Predictors of thermal increase in magnetic resonance-guided focused ultrasound treatment for essential tremor: histogram analysis of skull density ratio values for 1024 elements

(本態性振戦に対する MR ガイド下超音波収束治療における温度上昇予測因子：１０２４本のエレメントの Skull density ratio 値のヒストグラム解析による)

千葉大学大学院医学薬学府

先端医学薬学専攻

（主任：宇野　隆　教授）

飯島　健

Abstract

Objective

Sufficient thermal increase capable of generating thermocoagulation is indispensable for an effective clinical outcome in patients undergoing magnetic resonance-guided focused ultrasound (MRgFUS). The skull density ratio (SDR) is one of the most dominant predictors of thermal increase prior to treatment. However, users currently rely only on the average SDR value (SDR_{mean}) as a screening criterion, even though some patients with low SDR_{mean} values can achieve sufficient thermal increase. The present study aimed to examine the numerical distribution of SDR values across 1,024 elements to identify more precise predictors of thermal increase during MRgFUS.

Methods

We retrospectively analyzed the correlations between skull parameters and the maximum temperature achieved during unilateral ventral intermediate nucleus (VIM) thalamotomy with MRgFUS in a cohort of 55 patients. In addition, we quantified the numerical distribution of SDR values across 1,024 elements using the skewness, kurtosis, entropy, and uniformity of the SDR histogram. We then evaluated the correlation between the aforementioned indices and a peak temperature over 55°C using univariate and multivariate logistic regression. Receiver operating characteristic (ROC) curve analysis was performed to compare the predictive ability of the indices. The diagnostic performance of significant factors was also assessed.

Results

SDR skewness ($SDR_{skewness}$) was identified as a significant predictor of thermal increase in both the univariate and multivariate logistic regression analyses ($P < 0.001$, $P = 0.013$). Moreover, the ROC curve analysis indicated that $SDR_{skewness}$ exhibited a better

predictive ability than SDR_{mean}, with area under the curve values of 0.847 and 0.784, respectively.

Conclusion

$SDR_{skewness}$ is a more accurate predictor of thermal increase than conventional SDR_{mean}.

We propose to set the cut-off value of $SDR_{skewness}$ to 0.68. $SDR_{skewness}$ may allow for the inclusion of treatable patients with essential tremor who would have been screened out based on the SDR_{mean} exclusion criterion.

Introduction

Transcranial magnetic resonance-guided focused ultrasound (MRgFUS) therapy is one of the newest neurosurgical approaches for the treatment of various movement disorders.[1-4] This technique uses a phased-array ultrasound beam unit composed of 1,024 elements attached to the cranial bone to generate thermal increase, resulting in thermocoagulation with millimeter precision inside a small intracranial nucleus in the brain. The targeted thermal increase is important for effective outcomes. Several prior publications have shown that achieving a peak voxel maximum temperature of 54–55°C is necessary to obtain sufficient thermocoagulation.[4-7]

The main advantage of MRgFUS is that it is less invasive than other techniques, such as deep brain stimulation (DBS) or thalamotomy procedures with radiofrequency (RF), given that the energy generated by the ultrasound beams penetrates the bones of the human skull. However, the human skull bone itself is a major impediment to effective thermal increase via the transmission of energy. In fact, the skull bone causes ultrasound waves to attenuate, disperse, and refract within the bone, resulting in loss of energy and distortion of the penetrating ultrasound beam.[8-10]

The skull density ratio (SDR) is one of the most important predictors of ultrasound skull permeability.[5,11] The SDR is defined as the ratio of the computed tomography (CT) density of bone marrow to that of cortical bones, and it is calculated for the region associated with each transducer element. A mean SDR value for 1,024 elements is used clinically. Several previous studies have reported that the mean SDR (SDR_{mean}) strongly correlates with an effective thermal increase,[5-7,11] and the SDR value is used as a criterion for MRgFUS worldwide. For example, in the United States, an SDR of 0.45 (± 0.05) or less is used as an exclusion criterion for MRgFUS for essential tremor.[12] While previous studies have indicated that the thickness and volume of the skull are also associated with thermal increase, most studies have concluded that SDR_{mean} is the most strongly correlated variable.[5-6]

However, in actual clinical cases, the SDR value and the degree of thermal increase do not always correlate. For example, temperatures increase easily in some patients with lower SDR_{mean} values (especially below 0.40) in comparison to the thermal increase predicted based on the SDR_{mean}. As such, there is a constant risk of excluding treatable patients by screening based on SDR_{mean} alone.

We hypothesized that SDR_{mean} is not a sufficiently effective indicator of a patient's suitability for MRgFUS treatment because it does not consider the distribution of SDR values. In contrast, histogram analysis has the potential to quantify the distribution of SDR, because the distribution of SDR is reflected in the shape of the histogram, from which skewness, kurtosis, entropy, and uniformity are measured . Therefore, the present study aimed to perform a histogram analysis for the SDR of 1,024 elements and investigate the predictors of sufficient thermal increase. The calculated parameters were compared with SDR_{mean}.

Materials and methods

Patients

Between June 2019 and December 2020, 55 consecutive patients with medically refractory essential tremor underwent ventral intermediate nucleus (VIM) thalamotomy using MRgFUS at our institution. No cut-off value for SDR_{mean} was applied as an exclusion criterion. The treatment protocol and study design were approved by the ethics committees of our institution, and informed consent was obtained from all patients and their nearest family members prior to treatment.

CT images and SDR

All CT images were obtained using a SOMATOM Definition AS system (Siemens Healthineers AG, Erlangen, Germany) at a tube voltage of 120 kV and an X-ray dose of 400 mAs. SDR was defined based on the Hounsfield units of the cortical bone (maximum value) and bone marrow (minimum value) on CT images of the skull. For each region of the ultrasound beam unit, SDR was automatically calculated using the ExAblate 4000 Neuro System Version 7.0 (InSightec, Haifa, Israel). A total of 1,024 SDR values were obtained for each patient.

MRgFUS procedure

Under local anesthesia, a stereotactic frame was attached over the skull. All patients with essential tremor were treated with MRgFUS using the Exablate Neuro system (Insightec, Haifa, Israel) with a 3.0-T (DV25) Discovery MR750w scanner (GE Healthcare, Milwaukee, WI, USA). The unilateral VIM nucleus was targeted in all cases. The target was set at 5.6–9.4 mm (mean ± standard deviation: 6.77 ± 0.65 mm) anterior to the posterior commissure on the anterior commissure–posterior commissure line, 1.5–3.0 mm (1.92 ± 0.35 mm) superior to the anterior commissure–posterior commissure plane, and 10–15.5 mm (11.76 ± 0.95 mm) lateral to the ipsilateral wall of the third ventricle. Sonications were repeated until relief of tremor was noted, and the number of sonications ranged from 5 to 15 (7.58 ± 1.81). The maximum temperature at the target and delivered energy ranged from 48°C to 68°C (62.8 ± 4.46℃) and from 7,557 J to 36,092 J (24,577 ± 9877.79 J), respectively.

Histogram analysis

The skull density and treatment parameters were retrospectively extracted from the ExAblate 4000 Neuro System Version 7.0 (InSightec, Haifa, Israel). In addition, histogram analysis was performed to evaluate the distribution of the SDR values for each of the 1,024 elements, and the skewness, kurtosis, entropy, and uniformity were calculated.

Statistical analysis

SPSS (Version 27.0; IBM SPSS; Chicago, IL, USA) was used for all statistical analyses. The significance level was set at $P < 0.05$. We divided the patients into two groups as follows: Group I included those who did not achieve a maximum temperature of more than 55°C during treatment (insufficient thermal increase), while Group Ⅱ included those who did (sufficient thermal increase). Fisher’s exact test and Mann–Whitney U-tests were used to compare data between Groups I and II. Skull thickness, area, and volume were also compared. Univariate logistic regression analyses were performed to identify predictors of sufficient temperature increase. Multivariate logistic regression analysis was performed using factors identified as significant in the univariate analyses. Receiver operating characteristic (ROC) curves were plotted, and the area under the curve (AUC) was calculated to evaluate the predictive ability of the skull parameters. The cutoff point for the ROC curve was defined as the maximum Youden index (sensitivity + specificity).

Results

Participants and treatment data

The demographic characteristics and procedure-related variables for the included patients are described in Table 1. Differences in clinical and skull parameters between Group I and II are summarized in Table 2. Groups I and II exhibited significant differences in SDR_{mean} and $SDR_{skewness}$ values.

Logistic regression and ROC curve analyses

In the univariate analysis, SDR_{mean} (odds ratio [OR] = 7,231,226.4, 95% confidence interval [CI] = 40.537–1.29×10^{12}, p = 0.0105) and $SDR_{skewness}$ (OR = 0.0012796, 95% CI = 7.36×10^{-4}–0.173, p <.001) were significant predictors of sufficient thermal increase. In the multivariate analysis, only $SDR_{skewness}$ was a significant predictor leading to sufficient thermal increase (OR = 0.017, 95% CI =7.18×10^{-4}–0.421, p =0.013) (Table 3). The AUC, cutoff point, sensitivity, and specificity are summarized in Table 4 and Figure 1. The AUC for $SDR_{skewness}$ was higher than that for SDR_{mean} (0.847 vs. 0.784). A scatter plot description using this cut-off value for $SDR_{skewness}$ is shown in Figure 2, which shows the relationship between SDR_{mean} and $SDR_{skewness}$.

Representative cases

Histograms and treatment data of two representative clinical cases are shown in Figure 3. The SDR_{mean} values of Patients 1 and 2 were 0.36 and 0.34, respectively, and the values were similar and matched the exclusion criteria for MRgFUS. In contrast, the

$SDR_{skewness}$ values of Patients 1 and 2 were much different (0.31 and 0.77, respectively). The shape of the histogram for Patient 2 was biased toward a lower SDR when compared to that for Patient 1. During MRgFUS, Patient 1 achieved a maximum temperature of 63°C, whereas Patient 2 achieved a maximum temperature of 52°C. The skull was thinner in Patient 2 than in Patient 1.

Discussion

In the present study, we performed a histogram analysis for the SDR of 1,024 elements and investigated predictors of sufficient thermal increase in patients undergoing MRgFUS for the treatment of essential tremor. Our findings indicated that $SDR_{skewness}$ was a significant predictor of thermal increase, exhibiting better predictive ability than SDR_{mean}. The skewness value indicates the degree of distortion of the distribution. It indicates the degree to which the distribution is symmetrical, like a normal distribution, or asymmetrical, skewed to the left or right. In this study, low $SDR_{skewness}$ indicates that elements with high SDR values are dominant, and one can expect that the temperature will increase even if the SDR_{mean} is low. This information regarding the distribution cannot be determined from a simple arithmetic mean and allows patients with the potential for sufficient thermal increase despite a low SDR_{mean} to be indicated for MRgFUS treatment.

MRgFUS exerts its effects by generating thermocoagulation with millimeter precision. Therefore, inducing this precise thermal coagulation is the most important factor in ensuring the efficacy and safety of MRgFUS, for which a thermal increase of 55°C is indispensable. If the treatment fails to achieve thermocoagulation, it is unlikely to exert a clinical effect.

The skull is a major barrier to the ultrasound convergence required to achieve a thermal increase. Currently, SDR_{mean} is the only predictor of thermal increase for the skull and is used as an exclusion criterion worldwide. Chang et al. reported that, in patients with lower SDR values, the conduction velocity in tissue and the density difference within the skull can also affect energy reflection and contribute to reduced thermal increase.[5] Although SDR_{mean} is an excellent predictor of thermal increase, using only SDR_{mean} as an exclusion criterion may exclude some treatable patients with low SDR values.

In our multivariate logistic regression analysis, $SDR_{skewness}$ was the only predictor of sufficient thermal increase. In this analysis, lower $SDR_{skewness}$ values were associated with greater increases in temperature. The $SDR_{skewness}$ value indicates whether the histogram of SDR values measured for 1,024 elements is skewed toward higher or lower values. In other words, $SDR_{skewness}$ decreases as the number of elements with higher SDR values increases. Low SDR may attenuate decreases in ultrasonic energy due to reflection between different tissues with different acoustic impedances. In a case with low $SDR_{skewness}$, increasing the number of elements in which energy losses can be attenuated may result in successful ultrasound focusing and thermal increase even if the SDR_{mean} is low.

There are two major merits of $SDR_{skewness}$. First, $SDR_{skewness}$ can help include potential patients more precisely than SDR_{mean}. The current exclusion criterion for MRgFUS based on SDR_{mean}, which reflects only the arithmetic mean of the SDR values, excludes a certain number of patients from treatment, even though they may be treatable. $SDR_{skewness}$ may allow for the inclusion of such patients. Second, $SDR_{skewness}$ can provide a more detailed preoperative temperature prediction than SDR_{mean}, allowing us to develop more appropriate preoperative plans, improve the effectiveness of treatment, and reduce the risk of adverse events.

Based on these results, we propose to set the cut-off value of $SDR_{skewness}$ to 0.68. Using this cut-off value, as shown in Figure 3, the efficient thermal increase were observed in three out of three of the cases with low SDR_{mean} (< 0.40) and low $SDR_{skewness}$ (< 0.68), which could have been predicted preoperatively.

Other skull parameters, such as $SDR_{kurtosis}$, $SDR_{entropy}$, and $SDR_{uniformity}$, do not exhibit significant relationships with peak temperature. These results suggest that skull heterogeneity and variability have a smaller effect on thermal increase than $SDR_{skewness}$. In addition, neither skull thickness nor volume was significantly associated with thermal increase in the present study. Chang et al. reported that the maximal temperature was related to only SDR_{mean} and not to skull volume.[13] To our knowledge, their study had the largest number of cases (n=318) examining the relationship between skull volume and maximum temperature, and our study obtained similar results.

Our study has several limitations. First, we only considered the distribution of the SDR values and not the location in the skull. Further research is required to analyze the locations of the SDR values. Secondly, the number of included cases was small. Further studies are required to verify our hypothesis and explore other complex predictors of thermal increase. Third, only this study could not explain why 9 out of 20 patients with low SDR_{mean} and low $SDR_{skewness}$ achieved sufficient thermal increase. Further studies are required to make it possible to rescue them preoperatively.

Conclusion

Our histogram analysis of skull parameters for each of the 1,024 elements in MRgFUS revealed that $SDR_{skewness}$ was a more accurate predictor of thermal increase than SDR_{mean}. These findings indicate that $SDR_{skewness}$ may allow for the inclusion of treatable patients with essential tremor who would have been screened out based on the SDR_{mean} exclusion criterion.

References

1. Gallay MN, Moser D, Rossi F, et al. Incisionless transcranial MR-guided focused ultrasound in essential tremor: cerebellothalamic tractotomy. *J Ther Ultrasound*. 2016;4(1):5.

2. Lipsman N, Schwartz ML, Huang Y, et al. MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study. *Lancet Neurol.* 2013;12(5):462–468.

3. Martin E, Jeanmonod D, Morel A, et al. High-intensity focused ultrasound for noninvasive functional neurosurgery. *Ann Neurol.* 2009;66(6):858–861.

4. Elias WJ, Lipsman N, Ondo WG, et al. A randomized trial of focused ultrasound thalamotomy for essential tremor. *New Engl J Med.* 2016;375(8):730–739.

5. Chang WS, Jung HH, Zadicario E, et al. Factors associated with successful magnetic resonance-guided focused ultrasound treatment: efficiency of acoustic energy delivery through the skull. *J Neurosurg.* 2016;124(2):411–416.

6. D'Souza M, Chen KS, Rosenberg J, et al. Impact of skull density ratio on efficacy and safety of magnetic resonance-guided focused ultrasound treatment of essential tremor. *J Neurosurg.* 2019;132(5):1–6.

7. Jones RM, Kamps S, Huang Y, et al. et al. Accumulated thermal dose in MRI-guided focused ultrasound for essential tremor: repeated sonications with low focal temperatures. *J Neurosurg.* 2020;132(6):1802–1809.

8. Elias WJ, Huss D, Voss T, et al. A pilot study of focused ultrasound thalamotomy for essential tremor. *New Engl J Med.* 2013;369(7):640–648.

9. Halpern CH, Santini V, Lipsman N, et al. Three-year follow-up of prospective trial of focused ultrasound thalamotomy for essential tremor. *Neurology.* 2019;93(24):e2284–e2293.

10. Sinai A, Nassar M, Eran A, et al. Magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: a 5-year single-center experience. *J Neurosurg*. Published online July 5, 2019. doi: 10.3171/2019.3.JNS19466.

11. Boutet A, Gwun D, Gramer R, et al. The relevance of skull density ratio in selecting candidates for transcranial MR-guided focused ultrasound. *J Neurosurg*. Published online May 3, 2019. doi: 10.3171/2019.2.JNS182571.

12. Food and Drug Administration. SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED), Magnetic Resonance Guided Focused Ultrasound Surgery System (MRgFUS). Date of FDA Notice of Approval: December 16, 2018. (Accessed: 27 March 2021) https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150038S006B.pdf

13. Chang KW, Park YS, Chang JW, et al. Skull factors affecting outcomes of magnetic resonance-guided focused ultrasound for patients with essential tremor. *Yonsei Med J*. 2019;60(8):768–773.

Figure legends

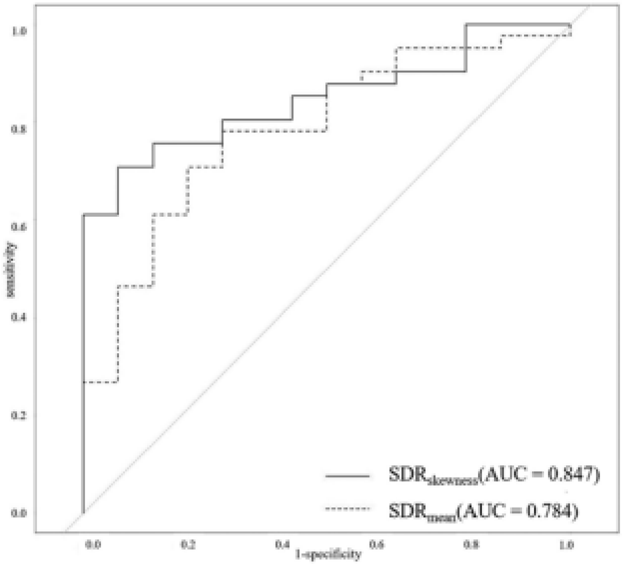
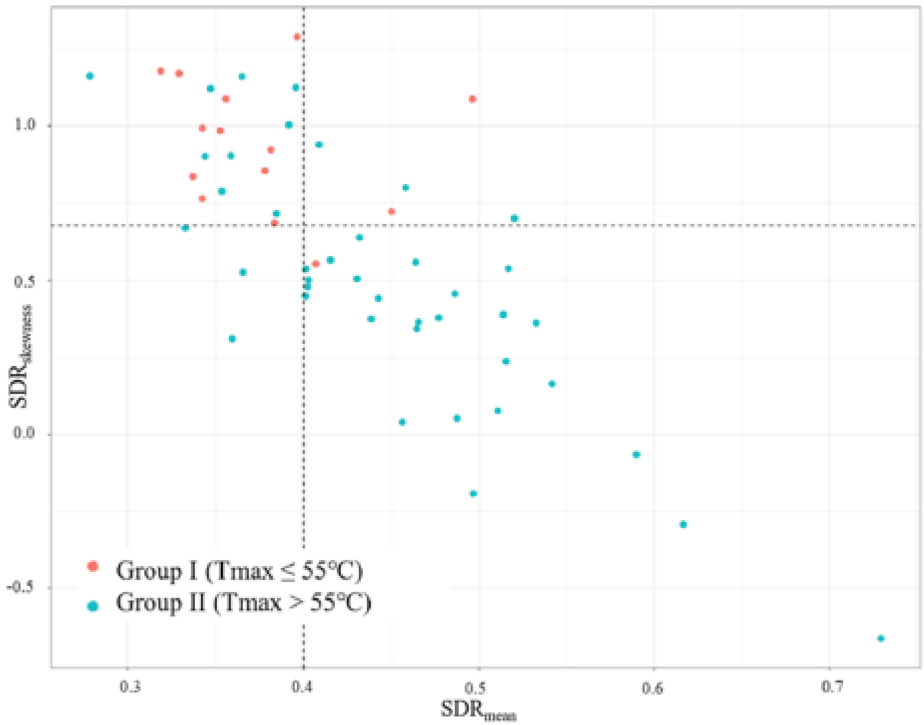


FIG. 1. ROC curves for the $SDR_{skewness}$ and the SDR_{mean} obtained using the prediction model.



IG. 2. The scatterplot description shows the relationship between the SDR_{mean} and the $SDR_{skewness}$. The vertical and horizontal *otted lines* show the cutoff value of the SDR_{mean} (0.40) and the $SDR_{skewness}$ (0.68). Figure is available in color online only.

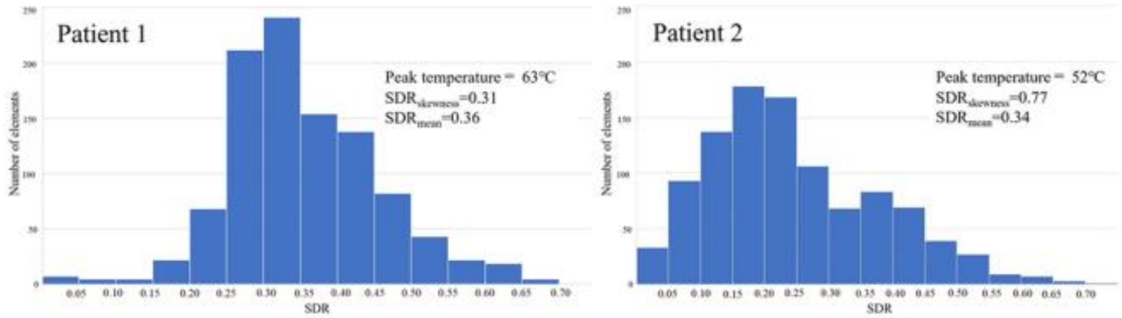


FIG. 3. Histograms and treatment data for two representative clinical cases. Figure is available in color online only.

Tables

Table 1. Characteristics and therapeutic parameters of patients who underwent MRgFUS

Factors	Values
Number of patients	n = 55
Age (y)	71.4 ± 10.7
Sex (male : female)	39 : 16
Treatment side (left : right)	49 : 6
Number of active transducer elements	972.35 ± 33.15
Number of sonications	7.64 ±1.82
Peak temperature (℃)	58.36 ± 4.46
Maximal energy delivered (J)	24,577.68 ± 9,877.79

MRgFUS: magnetic resonance-guided focused ultrasound

Values are presented as the mean ± standard deviation.

Table 2. Differences in clinical and skull parameters between Group I (Tmax ≤ 55°C) and II (Tmax > 55°C)

	Group I (n = 14)	Group II (n = 39)	p value
	Tmax[a] ≤ 55°C	Tmax > 55°C	
Age (y)	71.14 ± 7.10	71.53 ± 11.63	0.395 [b]
Sex (male : female)	12: 2	17: 12	0.277 [c]
Treatment side (left : right)	12:2	35: 4	0.66 [c]
SDR mean	0.38 ± 0.09	0.45 ± 0.09	< .001 [b]
SDR skewness	0.94 ± 0.20	0.48 ± 0.40	< .001 [b]
SDR kurtosis	0.41 ± 0.61	0.01 ± 0.67	0.060 [b]
SDR entropy	3.97 ± 0.15	3.93 ± 0.20	0.575 [b]
SDR uniformity	0.02 ± 0.01	0.02 ± 0.01	0.907 [b]
Skull thickness (mm)	6.73 ± 0.96	6.29 ± 0.90	0.208 [b]
Skull area (cm^2)	361.57 ± 27.74	362.0 ± 26.59	0.938 [b]
Skull volume (cm^3)	243.62 ± 41.65	227.8 ± 378.3	0.208 [b]

SDR: skull density ratio

Continuous data are expressed as the mean ± standard deviation

[a] Tmax refers to the peak temperature during treatment

[b] Mann–Whitney U-test

[c] Fisher's exact test

Table 3. Univariate and multivariate analysis of skull parameters as predictors of sufficient thermal increase (> 55°C)

	Univariate analysis			Multivariate analysis		
Variable	OR[a]	95% CI[b]	p value	OR	95% CI	p value
Age (y)	1.003	0.0949-1.061	0.905			
SDR mean	7231226.4	40.537-1.29×10^{12}	0.0105	43.251	1.52×10^{-5}-123083425.4	0.619
SDR skewness	0.0012796	7.36×10^{-4}-0.173	$<$ .001	0.017	7.18×10^{-4}-0.421	0.013
SDR kurtosis	0.355	0.164-1.068	0.068			
SDR entropy	0.526	0.011-9.824	0.355			
SDR uniformity	0.723	2.95×10^{-42}-7.411×10^{59}	0.723			
Skull thickness (mm)	0.595	0.304-1.164	0.595			
Skull area (cm^2)	1.001	0.978-1.023	0.954			
Skull volume (cm^3)	0.999	0.998-1.001	0.207			

OR: odds ratio; CI: confidence interval; SDR: skull density ratio

Table 4. Diagnostic performance of texture features as independent predictors of sufficient thermal increase (> 55℃)

Variable	AUC	95% CI	Cut-off point	Sensitivity	Specificity
SDR skewness	0.847	0.746-0.947	0.670	0.929	0.701
SDR mean	0.784	0.648-0.919	0.384	0.714	0.780

AUC: area under the curve; CI: confidence interval; SDR: skull density ratio

Table 5. Skull parameters and peak temperatures of two representative clinical cases

Patient number	Peak Temperature	SDR skewness	SDR mean	Skull thickness
1	63℃	0.31	0.36	6.95
2	52℃	0.77	0.34	5.89

SDR: skull density ratio

Journal of Neurosurgery, Online ahead of print.

2021年10月15日公表済

DOI: 10.3171/2021.5.JNS21669