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Voxel-Based Analysis of I-123 IMP by SPECT/CT in Patients with Uveal Malignant Melanoma: A Comparison with ROI Analysis

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1. Abstract

1.1. Purpose: To estimate I-123 N-isopropyl-p-iodoamphetamine (IMP) accumulation using a voxel-based analysis method for the differentiation of malignant melanoma from other ocular lesions.

1.2. Materials and Methods: Fifty patients (53 examinations) with malignant melanoma (n = 30) or benign pigmented lesions or tumors other malignant melanoma (n = 20) were analyzed. Voxel-based analysis using 3-dimensional images and pixel-based analysis using 2-dimensional images with small and large VOI (ROI) for each ocular region that were manually drawn over the areas of abnormal I-123 IMP uptake, were performed using the CT findings. Then, VOIs (ROIs) of the same size as that of the corresponding tumor were drawn on the contralateral orbital space. Sixteen parameters were assessed by receiver operating characteristic (ROC) curve analysis with the area under the curve to differentiate malignant melanoma from the other lesions. ROC curves were finally compared using the method of DeLong et al. A p-value of less than 0.05 was considered to indicate a statistically significant difference between 2 groups.

1.3. Results: When the cutoff value was set at 1.140, the sensitivity, specificity, and positive predictive value of malignant melanomas were 90.3%, 95.2%, and 96.6%, respectively, using a delayed tumor to normal ratio (T/N ratio) T/N ratio with large VOI.

1.4. Conclusions: A delayed T/N ratio with a large VOI that fits inside the orbital wall was the most useful parameter regarding reproducibility and objectivity, and also showed high sensitivity and specificity.

2. Introduction

At present, I-123 N-isopropyl-p-iodoamphetamine (IMP) is the most accurate tool for evaluating uveal malignant melanomas [1-3]. Therefore, establishing an objective quantification method is thought to be very important. For semiquantification of I-123 IMP images of ocular lesions, Region of Interest (ROI) analysis has been discussed in several reports. We also previously reported that using ROI analysis, the sensitivity and specificity of detecting malignant melanoma was 89.5% and 68.8%, respectively, when the retention index cutoff value was set at 30, and 94.7% and 88.6%, respectively, when the T/N ratio cutoff value was set at 1.5 [4]. This conventional ROI analysis has some problems. One is that small or flat lesions can be missed when drawing reproducible ROIs. The other is that larger lesions do not fit in a single ROI.

Therefore, towards resolving the above problems, the purpose of this study was to estimate I-123 IMP accumulation using a voxel-based analysis method for the differentiation of malignant melanoma from other ocular lesions

3. Materials and Methods

3.1. Patients

Fifty patients (14 men and 36 women) were examined a total of 53

times, from November 2011 to November 2016 (Table 1). Thirty patients had malignant melanoma (group A), and 20 patients had either benign pigmented lesions or tumors other than malignant melanoma (group B). Malignant melanoma was diagnosed by surgery or clinically. Other benign lesions that were not operated on showed stable clinical findings for 1 or more years. This study was approved by the Institutional Review Board of our Tokyo Medical University.

Table 1: Patient Characteristics

group A	malignant melanoma	choroidea	24
		cilliary body	4
		conjunctiva	2
group B	melanocytoma	iris	1
		optical disc	3
		choroidea	4
	nevus	choroidea	2
		conjunctiva	1
	metastatic choroidal tumor (lung/ovary)		2
	cilliary leiomyoma		1
	shwannoma		1
	iridociliary pigmented tumor		1
	choroidal hemangioma		1
	proliferative vitreoretinopathy		1
	branch retinal vein occlusion		1
	age-related macular degeneration		1

3.2. Image Acquisition

SPECT/CT was performed using a 2-headed camera (SymbiaT16, Siemens Medical Solutions, Germany) equipped with a low-medium energy general purpose collimator. Imaging was started from 15 min (early imaging) and from 24 h (delayed imaging) after intravenous injection of 111 MBq of I-123 IMP. Whole-body data collection was performed for about 10 min (16 cm/min), and SPECT data collection (25 s/step, 45 steps) was performed for 20 min. The matrix size was 128 × 128, and the collection window was 159 keV centered at 20% width. Raw data was reconstructed using Flash 3D.

Immediately after SPECT acquisition, an unenhanced CT scan was performed. Regional CT was performed using the following parameters: 512 × 512 matrix, 110 kVp, 0.6 s rotation time, and 0.7 mm pitch. CT-based attenuation correction was used.

3.3. Voxel-Based Analysis of I-123 IMP SPECT/CT

Voxel-based analysis was performed using 3-dimensional images. The smaller VOI of the ocular tumor was manually placed over the area of abnormal I-123 IMP uptake and determined according to the CT findings. The larger VOI was set in contact with the orbital wall, and the smaller and larger VOIs were drawn on the contralateral orbital space with the same voxel size as the corresponding tumor VOI (Figure 1). In addition, 8 parameters of VOI analysis were defined in the same manner as ROI analysis in previous reports, as follows:

A: early T/N ratio (L) = mean count in tumor VOI/mean count in normal tissue in the early image with larger VOI

B: early T/N ratio (S) = mean count in tumor VOI/mean count in normal tissue in the early image with smaller VOI

C: delayed T/N ratio (L) = mean count in tumor VOI/mean count in normal tissue in the delayed image with larger VOI

D: delayed T/N ratio (S) =mean count in tumor VOI/mean count in normal tissue in the delayed image with smaller VOI

E: increasing rate (L) = C/A

F: increasing rate (S) = D/B

G: retention index (L) = (C–A)/A

H: retention index (S) = (D–B)/B

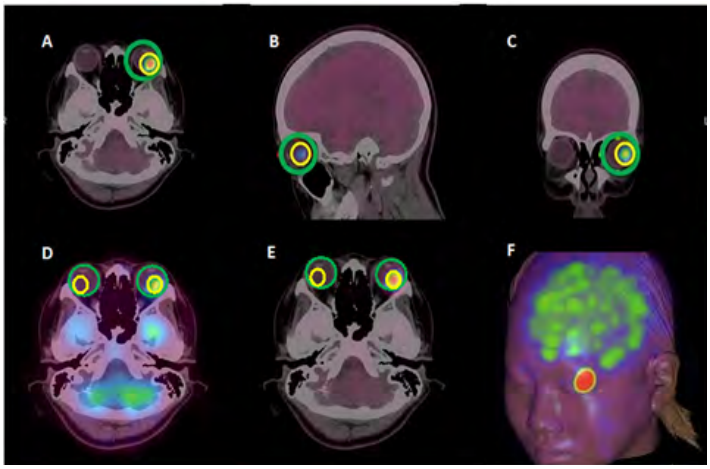

Figure 1: VOI setting. Large (green circle) and small (yellow circle) VOIs in axial (A), sagittal (B), and coronal (C) images. Early (D) and delayed (E) images with VOIs of the tumoral and contralateral side. (F) 3D image of I-123 IMP accumulation in a patient's tumor.

3.4. ROI Analysis of I-123 IMP SPECT/CT Images

ROI analysis was performed according to previous reports. Four ROIs were drawn on every case. The smaller ROI for the ocular tumor was manually placed over the areas of abnormal I-123 IMP uptake determined according to the CT data, and the larger ROI was set on the same slice in contact with the orbital wall. In addition, smaller and larger ROIs on the same slice were drawn on the contralateral orbital space with the same pixel size as the corresponding tumor ROI.

The 8 parameters in the ROI analysis were defined as follows:

I: early T/N ratio (L) = mean count in tumor ROI/mean count in normal tissue in the early image with larger ROI

J: early T/N ratio (S) = mean count in tumor ROI/mean count in normal tissue in the early image with smaller ROI

K: delayed T/N ratio (L) = mean count in tumor ROI/mean count

in normal tissue in the delayed image with larger ROI

L: delayed T/N ratio (S) = mean count in tumor ROI/mean count in normal tissue in the delayed image with smaller ROI

M: Increasing rate (L) = K/I

N: Increasing rate (S)= L/J

O: Retention index (L) = (K–I)/I

P: Retention index (S) = (L–J)/J

3.5. Statistical Analysis

All of the 16 parameters were presented as the mean ± standard deviation. Receiver operating characteristic (ROC) curve analysis with areas under the curve was used to differentiate malignant melanoma from other lesions. Optimal cutoff values of the 16 indices for sensitivity and specificity were calculated as the highest value of sensitivity and (1 − specificity), respectively. ROC curves were finally compared using the method of DeLong et al. A p-value of less than 0.05 was considered to indicate a statistically significant difference between 2 groups.

4. Results

ROC curve analysis for the diagnostic accuracy of the 16 parameters are shown in Figure 2 and Table 2. All VOI methods except for A was superior to the ROI method of the same formula. Regarding the VOI methods, 6 parameters except for A (AUC value: 0.524) and B (AUC value: 0.627), which utilized early accumulation, showed high AUC values (0.966–0.977). C and D were more useful than E to H because they did not need early phase examination. In terms of VOI size, larger VOIs showed lower AUC values.

Next, the results of ROC analysis of C and D were compared. AUC values of C and D were 0.966 and 0.977, respectively, and optimal cutoff values for malignant melanoma were 1.140 and 1.153, respectively. Delong test showed that there was no significant difference between the 2 parameters ($p < 0.05$).

Box-and-whisker plots of parameter C are shown in Figure 3. The mean ± SD of melanoma (group A) and non-melanoma (group B) were 1.766 ± 0.192 and 0.997 ± 0.095, respectively. There was a significant difference between the 2 groups using the Welch t-test ($p < 0.05$). When the cutoff value was determined as 1.140, the sensitivity, specificity, and positive predictive value (PPV) of malignant melanoma were 90.3%, 95.2%, and 96.6%, respectively.

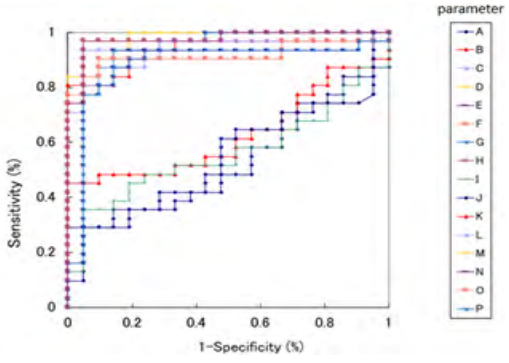

Figure 2: ROC curve analysis of each parameter (A-P).

Table 2: AUC value of each parameter

parameter			AUC value
VOI	A	early T/N (L)	0.524
	B	early T/N (S)	0.627
	C	delayed T/N (L)	0.966
	D	delayed T/N (S)	0.977
	E	increased ratio (L)	0.977
	F	increased ratio (S)	0.974
	G	retention index (L)	0.959
	H	retention index (S)	0.974
ROI	I	early T/N (L)	0.559
	J	early T/N (S)	0.546
	K	delayed T/N (L)	0.932
	L	delayed T/N (S)	0.931
	M	increased ratio (L)	0.916
	N	increased ratio (S)	0.883
	O	retention index (L)	0.916
	P	retention index (S)	0.883

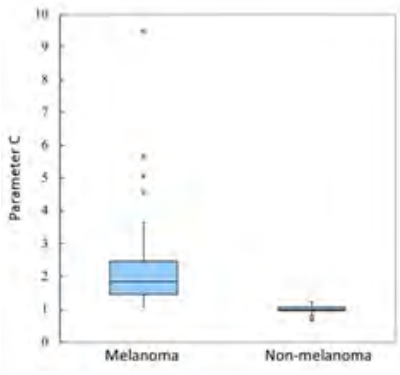

Figure 3: Box-and-whisker plots of parameter C. Values of parameter C (mean ± SD) of melanoma and non-melanoma patients were 1.766 ± 0.192 and 0.997 ± 0.095, respectively, which showed a statistically significant difference in the Welch t-test ($p < 0.05$).

5. Discussion

The effectiveness of I-123 IMP to differentiate malignant melanomas from other types of tumors and melanotic lesions of the choroid is well known [1-3]. We previously reported high sensitivity and specificity of semiquantitative analysis of malignant melanomas by the ROI method [4]. However, regarding clinical use of the ROI method, it is used for evaluating the efficacy of conservative therapies, such as heavy particle beam therapy for malignant melanomas, and the follow up of nevi that may have malignant potential (Figure 4). In these situations, to evaluate slight accumulations reproducibly while avoiding arbitrariness is the most important point. In this study, the ROI method was found to be inferior to the VOI method. A small VOI was superior to a large VOI in diagnostic accuracy, but accurately drawing the VOI surrounding the lesion was sometimes difficult, particularly when the accumulation

was slight, and when the accumulation spread over several slices in the longitudinal direction. Therefore, we used parameter C, that is, the delayed T/N ratio with a large VOI that fits inside the orbital wall. The cutoff value to differentiate melanoma from nonmelanoma was determined as 1.14, and the sensitivity, specificity, and PPV were calculated to be 90.3%, 95.2%, and 96.6%, respectively. One false-positive case and 3 false-negative cases were identified in this study. Two of the 3 patients who showed false-negative results by delayed T/N with a large VOI were found to be true positives on delayed T/N with a small VOI. Smaller VOIs were advantageous when the accumulation was obvious. The other 2 patients who showed false-negative and false-positive results had values that were very close to the cutoff level, and hence it was difficult to differentiate a tumoral lesion from the signal noise even by visual judgement. Therefore, in such cases, it is also difficult to make a small VOI. This is thought to be a limitation of this study.

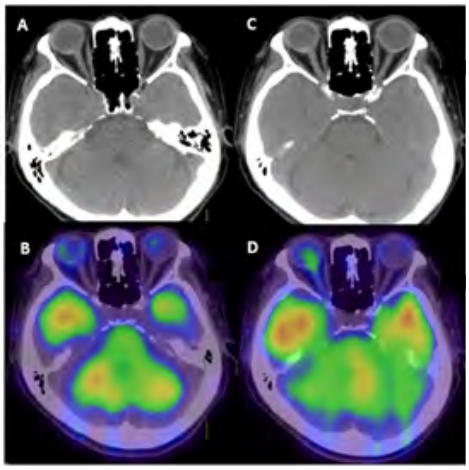

Figure 4: I-123 IMP SPECT/CT images of a 64-year-old woman, who was being followed for several years for a right choroidal nevus. (A, B) Images taken 6 months after the previous examination, indicating that the tumor had expanded slightly from 6.4 mm × 3.0 mm to 7.5 mm × 3.0 mm, together with pigmentation. I-123 IMP SPECT/CT accumulation increased from 1.15 to 1.29 in parameter C, in which the cutoff value was 1.14. Although the CT image remained stable, this suggested malignant transformation.

6. Conclusion

In this study, we demonstrated 16 parameters for the assessment of malignant melanoma. A delayed T/N ratio with a large VOI that fits inside the orbital wall was the most useful parameter regarding reproducibility and objectivity, and also had high sensitivity and specificity.

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