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Diagnostic performance of SPECT–CT imaging in unilateral condylar hyperplasia

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Abstract. Nuclear imaging plays an important role in the diagnostic path of patients with unilateral condylar hyperplasia (UCH). The purpose of this study was to determine the performance of single-photon emission computed tomography–computed tomography (SPECT–CT) in a large group of patients with suspected UCH. This study prospectively included 156 patients with a clinical presentation of progressive mandibular asymmetry. All patients underwent $^{99\,m}$Tc-HDP SPECT–CT and extensive baseline and follow-up documentation. The relative activity of the ipsilateral condyle in relation to the contralateral condyle was calculated for both the mean and maximum count, and the diagnostic accuracy of different cut-off values was determined. The area under the receiver operating characteristic curve of the SPECT–CT scan was 0.892 for the mean count and 0.873 for the maximum count. The optimal cut-off of > 8% (SPECT–CT mean count) resulted in a sensitivity of 87.0% and a specificity of 88.6%. SPECT–CT showed good diagnostic performance in UCH; however the benefit of the CT scan is questionable and the potential disadvantages have to be weighed against the benefits when compared to standard SPECT scanning. When using SPECT–CT in the diagnostic path in UCH, a mean value cut-off of > 8% for the relative activity between the condyles is most accurate.

Keywords: Mandible; Hyperplasia; Mandibular condyle; Tomography; SPECT CT; Growth; Osteotomy.

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Unilateral condylar hyperplasia or hyperactivity (UCH) is a pathological condition in which increased bone cell activity in one of the mandibular condyles results in a growth-resembling progressive asymmetry of the face. The condition evolves over an uncertain period and at an uncertain rate, and the progression is typically self-limiting but results in a persistent asymmetry.[1] One of the main goals and challenges in the diagnostic path of patients with suspected UCH is to confirm or exclude ongoing hyperactivity in the mandibular condyle. This is particularly important, because the treatment of a patient with ongoing hyperactivity differs from that of a patient with asymmetry and ceased UCH. The former may be treated with a condylectomy to arrest the progression of the condition, while the latter does not need a condylectomy and treatment can be aimed directly at restoration of function, without the need to perform a condylectomy.[2] Patients treated in the early active phase of UCH tend to have a more symmetric final outcome after corrective osteotomy compared to patients with a more advanced asymmetry due to postponed or no treatment of condylar hyperactivity.[3] This emphasizes the importance of adequately establishing the actual ongoing activity in the condyles in the individual patient.

Nuclear bone scanning is the preferred diagnostic method to determine this condylar bone activity. It is performed by intravenous application of a technetium-99 m (^{99m}Tc)-labelled diphosphonate, which has a particular affinity for osteoblastic activity. The scanning techniques have developed from simple two-dimensional (2D) planar imaging towards three-dimensional (3D) imaging, called single-photon emission computed tomography (SPECT), and the introduction of a hybrid technique that combines SPECT images with computed X-ray tomography (CT) images (SPECT–CT). SPECT imaging is a sensitive and accurate diagnostic method for detecting the hyperactivity in UCH.[4] The benefit of the SPECT–CT hybrid technique compared to SPECT imaging in UCH has not yet been established. Only a few case reports and small patient series are available on this subject.[5–11] The aim of this prospective study was to determine the diagnostic performance of SPECT–CT in a large group of patients with suspected UCH.

Materials and methods

Patient selection

Patients who underwent SPECT–CT for mandibular asymmetry were prospectively included in this study. All patients were evaluated between 2013 and 2017 in the Spaarne Gasthuis in Haarlem, the Netherlands, which serves as a tertiary centre for UCH in close cooperation with the Department of Oral and Maxillofacial Surgery of Amsterdam University Medical Centre. The patients were referred to the Department of Oral and Maxillofacial Surgery with progressive asymmetry by their dentist, orthodontist, or maxillofacial surgeon. An anamnestic or clinical presentation of progressive mandibular asymmetry was present in all cases, and therefore an indication for nuclear diagnostic evaluation was determined.

The patients were evaluated in accordance with the algorithm described by Nolte et al.[12] (Fig. 1). Extensive baseline documentation was conducted for all patients, including – as a minimum – standardized clinical documentation, a cone beam computed tomography (CBCT) scan, dental cast models, clinical pictures, and 3D photographs. Patients were referred to the Nuclear Medicine Department for a SPECT–CT scan if there was a suspicion of progressive asymmetry and UCH based on the patient's history and the baseline documentation. The Medical Ethics Committee of VU University Medical Centre reviewed and approved the research protocol (12/112).

SPECT–CT imaging and processing

The patients were intravenously injected with ^{99m}Tc-hydroxymethylene diphosphonate (HDP). The injected dose was determined by correcting the standard 600 MBq dose according to the patient's body surface area,[13] using the following formula: injected dose (MBq) = (body surface area/1.73) × 600 MBq.

SPECT–CT of the head was acquired using a Symbia dual head scanner (Siemens Medical Solutions, Erlanger, Germany), in a three-phase protocol. The SPECT imaging was acquired with a collimator with a matrix size of 256 × 256 at 15 s per frame and 180 degrees of rotation. The CT imaging was acquired using settings of 80 kV, 60 mA, and 3.0 mm slice thickness. The images were processed and analysed using standard Siemens e.soft software and Flash3D reconstruction with six iterations and eight subsets.

SPECT–CT analysis

The analysis of the reconstructed SPECT–CT images was done by an experienced nuclear medicine physician. If necessary, the fused images were manually aligned to correct for incorrect automatic alignment between the CT scan and SPECT scan. In the attenuated corrected axial slices of the SPECT–CT scans, a 9 × 9 voxel volume of interest (VOI) was drawn in both the left and right mandibular condyles. The mean and maximum numbers of counts per pixel in an image were determined. The left-to-right difference between the two condyles was calculated using the equation of Saridin et al.[14]: relative activity = (counts per pixel in the ipsilateral VOI)/(counts per pixel in the ipsilateral + contralateral VOIs) × 100 (%). This activity was calculated for both the mean and maximum count.

The SPECT–CT scan was considered positive if the relative activity was more than 55%, which is a difference in activity of more than 10% between the ipsilateral and contralateral condyles.

Follow-up

The gold standard was a combination of the patient's history, serial assessment of the clinical and radiological situation, and postoperative histopathological assessment of the resected condyle. Patients with progressive mandibular asymmetry and a positive SPECT–CT scan, who underwent a condylectomy were identified as disease-positive (active UCH) Patients with a negative SPECT–CT scan and clinical progression of the asymmetry during follow-up were also considered disease-positive. The condylar hyperplasia team assessed the progression by comparing the baseline documentation with the follow-up documentation using dental casts, clinical and 3D pictures, and CBCT scans. Patients with a negative SPECT–CT whose condition remained stable during follow-up were considered disease-negative (stable UCH). Patients with a positive SPECT–CT scan who refused a condylectomy were identified as disease-positive if the asymmetry progressed and were identified as disease-negative if the asymmetry was stable during follow-up. After condylectomy, all condyle specimens were sent for histopathological assessment.[15]

Statistical analysis

The results were recorded as the mean ± standard deviation (SD) values. Variables were analysed using the Student *t*-test or Pearson χ^2 test. A *P*-value less than 0.05 was considered statistically significant. The diagnostic accuracy of the SPECT–CT was quantified by determining the sensitivity and specificity, and analysis of the receiver operating characteristic (ROC) curves. To describe the discriminative power of the tests, the area under the ROC curve (AUC) was calculated. All data were analysed with IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA).

Results

The study group consisted of 156 consecutive patients, 84 female (53.8%) and

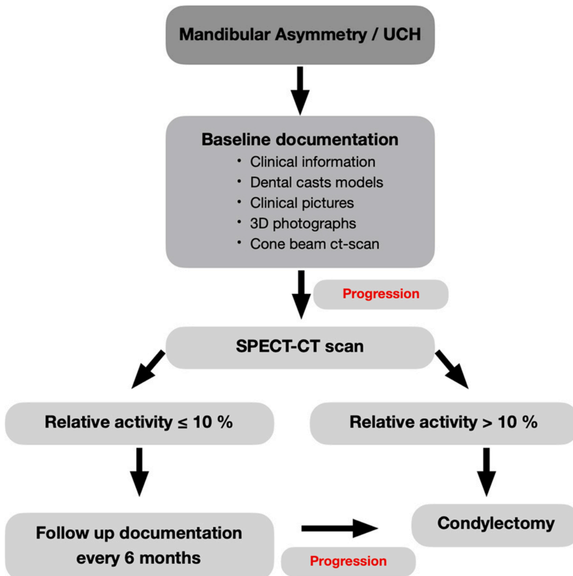

Fig. 1. Clinical protocol according to Nolte et al., 2018.[12]

72 male (46.2%). The mean ± SD age at first presentation in the outpatient clinic was 19.7 ± 7.6 years (range 10.5–54 years). A right-side UCH was suspected in 87 patients (55.8%) and left-side UCH in 69 patients (44.2%) (Table 1).

According to the protocol, a SPECT–CT scan was considered positive when there was a left–right difference of the mean activity in the VOI of more than 10%.[14] In total, 77 patients were considered disease-positive (i.e. active UCH) (Table 2). This group included 42 female (54.5%) and 35 male (45.5%) patients, with a mean ± SD age of 18.7 ± 5.9 years (range 10.5–49.2 years); the condylar hyperplasia was righted-sided in 53.2%. The mean follow-up time was 2.2 ± 1.3 years (range 0.3–6.5 years) for the total group, with a minimum follow-up time of 1 year for the disease-negative patients. In the SPECT–CT negative group, 16 patients received a condylectomy because of clear clinical progression of the asymmetry; together with the patients who showed progression of the asymmetry during the follow-up time, these patients were classified as false-negative (22 patients). A follow-up policy was adopted for 10 patients in the positive SPECT–CT group. Eight of these patients showed no progression of the asymmetry; these patients were classified as false-positive (Fig. 2).

Regarding the diagnostic performance, the AUC for the mean SPECT–CT values was 0.892 (95% confidence interval 0.836–0.948) and the AUC for the maximum SPECT–CT values was 0.873 (95% confidence interval 0.816–0.931) (Fig. 3).

Table 1. Summary of patient characteristics for the total group ($N = 156$).

	n (%)
Lateralization	
Left side	69 (44.2)
Right side	87 (55.8)
Sex/lateralization	
Female	84 (53.8)
Left side	40 (47.6)
Right side	44 (52.4)
Male	72 (46.2)
Left side	29 (40.3)
Right side	43 (59.7)
SPECT–CT: mean, > 10%	
Positive	63 (40.4)
Negative	93 (59.6)
SPECT–CT: max, > 10%	
Positive	72 (46.2)
Negative	84 (53.8)

SPECT–CT, single-photon emission computed tomography–computed tomography.

The optimal cut-off for the mean SPECT–CT VOI counts was > 8%; this resulted in a sensitivity of 87.0% and a specificity of 88.6% (Table 3; Supplementary Material Table S1). The optimal cut-off for the maximum SPECT–CT VOI was 9.5%, resulting in a sensitivity of 80.6% and a specificity of 88.6%. When using the > 10% VOI count cut-off, as used in the protocol, the sensitivity and specificity of the SPECT–CT scan for the mean counts were 71.4% and 89.9%, respectively. When using the maximum counts in the SPECT–CT VOI, the sensitivity and specificity were 80.5% and 88.6% for the > 10% cut-off. All histopathological specimens showed a non-specific bone condition in line with the clinical diagnosis of UCH.[15,16] No other benign or malignant diseases were found.

Discussion

This study describes the diagnostic performance of SPECT–CT in a large group of consecutive patients with progressive mandibular asymmetry. The study showed good diagnostic performance for the SPECT–CT scan in condylar hyperplasia. All patients were evaluated by a highly experienced condylar hyperplasia team, with standardized documentation, diagnostics, and treatment algorithm. The demographic data of the study patients are in concordance with earlier reports of demographics in condylar hyperplasia.[12,17,18]

The main problem when comparing diagnostic studies for condylar hyperplasia is the lack of a clear definition of the gold standard. In the present study, a combined gold standard consisting of the patient's history, the evolution of the clinical situation at multiple moments (dental casts, CBCT scans, 2D/3D photographs), and the histopathology of the resected specimens was used. Other studies have used only histopathological analysis[19,20] or clinical data[14] as the reference standard. Although multiple reports have described common histopathological features of condylar hyperplasia (mainly greater thickness of the cartilage, presence of included cartilage islands in the subchondral bone), condylar hyperplasia has a non-specific histopathology.[15,21] A recent systematic review showed no consensus on a characteristic histopathological description in condylar hyperplasia. The common histopathological features mentioned above could well be related to the age of the specimens, and the available studies on this subject show a high risk of bias. Other authors have also concluded that condylar hyperplasia is a diagnosis based on a combination of clinical evaluation, imaging, and histological evaluation.[16] Together with the long follow-up period, the combined gold standard used in the present study aims to overcome the disadvantages of using a single gold standard. However, there are some drawbacks of the combined gold standard in the present study setting: UCH is not defined by a clear quantification

Table 2. Summary of subgroup characteristics.

	Active UCH ($n = 77$, 49.4%)	Stable UCH ($n = 79$, 51.4%)	*P*-value
Age (years), mean ± SD	18.7 ± 5.9	21.0 ± 8.8	0.48
Sex, *n* (%)			
Female	42 (54.5%)	42 (53.2%)	0.83
Male	35 (45.5%)	37 (46.8%)	0.91
Lateralization, *n* (%)			
Left	36 (46.8%)	33 (41.8%)	0.84
Right	41 (53.2%)	46 (58.2%)	0.78
Δ relative activity mean (%), mean ± SD	14.59 ± 7.95	0.79 ± 7.44	< 0.001
Δ relative activity maximum (%), mean ± SD	16.52 ± 9.53	− 0.12 ± 8.86	< 0.001

SD, standard deviation; UCH, unilateral condylar hyperplasia.

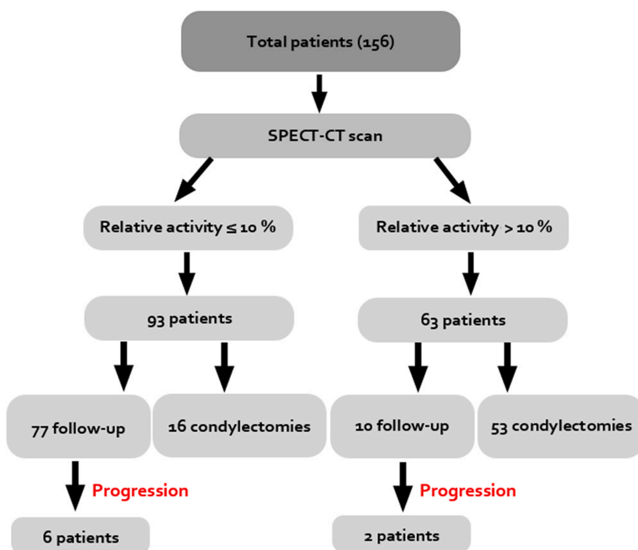

Fig. 2. Flowchart of study patients, using the clinical protocol shown in Fig. 1.

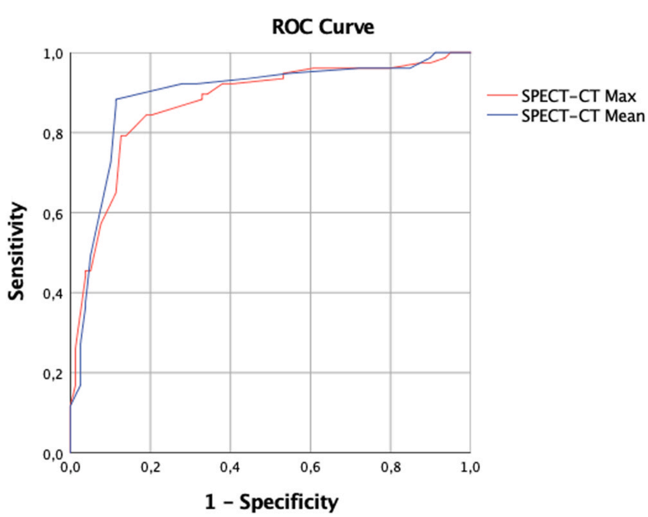

Fig. 3. ROC curves for SPECT–CT mean values (AUC = 0.892) and SPECT–CT maximum values (AUC = 0.873).

of the progression and still relies on the interpretation of the follow-up documentation as performed by the condylar hyperplasia team.

Since the first reports in the early 1980 s, nuclear imaging has gained a central role in the evaluation of patients with facial asymmetry.[22,23] During the last decades, several new nuclear modalities besides basic planar scanning have been introduced into this field, such as SPECT imaging and hybrid modalities like SPECT–CT and positron emission tomography (PET)–CT scans.[5,24] With these technological developments, possibilities arise for more detailed visualization of the growth centre and a more accurate representation of the actual growth potential of the mandible.

Compared with qualitative analysis and planar bone scanning, there is a well-established added value of quantitative analysis and SPECT imaging in condylar hyperplasia.[4,25] For SPECT–CT imaging, this potential added value has not yet been established. The present study showed good diagnostic performance for both the mean and maximum relative activity of SPECT–CT in UCH. When using a mean counts cut-off value of > 8% of the relative activity between the condyles, the sensitivity was 87.0% with a specificity of 88.6%. This optimal cut-off of > 8% is different from the optimal cut-off of > 10% to > 12% normally used in SPECT scanning.[14,26]

The diagnostic performance of SPECT–CT in patients with UCH demonstrated in the present study is partially in line with the results of studies by Liu and Shi[10] and Agarwal et al.[9] The study by Liu and Shi[10] evaluated the diagnostic performance of SPECT and SPECT–CT in condylar hyperplasia in a group of 56 patients. The study found a sensitivity of 66.7% and specificity of 76.7% for the SPECT–CT mean counts and 76.7% and 84.6%, respectively, for the SPECT–CT maximum counts, when using a relative activity threshold of > 10%. The AUC of 0.896 for the SPECT–CT maximum counts is in line with the results of the present study; however, the AUC of

Table 3. Diagnostic accuracy with different relative activity cut-offs.

	Sensitivity (%)	Specificity (%)
SPECT–CT mean count		
> 12%	61.0	92.4
> 10%	71.4	89.9
> 8%	87.0	88.6
SPECT–CT max count		
> 12%	67.5	88.6
> 10%	80.5	88.6
> 8%	84.4	81.0

SPECT–CT, single-photon emission computed tomography–computed tomography.

0.720 for the SPECT–CT mean counts is lower than that found in the present study. The study of Liu and Shi[10] showed no better diagnostic performance of SPECT–CT when compared to that of conventional SPECT in condylar hyperplasia. It is, however, not clear from their study design what the gold standard was, nor was it clear which diagnostic modality (SPECT or SPECT–CT, maximum or mean counts) was used in their clinical decision-making. Agarwal et al.[9] used a comparable combined reference standard as used in the present study. Compared with SPECT scanning, their study showed a higher diagnostic accuracy for the SPECT–CT modality. This was not supported by the study of Theerakulpisut et al.,[8] who found a trend towards a lower sensitivity for condylar hyperplasia detection when using SPECT–CT. The only systematic review assessing the diagnostic accuracy of bone scanning in UCH reported a pooled sensitivity of 90% and a pooled specificity of 95% for SPECT scanning.[4] This is slightly better than the diagnostic performance of the SPECT–CT scan in the present study.

The diagnostic performance of SPECT and SPECT–CT in UCH hardly differ from each other. Therefore, it is of the utmost importance to weigh all of the benefits and disadvantages of each modality. Firstly, a potential beneficial aspect of the added CT scan in SPECT–CT is the use for identification of the region of interest (ROI) and for the assessment of the bone pathology. However, the mandibular condyle can usually be localized with common anatomical knowledge, and when a CBCT scan is part of the primary work-up for patients with asymmetry of the mandible, as in the present study, there is no need at all for an additional CT scan. The advantages of CBCT are the easy accessibility and the large field of view. This makes CBCT a common tool to assess mandibular and facial morphology and asymmetry. In UCH, CBCT is also suitable for quantifying the asymmetry, for planning a surgical intervention (condylectomy or corrective osteotomies), and for serial growth assessment in the follow-up when conservative management is adopted. CBCT is used in any work-up towards an established diagnosis of UCH. Therefore, in almost all asymmetry cases, a CBCT was part of the work-up before deciding whether a bone scan was indicated. In the present study population, there were no incidental pathological findings when the added CT scan of the SPECT–CT was evaluated.

The CT scan is also used to identify the mandibular condyle when drawing the ROI or VOI on the SPECT–CT. However, previous reports in the literature examining the intra- and inter-observer agreement of SPECT scans have reported excellent agreement for all methods when drawing a ROI of VOI in the condyles without the use of a CT scan.[27,28] It seems that, due to the predictable location of the mandibular condyles and the absence of other nearby ^{99m}Tc-HDP-SPECT hot spots, SPECT imaging is sufficient to identify the condyles. So the need to add a CT scan to the SPECT–CT for anatomical or diagnostic reasons is questionable.

Finally, one of the major advantages of SPECT–CT scanning is the use of the CT scan for attenuation correction.[29] Reconstructed SPECT-only images show a decrease in activity at the centre of the image due to weakening of the photons when they cross human tissue. CT imaging can be used as a transmission map and an indirect representation of tissue attenuation. When integrating SPECT and CT images, a dataset can be provided that corrects for the attenuation of the activity. The present study did not include a head-to-head comparison between SPECT and SPECT–CT; this should ideally be the trial design when the value of attenuation correction is determined. However, one previous report on condylar hyperplasia failed to demonstrate added value of attenuation correction and even showed only a moderate correlation between anatomical CT and SPECT imaging.[8] Possible reasons for the decreased benefit of attenuation correction in condylar hyperplasia are the very lateral localization of the mandibular condyle with only minimal overlying soft tissue and the small size of the condyles; this could also contribute to a greater susceptibility for mismatching the CT scan with the SPECT scan. Mismatch of CT and SPECT imaging may result in errors of attenuation correction, leading to potential errors in the calculation of condylar activity.[30]

These are not the only possible disadvantages of the SPECT–CT scan. The addition of a CT scan to nuclear medicine imaging increases the radiation dose to the patient and increases costs. In the present study, the added effective dose of the CT scan was between 0.1 mSv and 0.2 mSv. This is of paramount importance, particularly in this study population, with the majority of the patients being in the adolescent age group.

In conclusion, SPECT–CT showed good diagnostic performance in UCH; however the added value of the CT scan is questionable and the potential disadvantages have to be weighed against the benefits when compared to standard SPECT scanning. When using SPECT–CT in the diagnostic path in UCH, a cut-off in the mean value of > 8% of the relative activity between the condyles is most accurate; this represents a refinement when compared to the current cut-off value of > 10%.

Funding

None.

Competing interests

None.

Ethical approval

Ethical approval was granted by the Vrije Universiteit Amsterdam Medical Centre Ethics Commission (number 12/112).

Patient consent

Patient consent was obtained.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ijom.2022.08.002.

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