.

The VGAS show that the most considerable improvement of the image quality when using B30 instead of B45 is in terms of subjective experienced image noise, overall diagnostic image quality and the visually sharp reproduction of liver lesions, while the effect on the reproduction of lymph nodes smaller than 15 mm in diameter is least significant. The differences in image quality between the two kernels were statistically significant for all criteria ($p<0.001$ for difference analysed using the Wilcoxon signed-rank test).

In almost 30% of cases, the images reconstructed with the B30 kernel were considered much better than the images reconstructed with the B45 kernel (Figure 2).

There was high level of agreement between the two radiologists regarding the preferred kernel for all criteria, with the exception of the visually sharp reproduction of the liver parenchyma and overall sharpness. However, in terms of the magnitude of the image quality difference between the two kernels, there was only fair inter-observer agreement (κ in the range of 0.2–0.4).

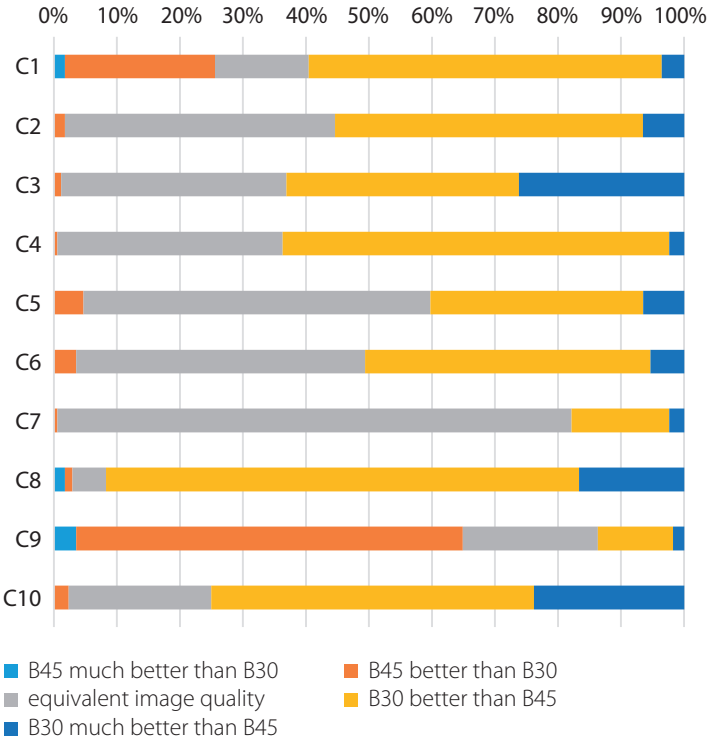

Figure 2: Comparison of the images reconstructed with the two kernels

Table 4: Results of criteria-based image quality comparation for B30 and B45 reconstruction kernels presented as VGA scores, preferred option, and percent agreement between the radiologists regarding preferred kernel

Criteria*	VGAS (B30>B45)	Preferred kernel	Percent agreement
C1	0.345	B30	67
C2	0.601	B30	96
C3	0.880	B30	98
C4	0.655	B30	99
C5	0.423	B30	98
C6	0.524	B30	95
C7	0.196	B30	99
C8	1.036	B30	94
C9	-0.529	B45	39
C10	0.964	B30	95

* C1 visually sharp reproduction of the liver parenchyma, C2 visually sharp reproduction of the intrahepatic vessels, C3 visually sharp reproduction of liver lesions, C4 visually sharp reproduction of the spleen parenchyma, C5 visually sharp reproduction of the pancreas, C6 visually sharp reproduction of the kidneys and proximal ureters, C7 visually sharp reproduction of lymph nodes smaller than 15 mm in diameter, C8 image noise, C9 overall sharpness, and C10 total assessment of diagnostic image quality

Objective assessment of image quality

Noise levels measured in all organs were substantially lower and CNR considerably higher for the B30 kernel (Table 5). The differences were statistically significant and the percentual differences were around 45% in all organs.

The correlation between the subjective assessed score for image noise and measured noise in the liver, spleen and muscle was statistically significant. The correlation between the subjective evaluation of the reproduction of liver lesions and the measured image noise both in the liver and in liver lesions was statistically significant.

Discussion

This study compared abdominal CT scans reconstructed with two different kernels in routine clinical settings. B30 was the preferred kernel in this study for all criteria except for one and for the overall image quality. The difference in both measured image quality parameters and subjective image quality assessment between B30 and B45 were statistically significant for all criteria.

As expected, the results show a difference in both measured and perceived image noise, which was significantly lower in B30 images. Image noise reduction is proven to result in higher confidence in lesion detection (8). This is confirmed by the correlation between the assessment of the reproduction of liver lesions and measured image noise in the liver in

Table 5: Average values and standard deviations for image quality parameters measured for the two kernels and percentual difference (p<0.001 for all parameters in all organs)

	B30		B45		Percentual difference (%)	
	Noise (SD in HU)	**CNR**	**Noise (SD in HU)**	**CNR**	**Noise (SD in HU)**	**CNR**
Liver	15.43±3.49	4.63±1.52	28.87±6.41	2.51±0.74	46.6	45.78
Liver lesion	16.81±4.50	4.55±2.25	30.30±7.93	2.43±1.19	44.52	46.59
Spleen	15.01±3.01	4.70±1.64	28.66±5.66	2.56±0.86	47.63	45.53
Pancreas	18.41±4.38	3.01±1.44	32.29±8.42	1.64±0.79	42.99	45.51
Aorta	16.71±3.76	8.59±2.64	29.90±7.20	4.69±1.45	44.11	45.40
Muscle	15.55±3.57	-	28.44±6.37	-	45.32	

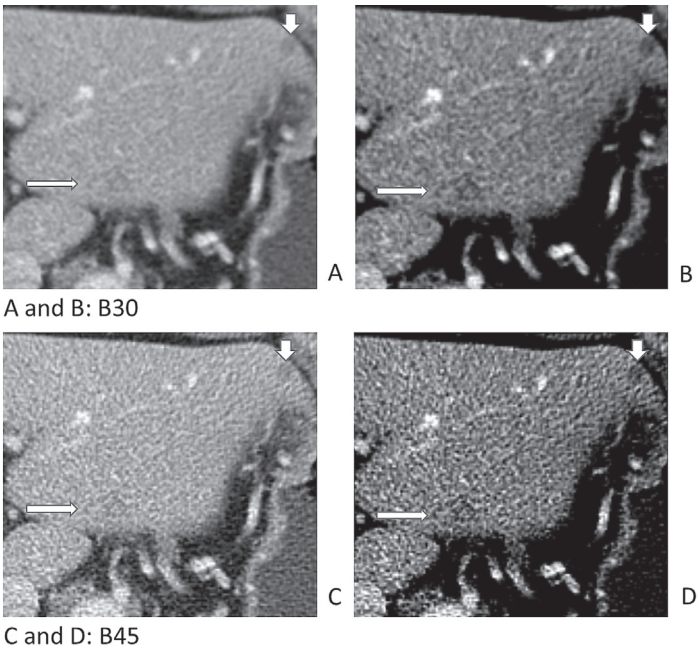

Figure 3: The figure shows two different window settings in A and B for the B30 kernel reconstruction, C and D for B45 of the CT images of this 62-year-old patient with primary neuroendocrine tumour of the small intestine (window levels are C:50, W:380 in A and C, C: 120, W: 200 in B and D). Two small liver lesions are shown in the left liver. The one anteriorly (thick arrow) is quite easy to see in all reconstructions. The other lesion (thin arrow) more posteriorly and medially is difficult to see. A change in window level helps the demarcation in the B30 algorithm. In the B45 reconstruction, the noise makes it much harder to detect it in both window settings.

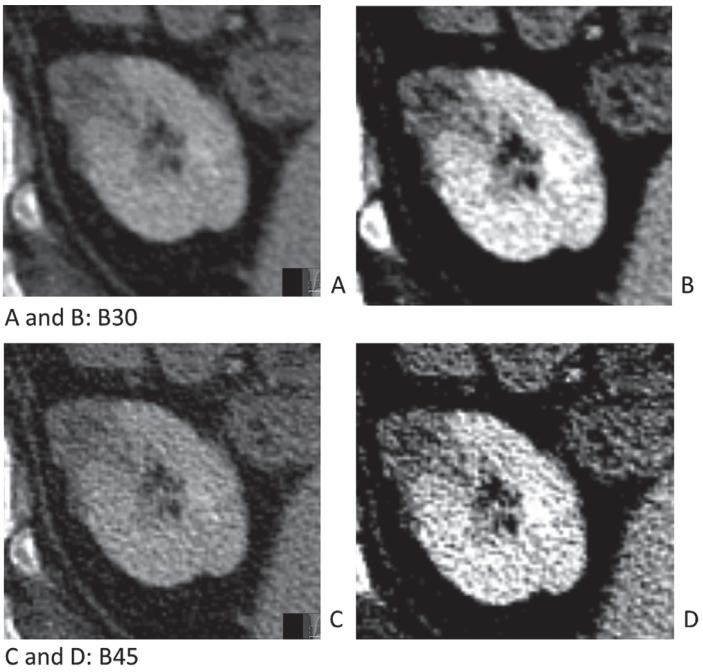

Figure 4: This 52-year-old patient had a primary thymus malignancy with metastasis to the left kidney. A and B are a B30, C and D a B45 reconstruction. A and C are shown with a soft tissue window level C:160, W:450, B and D in window level C: 120, W: 200. While the metastatic lesion is somewhat more sharply demarcated in the B45 kernel reconstruction (right), the subtle internal structure of both tumour tissue as well as kidney parenchyma is much better on B30 reconstructed images.

our study (Figure 3). The image noise reduction obtained using B30 instead of B45 (Table 5) was higher than the value obtained by Bhosale et al. (9) when comparing a soft kernel and standard kernel.

B45 performed better than B30 for overall sharpness (C9). The importance of sharpness depends on the diagnostic task, while the assessment of its clinical relevance is beyond the scope of this paper. Sharpness, however, is most relevant for demarcation in areas with high contrast, such as parenchyma against fat. Internal parenchymal structures, such as lobes or subtle contrast heterogeneities, are better depicted in B30 images (Figure 4). Therefore, the overall diagnostic image quality scores show that B30 was much better than B45 in almost 30% of cases. This, together with a low percent

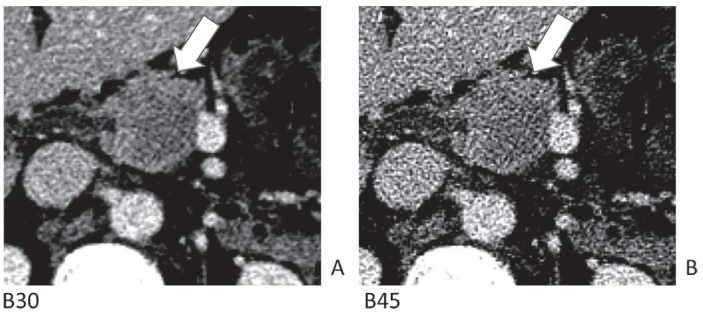

Figure 5: This 52-year-old patient had a primary thymus malignancy with metastasis to the head of the pancreas (same patient as in Figure 4, window level C: 120, W: 200). In A, the reconstruction kernel is B30, while in B it is B45. The edge of the metastasis and subtle tissue structure of the surroundings are blurred by the noise on reconstructions with B45.

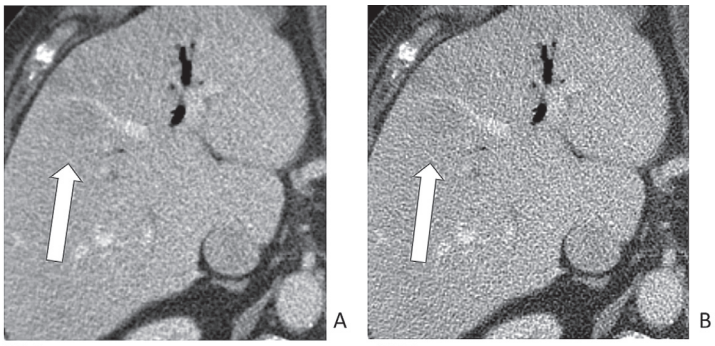

Figure 6: An 82-year-old patient with a duodenal malignancy obstructing the papilla vateri, with metastatic liver disease. Air in the intrahepatic biliary tree after Endoscopic retrograde cholangiopancreatography (ERCP) with stenting. The patient was inoperable due to comorbidity. Metastases to the liver are clearly more visible on the B30 kernel reconstruction (A) compared to B45 (B), window level C:50, W: 380

agreement between the radiologists when scoring overall sharpness and no significant correlation between this criterion in either the visually sharp reproduction of liver lesions or overall diagnostic image quality, suggests that the clinical relevance of the lower overall sharpness when using B30 might be negligible.

The considerable differences in CNR and quality assessment scores indicate the much better visually detectable reproduction of liver lesions in B30 and suggest that the increased image noise due to the choice of B45 might obscure small low-contrast lesions (Figure 5). At first glance, the sharp images often seem better, but when analysing the organs in more detail, the demarcation between parenchyma and pathology is sometimes blurred by noise on B45 reconstructions (Figure 6). This is especially true for small parenchymal lesions. The reason is the sacrifice of low contrast resolution due to particular image filtering and the post-processing technique, which increase the image noise when choosing a sharp kernel that gives better spatial resolution (1). It seems that a sharp kernel makes what is already obvious even more obvious. However, fine diagnostics are convincingly better with a softer kernel that gives better texture at the edge of metastases (Figure 5). Other criteria with high VGAS were subjective evaluated noise (C8) and overall diagnostic image quality (C10) (Table 4).

In the pancreas (C5), delimitation against fat looks better on B45 at first glance. However, in patients with low BMI, the delineation of organs' contours can be difficult on images with high noise level due to the low amount of intra-abdominal fat (10), while blurred lesions become more pronounced on B30, which is crucial in severe pathology. That gave a slight difference in image quality with regard to C5 (a VGAS of 0.423 out of a maximum possible 2 points).

The correlation between lower levels of measured image noise in the organs on the B30 images and the subjective assessed scores was statistically significant. However, not all the measurements correlated with the scores given by the radiologists, which might be explained by the fact that some anatomical structures may be more important than others for the anatomical region or pathology being investigated. More studies are required in this area to identify the weighting factors of the criteria, depending on the clinical indication (11).

The kappa values indicate some inter-observer differences. This difference might be caused by the difficulty in obtaining identical scores when a large scoring scale is used (12) or the different use of viewing tools, but it might also be an underlying difference between the reader's image quality expectancy or the fact that reader's preference scale might also change during the reading session which is described in literature as adaptation (13). VGA results when visualizing different noise textures might also be influenced by the experience of the radiologist (5). Another reason for the low kappa might be the ambiguity of the criteria, i.e. the sharp reproduction of the liver that might be subject to interpretation (it is worth noting that the percent agreement was also lower for C1) or difficulty in scoring normal anatomy with regard to diagnostic quality in the absence of pathology in the assessed organ. The use of image quality criteria stated in European guidelines is recommended for optimizing CT protocols based on the assumption that sharply reproduced anatomy results in sharply reproduced pathology. However, the relationship between the reproduction of anatomy and the detection of pathology is still unclear and further studies are needed, including an analysis in which pathology is taken into consideration to evaluate the relationship between image quality and diagnostic efficacy (10, 14). Similar kappa values were reported in studies using similar image quality assessment methods (10). However, the extent of differences showed by the kappa values is not confirmed by the percentual agreement which was over 90 for most of the criteria, while percentual agreement is considered a more informative agreement measure for clinicians (15).

The present study is subject to several limitations. 1. A statistically significant difference in image quality assessment results does not necessarily mean a difference in diagnostic performance. However, because CNR is considered a significant predictor for lesion detection, (16) image noise reduction may result in higher confidence in lesion detection. 2. Despite the randomization of the images, a truly blinded comparison was impossible due to the noticeable differences in image noise between the images reconstructed with the two kernels. 3. Only kernels from one vendor and only portal venous phase images were evaluated. 4. VGAS was the only scoring system used for quantifying the criteria-based image quality assessment. However, VGAS is still widely used to demonstrate the magnitude of the difference between options and providing a context to interpret the physical measurements (5) despite their shortcomings (17, 18), while a Wilcoxon test value is equal to the area under the curve (AUC) in a receiver operating characteristics (ROC) analysis of the same data (19).

Conclusion

The comparative image quality assessment demonstrates the superiority of B30 over B45 kernel reconstruction in abdominal CT examinations. This approach provides a statistically significant reduction in image noise, and an increase in CNR and higher VGA scores for all criteria except

for overall sharpness. With the main goal of achieving the highest subjective sensitivity for detecting focal lesions, the criterion "sharpness" proved to be a secondary factor in this study and is negligible.

References

1. Ehman EC, Yu L, Manduca A, Hara AK, Shiung MM, Jondal D, et al. Methods for clinical evaluation of noise reduction techniques in abdominopelvic CT. Radiographics. 2014;34(4):849-62. https://doi.org/10.1148/rg.344135128

2. Bushberg JT. The essential physics of medical imaging. 3rd ed. ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011.

3. Fletcher JG, Krueger WR, Hough DM, Huprich JE, Fidler JL, Wang J, et al. Pilot study of detection, radiologist confidence and image quality with sinogram-affirmed iterative reconstruction at half-routine dose level. J Comput Assist Tomogr. 2013;37(2):203-11. DOI: 10.1097/rct.0b013e31827e0e93

4. Jessen K, Shrimpton P, et al., Panzer W. European guidelines on quality criteria for computed tomography. Luxembourg: Luxembourg: OPOCE; 2000.

5. Verdun FR, Racine D, Ott JG, Tapiovaara MJ, Toroi P, Bochud FO, et al. Image quality in CT: From physical measurements to model observers. Physica Medica. 2015;31(8):823-43. https://doi.org/10.1016/j.ejmp.2015.08.007

6. Eichler M, May M, Wiesmueller M, Saake M, Heiss R, Uder M, et al. Single source split filter dual energy: Image quality and liver lesion detection in abdominal CT. European Journal of Radiology. 2020;126:108913. https://doi.org/10.1016/j.ejrad.2020.108913

7. Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data. Biometrics. 1977;33(1):159-74. PMID: 843571

8. Goenka AH, Herts BR, Dong F, Obuchowski NA, Primak AN, Karim W, et al. Image Noise, CNR, and Detectability of Low-Contrast, Low-Attenuation Liver Lesions in a Phantom: Effects of Radiation Exposure, Phantom Size, Integrated Circuit Detector, and Iterative Reconstruction. Radiology. 2016;280(2):475-82. https://doi.org/10.1148/radiol.2016151621

9. Bhosale PW-B, Nicolaus; Wei Wei; Kundra, Vikas; Tamm, Eric. Comparing CNR, SNR, and Image Quality of CT Images Reconstructed with Soft Kernel, Standard Kernel, and Standard Kernel plus ASIR 30% Techniques. International Journal of Radiology. 2016;2(2). http://www.ghrnet.org/index.php/IJR/article/view/1101/1773

10. Kataria B, Althén JN, Smedby Ö, Persson A, Sökjer H, Sandborg M. Assessment of image quality in abdominal CT: potential dose reduction with model-based iterative reconstruction. Eur Radiol. 2018;28(6):2464-73. DOI: 10.1007/s00330-017-5113-4

11. Zarb F, Rainford L, McEntee MF. Image quality assessment tools for optimization of CT images. Radiography. 2010;16(2):147-53. https://doi.org/10.1016/j.radi.2009.10.002

12. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb). 2012;22(3):276-82. PMID: 23092060

13. Helson H. Adaptation-level theory. Oxford, England: Harper & Row; 1964. xvii, 732-xvii

14. Jurik A, Petersen J, Jessen KA, Bongartz G, Geleijns J, Golding SJ, et al. Clinical Use of Image Quality Criteria in Computed Tomography: A Pilot Study. Radiation Protection Dosimetry. 2000;90(1-2):47-52. https://doi.org/10.1093/oxfordjournals.rpd.a033142

15. de Vet HCW, Mokkink LB, Terwee CB, Hoekstra OS, Knol DL. Clinicians are right not to like Cohen's κ. BMJ : British Medical Journal. 2013;346:f2125. https://doi.org/10.1136/bmj.f2125

16. Baker ME, Dong F, Primak A, Obuchowski NA, Einstein D, Gandhi N, et al. Contrast-to-Noise Ratio and Low-Contrast Object Resolution on Full- and Low-Dose MDCT: SAFIRE Versus Filtered Back Projection in a Low-Contrast Object Phantom and in the Liver. American Journal of Roentgenology. 2012;199(1):8-18. https://www.ajronline.org/doi/10.2214/AJR.11.7421

17. Båth M. Evaluating imaging systems: practical applications. Radiation Protection Dosimetry. 2010;139(1-3):26-36. https://pubmed.ncbi.nlm.nih.gov/20147386/

18. Månsson LG. Methods for the Evaluation of Image Quality: A Review. Radiation Protection Dosimetry. 2000;90(1-2):89-99. https://doi.org/10.1093/oxfordjournals.rpd.a033149

19. Precht H, Hansson J, Outzen C, Hogg P, Tingberg A. Radiographers' perspectives' on Visual Grading Analysis as a scientific method to evaluate image quality. Radiography. 2019;25:S14-S8. https://doi.org/10.1016/j.radi.2019.06.006

Review article

FLASH RADIOTHERAPY AS NEW PERSPECTIVE IN RADIOTHERAPY TECHNOLOGY

Flash radioterapija kot nova možnost v radioterapevtski tehnologiji

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ABSTRACT

Purpose: The purpose of this article is to present FLASH radiotherapy as a new radiation therapy method, to explain its mechanisms of action, to present possible sources and devices of radiation, and to identify its advantages and disadvantages compared to conventional radiotherapy.

Methods: Articles were reviewed for this study in online scientific research over the last 10 years (2012–2022). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram was used to document and report on all decisions made during the study selection process for this review paper.

Results and Discussion: Most studies have found that FLASH-RT reduces toxicity to healthy tissue adjacent to a tumour. At present, there is a lack of suitable radiation devices for the use of FLASH-RT, and it will be necessary to adapt existing devices.

Conclusion: FLASH-RT could be used in highly radioresistant tumours where CONV-RT would cause too much damage to healthy tissue with an increase in radiation dose. It could also be useful in tumours where CONV-RT is successful but too toxic for healthy tissue adjacent to a tumour. A great deal of research is required before the clinical implementation of FLASH-RT to determine the optimal dose rate, doses for different types of cancer with most the favourable effect/toxicity ratio and technical solution (i.e. radiation source).

Keywords: FLASH radiotherapy, radiotherapy, neoplasms, radiotherapy dosage

IZVLEČEK

Namen: Namen članka je predstaviti FLASH radioterapijo (FLASH-RT) kot novo obsevalno metodo, pojasniti do sedaj znane mehanizme delovanja, predstaviti možne vire in naprave sevanja ter ugotoviti kakšne so njene prednosti in pomanjkljivosti v primerjavi s konvencionalno radioterapijo (CONV-RT).

Metode in materiali: Za raziskavo so bili pregledani članki, objavljeni v zadnjih desetih letih (2012-2022) v spletni bazi podatkov. Za sistematični pregled literature in metaanalizo je bil uporabljen diagram za lažji izbor člankov, ki opisujejo značilnosti FLASH-RT.

Rezultati in razprava: Pri večini študij je bilo ugotovljeno, da FLASH-RT zmanjša toksičnost na zdrava tkiva ob tumorju. Trenutno je premalo primernih obsevalnih naprav za uporabo FLASH-RT in bo zato potrebno prilagoditi obstoječe naprave.

Zaključek: FLASH-RT bi lahko uporabili pri zelo radiorezistentnih tumorjih, kjer bi pri CONV-RT z višjo obsevalno dozo preveč poškodovali zdravo tkivo. Uporabna bi bila tudi pri tumorjih, kjer je CONV-RT uspešna, a ima preveč stranskih učinkov na zdrava tkiva ob tumorju. Pred klinično uporabo bo potrebno napraviti še veliko raziskav in ugotoviti: hitrost doze, dozni odmerek za različne vrste raka in najugodnejše razmerje med učinkom in toksičnostjo ter tehnično rešitev (tj. vir sevanja).

Ključne besede: FLASH radioterapija, radioterapija, neoplazme, dozni odmerki v radioterapiji

INTRODUCTION

Radiotherapy is one of the main types of treatment in oncology. In recent decades, a new radiation therapy method called FLASH radiotherapy (FLASH-RT) has been developed, and has been found to have fewer early and late radiation side effects, and the same antitumour efficacy. This is referred to as the FLASH effect. This could make FLASH-RT the main radiotherapy method in the future (1, 2). FLASH-RT is defined as irradiation with a single ultra-high dose rate (≥ 40 Gy/s) radiotherapy. FLASH irradiation is approximately 400 times faster than conventional irradiation (~5 Gy/min) (1).

The FLASH effect was first reported by Dewey and Boag in 1959. At that time, they irradiated Serratia marcescens bacteria with 1.5 MV X-rays at ultra-high dose rates. This study showed that bacteria in a nitrogen-oxygen mixture containing 1% oxygen were more radiosensitive than in a 100% nitrogen environment after irradiation at normal dose rates (1000 rad/min). However, lower radiosensitivity was observed when ultra-high dose rates (10-20 kilorad/2μs) were applied in the same nitrogen-oxygen mixture. Their study thus highlighted the fact that irradiation at ultra-high dose rates can protect bacteria better than conventional radiotherapy (CONV-RT) at normal dose rates (1).

FLASH-RT was first used in humans in 2018 at the University Hospital of Lausanne in Switzerland. The patient was a 75-year-old man who was diagnosed with CD30+ T-cell cutaneous lymphoma in 1999. From 2008 to 2018, the patient received CONV-RT, which successfully treated the lymphoma, but experienced severe side effects on the skin adjacent to the tumour. In 2018, he was treated with FLASH-RT using a total dose of 15 Gy delivered in 10 x 1 μs pulses (≥ 106 Gy/s, 1.5 Gy per pulse) with a total treatment time of 90 ms. The tumour was initially 3.5 cm in size and started to shrink after 10 days. Complete tumour response was achieved after 36 days and lasted five months. From the beginning, when the irradiated lesion started to shrink, there were only mild redness and minor oedema around the irradiation site, which was different from the patient's problems after conventional irradiation, where the surrounding tissue was more severely damaged and took three to four months to heal (2).

Flash-RT mechanism hypotheses

There are several different hypotheses regarding the mechanisms of FLASH-RT. However, the exact mechanism of action of FLASH-RT and its effects on cells are not yet known. The most commonly used hypotheses to explain the effects of FLASH-RT are the oxygen deprivation hypothesis, the role of reactive oxygen species (ROS) and redox reactions, the immune hypothesis and the differential response of normal and tumour tissue hypothesis (3).

Oxygen deficiency hypothesis

Oxygen is a critical molecule in the biological effect of FLASH-RT. It is known that hypoxic tissues are more radioresistant than oxygen-rich tissues. Radiochemical oxygen depletion occurs in FLASH-RT (4). There is an instantaneous consumption of oxygen, which is significantly faster than reoxygenation. Transient radioresistance occurs in healthy tissue due to transient hypoxia. There is thus less toxicity to such tissue (2, 5). This phenomenon is not as pronounced in CONV-RT because the dose rates are lower and repeated several times, so oxygen is replaced in between and the oxygen concentration in the irradiated tissue changes less (4).

ROS role hypothesis and redox biology

After irradiation with photons and electrons, water is radiolysed and ROS are formed, which cause 60–70% of indirect DNA damage, while 30–40% of the DNA damage is caused by direct interaction between the radiation and the DNA. If there is a lot of oxygen in the tissue, more ROS are produced and more DNA is damaged. This also explains why hypoxic tumours are more radioresistant than well-oxygenated tumours (2).

It is also hypothesised that ROS and other free radicals alter biochemical reactions in normal and tumour tissue, and thus contribute to the FLASH effect. This was also shown in a study where zebrafish embryos were irradiated with FLASH-RT and CONV-RT, and it was determined that there were fewer side effects after FLASH-RT. However, when the zebrafish were placed in an environment with ROS scavengers one hour before irradiation, no differences were identified. They concluded that FLASH-RT increases radioresistance in normal tissue due to a decrease in ROS (1). A study in which zebrafish embryos were irradiated with both radiotherapies confirmed the hypothesis that ROS and other free radicals alter biochemical reactions in tissue (2).

Normal and tumour tissue are distinguished both by the generation of free radicals and by the course of redox reactions. The same dose of FLASH-RT as CONV-RT triggers different redox pathways and a lower burden of pro-oxidants because they scavenge free radicals faster than tumour cells. In tumour tissue, peroxidation chain reactions take longer to occur, causing the accumulation of free radicals, resulting in cell damage and destruction (5).

Immune hypothesis

The FLASH effect is thought to be mediated by inflammatory and immune responses. TGF-beta is important as a pro-inflammatory cytokine and is thought to be involved in the different effect of FLASH-RT compared to CONV-RT. In an in vitro study, the level of TGF-beta in human lung fibroblasts was monitored and found to be less after FLASH-RT with proton beams than with conventional irradiation. The production was only 1.8 times higher in FLASH-RT than in non-irradiated tissue, and 6.5 times higher in CONV-RT, suggesting that FLASH-RT significantly reduced chronic inflammation relative to CONV-RT (2).

Similarly, another study in mice confirmed that CONV-RT increased the levels of five of the ten cytokines observed, whereas FLASH-RT increased only three. The exact effect of TGF-beta is not yet known, but it is thought to be involved in the anti-tumour immune response. It is thought to suppress the immune system and promote cancer progression, increasing the need for inhibitors of the TGF-beta pathway (2).

Hypothesis of differential response of normal and tumour tissue

It was hypothesised that different types of DNA damage after the two irradiations trigger different responses in healthy

and tumour tissue. Solid tumours are mostly hypoxic, so they will not be protected from the transient hypoxia induced by FLASH-RT, whereas healthy tissues will be, resulting in a differential effect. Cancer and normal cells have different abilities to scavenge hydrogen peroxide products (1). It has been found that it is precisely due to different redox metabolism, different levels of ROS and redox metals, such as labile iron, that normal cells scavenge the free radicals generated during irradiation more efficiently. The authors also found out that cancer cells have higher levels of labile iron and transferrin receptors, which results in an increase in catalytic processes (Fenton reaction) that convert hydrogen peroxide into hydroxyl free radicals, causing more oxidative damage in cancer cells. Healthy cells have less labile iron, and scavenge hydroperoxides formed more rapidly after FLASH-RT (3, 4).

Impact on radiotherapy

FLASH-RT has the potential to change the theory of radiobiology (1). The first change could be in the five Rs of radiobiology: DNA repair, reoxygenation, repopulation, redistribution and intrinsic radiosensitivity. The duration of FLASH-RT is too short for reoxygenation, repopulation and redistribution to occur, but the effect of FLASH-RT may be related to two Rs: DNA repair and intrinsic radiosensitivity (1). Another modification may be the threshold dose to healthy tissue, as pre-clinical studies have confirmed that a higher dose of FLASH-RT is required to induce the same level of toxicity as CONV-RT. This was confirmed in a study where CONV-RT irradiation with a dose of 15 Gy induced pulmonary fibrosis, whereas FLASH-RT irradiation with a dose of 20 Gy did not induce the same effect, even after 36 weeks. A similar finding was made in another study where CONV-RT irradiation at 17 Gy induced severe skin lesions, while FLASH-RT irradiation at 15 and 20 Gy did not. (1). A third option is a comprehensive change in treatment strategy. FLASH-RT can only be performed once for a very short period of time, so concomitant chemoradiotherapy cannot be performed. Only neoadjuvant and adjuvant chemotherapy can be performed (1). The fourth option is a change in the number of fractions in radiotherapy. FLASH-RT is only performed once and could therefore displace CONV-RT (1).

Devices and radiation sources

In addition to the dose rate and the duration of FLASH-RT, the radiation source is also important. Electrons, photons and protons can be used (1). Most research has used linear accelerator electron beams. These beams are limited to the treatment of superficial cancers and intraoperative radiotherapy due to their low penetration and limited energy (4 to 20 MeV) (2). Higher energy electron beams could also be used, i.e. high-energy electron beams with energies of 100 to 250 MeV. Such beams have good depth penetration and are less sensitive to tissue heterogeneity than X-rays (4). Photon beams from linear accelerators are not sufficiently intense to achieve the required high doses with current technology. However, X-rays from synchrotrons have been successfully used (3). Synchrotron sources have similar beam energies to X-ray tubes, but also have the potential to use spatially fractionated, ultra-high-dose microbeam radiation therapy (MRT). The disadvantage is that synchrotrons are large, expensive and few in number (4). In proton beam radiotherapy, the penetration of the beams is deeper and facilitates the irradiation of deeper tumours. Another advantage is that most of the beam energy is deposited in a narrow area at Bragg's peak, facilitating the precise targeting of the tumour volume while protecting surrounding healthy tissue and organs at risk (2).

The aim of this review article is to present FLASH-RT as a new irradiation method, to explain the currently known mechanisms of action, to present possible sources and devices of radiation, and to identify its advantages and disadvantages compared to CONV-RT.

METHODS

The studies used in this paper were found in online scientific research databases and were published in the last 10 years (including 2012 to 2022). To simplify the literature review, we selected some exclusion criteria, such as studies published in the period before 2012, studies that are not in English, papers without full text and papers not related to the theme of our study. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram was used to document and report on all decisions made during the study selection process for this review paper (Diagram 1).

RESULTS AND DISCUSSION

The results present a systematic review of irradiation results for studies investigating toxicity to healthy tissue. The essential characteristics expected from FLASH-RT are equal or even higher antitumour efficacy and lower toxicity to healthy tissue adjacent to a tumour. The effects of FLASH-RT have been studied in various animal models of mice, rats, zebrafish, pigs and cats, and in organs such as lungs, skin, intestines and brain. The results of in vitro and in vivo studies were also compared. Researchers were also interested in the effects of FLASH-RT from different radiation sources. Most reported that there were fewer adverse effects on healthy tissue after FLASH-RT compared to CONV-RT (Table 1).

In 2014, Favaudon reported that the use of FLASH-RT to treat lung tumours can lead to a complete response, and reduce early and late toxicity affecting normal lung tissue. To investigate toxicity, he used healthy mice in which the lungs were irradiated, and the occurrence of pneumonitis and fibrosis was assessed. One group was irradiated with a high single dose of FLASH-RT (≥ 40 Gy/s) and the other group was conventionally irradiated at a dose rate of 0.003 Gy/s. After CONV-RT at 17 Gy, severe pneumonitis and fibrosis occurred in all mice, whereas FLASH-RT at the same dose resulted in neither pneumonitis nor fibrosis, but only at 30 Gy. At 17 Gy, FLASH-RT also prevented TGF-beta activation (6).

Similar conclusions were reached by Vozenin et al. (2019), who irradiated the skin of mini-pigs and cats in their study. For FLASH-RT, they used two prototype linear accelerators, the Kinetron (4.5 MeV) and the Oriatron (6 MeV) for the electron source, and a wider range of dose rates. They irradiated 10 equally sized circular patches of skin in each pig. Five different doses ranging from 22 to 34 Gy were used. A dose rate of 5 Gy/min was used for CONV-RT and 300 Gy/s for FLASH-RT. After 36 weeks, skin biopsies were taken. FLASH-

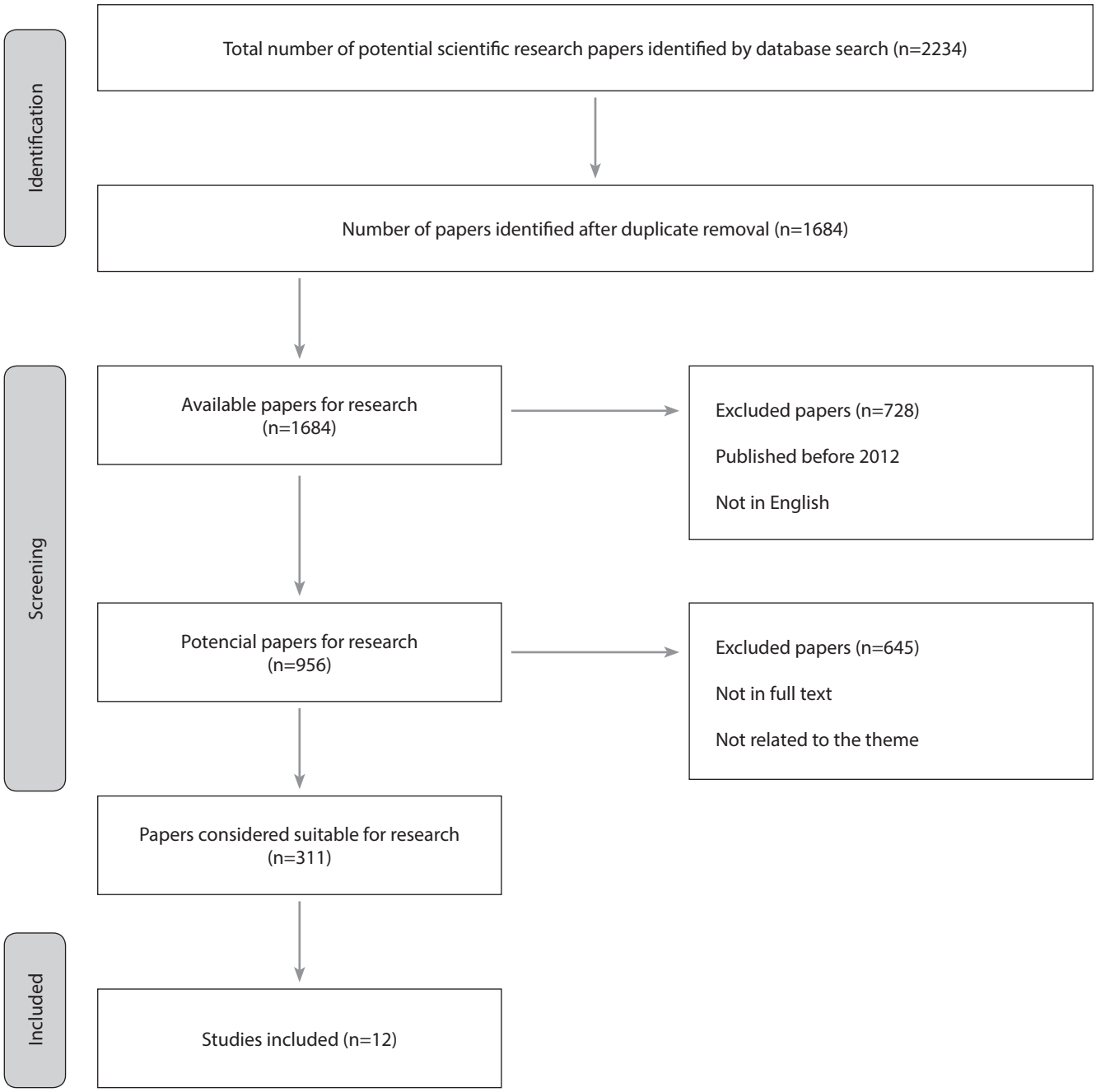

Diagram 1: Selection of documents for systematic review

RT had fewer side effects: only transient depilation occurred, but hair follicles were preserved. CONV-RT resulted in permanent hair follicle damage, skin fibronecrosis, epithelial ulceration and hyperkeratosis. In another study, he used cats irradiated for locally advanced squamous cell carcinoma of the nasal planum. A worse antitumour effect was observed with CONV-RT. FLASH-RT used a single dose, while different dose rates (from 25 to 41 Gy) were used to find the maximum acceptable dose. They were followed up for 18 months. There was permanent depilation at the irradiation site, but no disturbance of olfaction and nutritional functions. Tumour response was complete after six months and three of the six cats were still disease-free after 18 months. The results of this study are promising because larger mammals were studied and this would be more easily transferable to human research (7).

Table 1: Irradiation results for studies investigating toxicity to healthy tissues

Author	Model	Observed variable	Total dose (Gy)	Dose rate (Gy/s)		Modality of radiation	Which RT has the advantage?
				CONV-RT	FLASH-RT		
Favaudon et al. (2014)	Mice – Thoracic irradiation	Onset of pneumonitis and pulmonary fibrosis	17	≤ 0.03	≥ 40	electron	**FLASH-RT**
Vozenin et al. (2019)	Mini pigs – Skin irradiation	Skin toxicity	22-34	0.08	300	electron	**FLASH-RT**
Vozenin et al. (2019)	Cats – Skin irradiation	Skin toxicity	25-41	0.08	300	electron	**FLASH-RT**
Montay-Gruel et al. (2017)	Mice – Whole brain irradiation	Cognitive skills	10	0.1	30–5.6x106	electron	**FLASH-RT**
Montay-Gruel et al. (2018)	Mice – Whole brain irradiation	Cognitive skills	10	0.05	37	X-ray	**FLASH-RT**
Alaghband et al. (2020)	Mice (juvenile) – Brain irradiation	Cognitive skills	8	7.7×103	4.4×106	electron	**FLASH-RT**
Diffenderfer et al. (2020)	Mice – Abdomen irradiation	Acute cell loss and late fibrosis	12-18	0.5-1	60-100	proton	**FLASH-RT**
Venkatesulu et al. (2019)	Mice – Heart and spleen irradiation	Level of lymphocytes in the circulation	0-8	0.1	35	electron	**CONV-RT**
Venkatesulu et al. (2019)	Mice – Abdomen irradiation	Toxicity	16	0.1	35	electron	**CONV-RT**

Montay-Gruel et al. (2017) assessed cognitive skills after whole brain irradiation with FLASH-RT and CONV-RT in two separate studies. They used electrons from a linear accelerator for FLASH-RT in the first study, and synchrotron-generated X-ray radiation in the second. They found that FLASH-RT better preserved memory and neurogenesis in the hippocampus, with more than 37% of preserved neurogenesis clusters found in mice after FLASH-RT, but only 14% with CONV-RT. CONV-RT reduced cognitive abilities and significantly reduced cell divisions in the hippocampus (8, 9). Moreover, a study by Alahband (2020) showed that FLASH-RT after the irradiation of mouse brains better preserves the memory, learning and socialisation abilities of these mice for four months after FLASH-RT, whereas CONV-RT impairs these functions. This in turn suggests that FLASH-RT also gives encouraging results in the long term, which would be very good if FLASH-RT were used in the treatment of paediatric patients (10).

Diffenderfer (2020) also compared the two proton radiotherapies. He irradiated the abdomen of healthy mice, whole or only part. After FLASH-RT, he found greater cell preservation in intestinal crypts and better crypt regeneration. Analysis of the muscle layer in the intestine also showed less fibrosis after FLASH-RT, or changes comparable to those in non-irradiated mice. The effect of proton FLASH-RT on the tumour was then studied. Pancreatic cancer cells were inoculated and this area was irradiated. Both radiotherapies had the same effect on the tumour (11).

However, a few studies have found that there were more side effects after FLASH-RT. Venkatesulu et al. (2019) also observed that both radiotherapies caused lymphopenia, but this was more severe with FLASH-RT. There was even more severe gastrointestinal toxicity after whole abdomen irradiation and the worse survival of mice with FLASH-RT (12).

It is difficult to compare all studies published to date because the authors do not use the same conditions for both irradiation techniques. Some use electrons as the radiation source for FLASH-RT and photons for CONV-RT. The shape of the irradiation field is also important, as it is different if the irradiation field is circular or square, even if the same area has been irradiated. Vozenin et al. (2019) point out that often in in vitro studies, oxygen concentrations were significantly higher than in vivo. Due to such non-physiological oxygen concentrations (21%), the FLASH effect may not occur in these studies, but is observed when concentrations are physiological (3 to 7%) (5).

CONCLUSION

FLASH-RT is a new irradiation method that was first mentioned in 1959, but has only started to be studied again more intensively in the last two decades. The major benefits expected from this method are reduced toxicity to healthy tissue adjacent to a tumour, and an equal or, in some tumour types or conditions, even better antitumour effect than in CONV-RT. The mechanism of action of FLASH-RT is not yet fully understood, but there are some hypotheses that try to explain it. Various studies comparing FLASH-RT with CONV-RT are ongoing, but so far only in animals. There is only one known

example of FLASH-RT in humans, which is not sufficient to translate this method into clinical use. Extensive research is needed before this can be done to optimize the dose rate for different types of cancer, and to determine the dose with the most favourable effect/toxicity ratio. It will also be necessary to determine which radiation source is most appropriate for this type of radiation, which will require intensive technological developments in the field of irradiation devices.

FLASH-RT could be used for highly radioresistant tumours, where CONV-RT would damage healthy tissue if an increase in radiation dose would be used to overcome radioresistancy. It would also be useful for tumours where CONV-RT is successful in order to further reduce side effects on healthy tissue adjacent to a tumour.

REFERENCES

1. Lin B, Gao F, Yang Y, Wu D, Zhang Y, Feng G, et al. FLASH Radiotherapy: History and Future. Frontiers in oncology [Internet]. 2021 [cited 2022 Apr 15];11:644400. Available from: https://doi.org/10.3389/fonc.2021.644400

2. Hughes JR, Parsons JL. FLASH Radiotherapy: Current Knowledge and Future Insights Using Proton-Beam Therapy. International journal of molecular sciences [Internet]. 2020 [cited 2022 Apr 15];21(18):6492. Available from: https://doi.org/10.3390/ijms21186492

3. Marcu LG, Bezak E, Peukert DD, Wilson P. Translational Research in FLASH Radiotherapy-From Radiobiological Mechanisms to In Vivo Results. Biomedicines [Internet]. 2021 [cited 2022 Apr 15];9(2):181. Available from: https://doi.org/10.3390/biomedicines9020181

4. Wilson JD, Hammond EM, Higgins GS, Petersson K. Ultra-High Dose Rate (FLASH) Radiotherapy: Silver Bullet or Fool's Gold? Frontiers in oncology [Internet]. 2020 [cited 2022 Apr 15];9:1563. Available from: https://doi.org/10.3389/fonc.2019.01563

5. Vozenin MC, Hendry JH, Limoli CL. Biological Benefits of Ultra-high Dose Rate FLASH Radiotherapy: Sleeping Beauty Awoken. Clinical oncology (Royal College of Radiologists (Great Britain)) [Internet]. 2019 [cited 2022 Apr 15];31(7):407-415. Available from: https://doi.org/10.1016/j.clon.2019.04.001

6. Favaudon V, Caplier L, Monceau V, Pouzoulet F, Sayarath M, Fouillade C, et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Science Translational Medicine [Internet]. 2014 [cited 2022 Apr 21];6(245):245ra93. Available from: https://pubmed.ncbi.nlm.nih.gov/25031268/

7. Vozenin MC, De Fornel P, Petersson K, Favaudon V, Jaccard M, Germond JF, et al. The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients. Clinical Cancer Research [Internet]. 2019 [cited 2022 Apr 21];25(1):35-42. Available from: https://doi.org/10.1158/1078-0432.CCR-17-3375

8. Montay-Gruel P, Petersson K, Jaccard M, Boivin G, Germond JF, Petit B, et al. Irradiation in a flash: Unique sparing of memory in mice after whole brain irradiation with dose rates above 100Gy/s. Radiotherapy and Oncology [Internet]. 2017 [cited 2022 Apr 21];124(3):365-369. Available from: https://doi.org/10.1016/j.radonc.2017.05.003

9. Montay-Gruel P, Bouchet A, Jaccard M, Patin D, Serduc R, Aim W, et al. X-rays can trigger the FLASH effect: Ultra-high dose-rate synchrotron light source prevents normal brain injury after whole brain irradiation in mice. Radiotherapy and Oncology [Internet]. 2018 [cited 2022 Apr 21];129(3):582-588. Available from: https://doi.org/10.1016/j.radonc.2018.08.016

10. Alaghband Y, Cheeks SN, Allen BD, Montay-Gruel P, Doan NL, Petit B, et al. Neuroprotection of Radiosensitive Juvenile Mice by Ultra-High Dose Rate FLASH Irradiation. Cancers [Internet]. 2020 [cited 2022 Apr 21];12(6):1671. Available from: https://doi.org/10.3390/cancers12061671

11. Diffenderfer ES, Verginadis II, Kim MM, Shoniyozov K, Velalopoulou A, Goia D, et al. Design, Implementation, and in Vivo Validation of a Novel Proton FLASH Radiation Therapy System. International journal of radiation oncology, biology, physics [Internet]. 2020 [cited 2022 Apr 21];106(2):440-448. Available from: https://doi.org/10.1016/j.ijrobp.2019.10.049

12. Venkatesulu BP, Sharma A, Pollard-Larkin JM, Sadagopan R, Symons J, Neri S, et al. Ultra high dose rate (35 Gy/sec) radiation does not spare the normal tissue in cardiac and splenic models of lymphopenia and gastrointestinal syndrome. Scientific reports [Internet]. 2019 [cited 2022 Apr 21];9(1), 17180. Available from: https://doi.org/10.1038/s41598-019-53562-y