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FULL PAPER

Determination of optimal virtual monochromatic energy level for target delineation of brain metastases in radiosurgery using dual-energy CT

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Objective: Determination of the optimal energy level of virtual monochromatic image (VMI) for brain metastases in contrast-enhanced dual-energy CT (DECT) for radiosurgery and assessment of the subjective and objective image quality of VMI at the optimal energy level.

Methods: 20 patients (total of 42 metastases) underwent contrast-enhanced DECT. Spectral image analysis of VMIs at energy levels ranging from 40 to 140 keV in 1 keV increments was performed to determine the optimal VMI (VMI_{opt}) as the one corresponding to the highest contrast-to-noise ratio (CNR) between brain parenchyma and the metastases. The objective and subjective values of VMI_{opt} were compared to those of the VMI with 120 kVp equivalent, defined as reference VMI (VMI_{ref}; 77 keV). The objective measurement parameters included mean HU value and SD of tumor and brain parenchyma, absolute lesion contrast (LC), and CNR. The subjective measurements included five-point scale assessment of

“overall image quality” and “tumor delineation” by three radiation oncologists.

Results: The VMI at 63 keV was defined as VMI_{opt}. The LC and CNR of VMI_{opt} were significantly ($p < 0.01$) higher than those of VMI_{ref} (LC: 37.4 HU vs 24.7 HU; CNR: 1.1 vs 0.8, respectively). Subjective analysis rated VMI_{opt} significantly ($p < 0.01$) superior to VMI_{ref} with respect to the overall image quality (3.2 vs 2.9, respectively) and tumor delineation (3.5 vs 2.9, respectively).

Conclusion: The VMI at 63 keV derived from contrast-enhanced DECT yielded the highest CNR and improved the objective and subjective image quality for radiosurgery, compared to VMI_{ref}.

Advances in knowledge: This paper investigated for the first time the optimal energy level of VMI in DECT for brain metastases. The findings will lead to improvement in tumor visibility with optimal VMI and consequently supplement accuracy delineation of brain metastases.

INTRODUCTION

Brain metastases causes one of the most frequent neurological complications of cancer and occurs in 20–40% of cancer patients.¹ Owing to the advent of radiotherapy techniques, such as small radiation field and sophisticated immobilization system, stereotactic radiosurgery (SRS) is being increasingly employed for brain metastases and it can provide compromised outcome compared to surgery. A randomized trial reveals that SRS provides comparable performance to surgery in terms of overall survival and failure-free survival for solitary brain metastasis.² SRS delivers high-dose radiation in a single or small fraction for a limited target volume to protect the surrounding normal tissue. For such high-precision therapy, accurate target delineation is imperative.

The treatment planning is usually performed using a CT image, and simultaneously the targets are delineated with the use of gadolinium-enhanced MRI. In the absence of MRI due to contraindications that the tumor need to be identified at CT image, although a prior report indicates uncertainty about delineation of radiosurgical targets with CT images. Sidhu K et al described that the mean tumor volume increases by approximately 30% (range: 3–70%), and the isocenters shift by 1.3 mm (range: 0.2–4.6 mm) according to timing of CT image acquisition following the administration of contrast agent.³ Inaccurate target delineation may result in insufficient control of tumor as well as induce severe toxicity.

Recently, dual-energy CT (DECT) is being increasingly employed to improve diagnostic capabilities. DECT utilizes high- and low-energy photons, which enables differentiation of materials, such as iodine and water on the basis of different attenuation profiles.^{4,5} An additional post-processing application using DECT image data involves creation of virtual monochromatic images (VMIs) at specific energy levels. Several researchers have reported that VMI could improve image quality for various tumor sites.^{6–8} To our knowledge, there is no study investigating whether DECT can improve image quality for brain metastases.

Therefore, the aims of our study were to improve the image quality for sensitivity to detect tumor by optimizing the energy levels of VMI in contrast-enhanced DECT for radiosurgery treatment planning, and to assess the subjective and objective image quality of VMI at the optimal energy level.

METHODS AND MATERIALS

Patients

This retrospective study has been approved by our ethics committee. The subjects were 20 patients (median age (range) 70 (22–91) years; 15 males and five females) with 1–8 brain metastases, thus providing a total of 42 metastases. All patients underwent contrast-enhanced DECT for radiosurgery treatment planning using DECT scanner (Revolution HD: GE Healthcare, Waukesha, WI, USA) between April 2017 and January 2018. The metastases originated from lung cancer in 10 patients, esophageal cancer in three, breast cancer in three, thyroid cancer in one, rectal cancer in one, and diffuse astrocytoma in one.

Image acquisition and post-processing

The patients were immobilized with thermoplastic mask. The intravenous contrast medium was injected to achieve 80 s fixed injection interval with 500 mgI per body weight, and images were acquired at 180 s after initiation of administration. All scans were performed in dual-energy rapid 80 and 140 kVp switching mode by using the following imaging protocol: 600 mA tube current, large-body scan field of view (FOV), 64×0.625 mm beam collimation, 1 s rotation time, and 0.984:1 helical pitch. The images were reconstructed into 1 mm thickness, 35 cm display FOV, and 512×512 pixels. The VMI at 77 keV as reference VMI (VMI_{ref}) was reconstructed automatically for standard clinical use because it provided equivalent HU values with images acquired using conventional CT scanner (120 kVp).

Objective image analysis

Spectral quantitative image analysis of VMIs at energy levels ranging from 40 to 140 keV in 1 keV increments was performed on a workstation (Advantage workstation 4.7: GE Healthcare, Waukesha, WI, USA). On an axial slice including the center of the tumor, a circular or elliptical ROI for tumor was placed to cover the lesion. And a total of circular 12 ROIs with 5 mm diameter were placed on the midlevel of the basal ganglia section, based on previous report,⁹ at following anatomic locations: two each in the normal cortical gray matter and juxtacortical white matter of the frontal lobe, those of the occipital lobe, thalamic deep gray matter, and white matter of the posterior limb of the internal capsule (Figure 1). The HU values and SD within the ROIs was

Figure 1. Axial CT image at midlevel of basal ganglia showing ROI placement. Red circles represent ROI in the normal cortical gray matter of the frontal lobe, the occipital lobe, and the thalamic deep gray matter. Blue circles represent ROI in the juxtacortical white matter of the frontal lobe, occipital lobe, and the white matter of the posterior limb of the internal capsule.

measured on VMIs at different energy levels. The mean attenuation values of the brain parenchyma and the corresponding noise were defined by the average of the HU values and SD of the gray matter and white matter measured 12 ROIs, respectively. Subsequently, lesion contrast (LC) and contrast-to-noise ratio (CNR) were calculated using following formulae.

$$LC = HU_{tumor} - HU_{brain} \quad (1)$$

$$CNR = \frac{LC}{\sqrt{SD_{tumor}^2 + SD_{brain}^2}} \quad (2)$$

HU_{tumor} and SD_{tumor} are the attenuation values and SD of the measured value in the tumor, and HU_{brain} and SD_{brain} are the mean attenuation and noise of the brain parenchyma, respectively. The VMI with the highest CNR at a given energy level was determined as the optimal VMI (VMI_{opt}) for target delineation of brain metastases. The HU values in each ROI and CNR of VMI_{opt} were compared with those of VMI_{ref} . Statistical analysis was performed using Wilcoxon signed-rank test, where p value < 0.05 was considered to indicate statistical significance (SPSS, v. 24; SPSS Inc, Chicago, IL).

Subjective image analysis

Subjective image analysis was performed to assess the image quality of VMI_{ref} and VMI_{opt} . The images were displayed using a contrast-enhanced head window (window level, 50; window

Table 1. Subjective image assessment rating

	1 = Unbearable	2 = Poor	3 = Moderate	4 = good	5 = excellent
Overall image quality	Unavailable clinical use	Acceptable but poor quality	Available clinical	Positively acceptable	Excellent image quality
Tumor delineation	No definite differentiation	Uncertain delineation	Distinguishable delineation	Easily delineation	Definite delineation

width, 150) on the radiotherapy planning workstation (Eclipse 13.6; Varian Medical System, Palo Alto, CA). VMI_{ref} and VMI_{opt} were observed side-by-side with a fixed window setting at the axis slice by three radiation oncologists, and subjective image scores were evaluated with regard to “overall image quality” and “tumor delineation” on a scale of 1 to 5 (Table 1). “Overall image quality” included the magnitude of noise level, sharpness, soft tissue contrast, and beam hardening artifact. “Tumor delineation” included conspicuity and sharpness of the tumorous outline. The scores were analyzed with Wilcoxon signed-rank test to assess the statistical measure of the difference using SSPS software. A p value of < 0.05 was considered statistically significant.

Results

The median gross tumor size was 0.4 cc (range: 0.02–8.63 cc). The mean of attenuation and SD in tumor and brain parenchyma (gray matter and white matter) of VMIs at different energy levels are shown in Figure 2. The higher energy levels of VMIs were associated with declined HU values of both metastases tumor and brain parenchyma, and the difference between the attenuations in tumor and brain parenchyma increased as the energy levels of VMIs decreased (Figure 2a). Figure 2b shows how the variation of energy level affects the SD representing image noise. Lower energy VMIs yielded larger image noise in tumor

Figure 2. Spectral quantitative image analysis of the virtual monochromatic images at different energy levels in the range of 40–140 keV; mean attenuation (a), standard deviation (SD) of region of interest (b), and contrast to noise ratio (CNR) between brain parenchyma and tumor (c). The error bar indicates the SD. (d) Correlation scatterplot of CNR of VMI_{opt} and VMI_{ref} in each tumor, representing the degree of change in modifying 77 keV to 63 keV.

Figure 3. Comparison of quantitative values in reference virtual monochromatic image (VMI_{ref} , 77 keV) and optimal VMI (VMI_{opt} , 63 keV) for CT attenuation of tumor and parenchyma (a), lesion contrast (b), and contrast-to-noise ratio (c). ** $p < 0.01$

and brain parenchyma. Figure 2c displays the mean curve of CNR for each energy level. The CNR was the highest at 63 keV (mean $\pm$ SD, 1.1 ± 0.3), and the corresponding VMI was defined as VMI_{opt} . Figure 2d shows the correlation scatterplot of CNR of VMI_{opt} and VMI_{ref} in each tumor, representing the degree of change in modifying 77 keV to 63 keV. CNRs are improved by changing the energy level of VMI from 77 keV to 63 keV in all tumors.

Figure 3 summarizes the quantitative values for VMI_{ref} and VMI_{opt} ; the mean $\pm$ SD of each HU value of tumor, gray matter, and white matter were significantly higher ($p < 0.01$) in VMI_{opt} than in VMI_{ref} (tumor: 74.8 ± 10.1 HU vs 58.1 ± 6.6 HU; gray matter: 43.4 ± 4.4 HU vs 37.6 ± 3.2 HU; white matter: 33.3 ± 2.4 HU vs 30.6 ± 2.2 HU, respectively). Additionally, VMI_{opt} provided each significantly higher ($p < 0.01$) LC and CNR than VMI_{ref} (LC: 37.4 ± 9.4 HU vs 24.7 ± 6.4 HU; CNR: 1.1 ± 0.3 vs 0.8 ± 0.2 , respectively). Figure 4 shows a comparison of the VMI_{ref}

and VMI_{opt} for patients #2, 8, and 10, and their LC values were 30.8 HU, 33.2 HU, and 37.4 HU in VMI_{opt} and 21.5 HU, 26.2 HU, and 27.1 HU in VMI_{ref} respectively. Their CNR values were 0.91, 1.00, and 1.58 in VMI_{opt} and 0.66, 0.79, and 1.08 in VMI_{ref} respectively. In those cases, VMI_{opt} yielded improved visualization of tumor with adjacent brain parenchyma as compared with VMI_{ref} .

The subjective image analysis results are shown in Table 2. VMI_{ref} was provided an overall mean score of “3” or less in both the evaluation items, which implied that conventional image provide almost acceptable image quality for radiation oncologists. For VMI_{opt} , each mean score was significantly ($p < 0.01$) higher than that of VMI_{ref} with respect to both “overall image quality” (3.2 vs 2.9, respectively) and “tumor delineation” (3.5 vs 2.9, respectively), which suggests that improvement of visual image quality could be achieved by varying the energy level in VMI.

Figure 4. Comparison of reference virtual monochromatic image (VMI_{ref}, 77 keV) and the optimal VMI (VMI_{opt}, 63 keV) for patients #2, #8, and #10. The yellow arrows indicate brain metastases.

DISCUSSION

Control of brain metastases is known to have significant influence on morbidity and mortality.¹⁰ SRS is a primary therapeutic option for most patients with brain metastases. Because accurate target recognition is of critical importance in SRS, delineation of gross tumor volume (GTV) for radiosurgery treatment planning was often performed on CT image with registration of MRI or positron emission tomography (PET) images. However, the report of American Association of Physicists in Medicine Task Group – 132 stated that the process of image registration introduces uncertainties according to the quality of input images, registration algorithm, and incorrect interpolation of registration results.¹¹ Additionally, delineation with the image of past examination may underestimate the contour of tumor due to progression. Therefore, the treatment planning CT may assist in delineating the target for SRS.

However, considerable interobserver variation in target delineation using conventional CT scanner has been reported.^{12–14} Weltens et al reported that the GTV delineated on conventional CT images exhibits large difference for nine observers, with the ratio of the largest-to-smallest volume for each patient differing by a factor of 1.7–2.8,¹² and another report by Aoyama et al showed that the GTV defined on CT image varies by

approximately 20% among four observers.¹³ Thus, target delineation on conventional CT images involves uncertainty arising from interobserver variation, and consequently, SRS may induce unexpected radiation side-effect or cannot deliver sufficient dose to control tumor progression. We demonstrated that VMI at an optimal energy level significantly improves the visualization of tumor delineation compared to VMI with standard contrast. Further study is needed to elucidate whether VMI at the optimal energy level reduces the variation of target delineation among observers.

A few studies evaluated brain parenchyma contrast in an unenhanced DECT of the head with quantitative and qualitative values.^{9,15,16} Pomerantz SR et al sought the VMI energy levels that maximize brain parenchymal image quality in dual-energy unenhanced head CT and to assess the improvement with this technique compared with conventional polychromatic CT. The authors revealed that VMI at 65 keV provided maximizes image quality for supratentorial brain.⁹ To the best of our knowledge, this is the first study to focus on brain metastatic tumor regarding variation of VMI energy levels using intravenous contrast medium. Theoretically, iodine induced greater slope of the spectral HU attenuation curve than soft tissue, emphasizing that the lesion concentrated on the contrast agent against peripheral tissue in VMI at a lower energy level. In contrast, severe image noise existed at the lower VMI energies, representing a tradeoff between iodine attenuation and noise.¹⁷ The low energy level increased the difference between the tumor and brain parenchyma, and simultaneously promoted remarkable augmentation of noises. The high image noise caused loss of CNR at the low energy level compared to that at the middle level. Additionally, previous studies for other lesion also concluded that VMIs at 60–70 keV yielded the highest quantitative index.^{6,18,19} In our study, as VMI at middle level (63 keV) provides the highest objective quantitative measurement (CNR) for brain metastasis in enhanced head DECT, our findings corroborate the previous results on optimal energy-selective monochromatic reconstruction of DECT data.

The optimal VMI resulted in a superior image quality compared to the image equivalent to conventional CT scanner, having potential for contributing to accuracy delineation of brain metastases with optimal tumor-soft tissue boundary visualization for head. Although VMI at 77 keV provides a more accurate lookup table to convert HU value to electron density, lower energy levels may result in inaccurate HU values due to enlarged beam-hardening artifact.²⁰ Collectively, when using optimal VMI in treatment planning, it is necessary to pay attention not only to lookup table adjustment but also to the deviation in the HU value.

A few limitations of our study should be considered. This study could not take account of the effect of tumor location. At neighboring skull or posterior fossa, low energy level of VMI may deteriorate the visibility of tumor due to beam-hardening artifact. The higher energy level is expected to lower beam hardening artifacts in the images at the posterior or middle fossa levels.²¹ The required VMI may depend on the location of the tumor, as the

Table 2. Subjective image analysis results

Patient	Image quality				Tumor delineation			
	VMI _{ref} (77 keV)		VMI _{opt} (63 keV)		VMI _{ref} (77 keV)		VMI _{opt} (63 keV)	
	Mean	Min–Max	Mean	Min–Max	Mean	Min–Max	Mean	Min–Max
#1	3.0	3–3	3.7	3–4	2.3	2–3	3.7	3–4
#2	3.3	3–4	3.7	3–4	3.3	3–4	4.3	4–5
#3	3.0	3–3	3.0	2–4	2.7	2–3	3.0	3–3
#4	3.0	3–3	3.7	3–4	3.0	3–3	3.7	3–4
#5	3.0	3–3	3.7	3–4	3.3	3–4	4.0	3–5
#6	3.0	3–3	3.3	3–4	3.0	3–3	3.7	3–4
#7	2.7	2–3	3.3	3–4	2.7	2–3	3.3	3–4
#8	3.0	3–3	3.3	3–4	3.3	3–4	3.7	3–4
#9	2.7	2–3	3.0	3–3	2.7	2–3	3.3	3–4
#10	2.7	2–3	3.0	3–3	2.7	2–3	3.3	3–4
#11	3.0	3–3	3.3	3–4	3.0	3–3	4.0	4–4
#12	2.7	2–3	2.7	2–3	2.7	2–3	3.0	2–4
#13	3.0	3–3	3.0	3–3	3.0	3–3	3.3	3–4
#14	3.0	3–3	3.3	3–4	3.0	3–3	3.7	3–4
#15	3.0	3–3	3.0	3–3	2.3	2–3	3.0	3–3
#16	3.0	3–3	3.3	3–4	2.7	2–3	3.3	3–4
#17	2.7	2–3	3.3	3–4	2.3	2–3	2.7	2–3
#18	3.0	3–3	3.3	3–4	3.0	3–3	3.7	3–4
#19	3.0	3–3	3.3	3–4	3.3	3–4	3.3	3–4
#20	3.0	3–3	3.7	3–4	3.3	3–4	4.3	4–5
Overall	2.9	2–4	3.3	2–4	2.9	2–4	3.5	2–5
p value	<0.01				<0.01			

VMI_{ref}, reference virtual monochromatic image; VMI_{opt}, optimal virtual monochromatic image.

optimal energy levels at posterior fossa are higher compared with that at supratentorial brain as reported in earlier studies.^{9,15,16} Besides, the quantitative measurements were affected by the size or primary lesion of metastases due to a limited number of patients. Brain metastases on contrast-enhanced images present various features, such as necrosis with enhancement wall, cystic lesion, solid enhancing lesion, and their coexistence depending on the primary lesion of metastases.²² Additionally, the influence of the features depends on the size of the tumor, enlarging the variation in HU across a lesion. The measurement with low contrast such as centric necrosis might lack detectability for the tumor. However, the quantitative values in the optimal VMI were

indicated significantly better compared to that in the 120kV equivalent image despite the volume effects. Finally, our study did not attempt to evaluate DECT compared to MRI, which is currently considered as the gold standard tool for identifying brain metastases,²³ or conventional CT images.

CONCLUSION

The VMI at 63 keV yielded the highest CNR between brain parenchyma and tumor in contrast-enhanced head DECT. This VMI at the optimal energy level significantly improved the objective and subjective image quality compared to VMI with 120 kVp equivalent.

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