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Echogenicity of Palmar Dupuytren's Nodules Is Not a Predictor of Disease Progression in Terms of Increase in Nodule Size

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Background: Ultrasound might enable us to measure Dupuytren's disease activity and predict disease progression. The aim of this study was to analyze whether echogenicity of Dupuytren's nodules can be used to predict progression in terms of increase in nodule size.

Methods: Ultrasonographic assessment of a Dupuytren's nodule was performed in 91 patients participating in an existing longitudinal cohort study. Images were scored for echogenicity by two observers. Echogenicity of 89 nodules was matched to growth 1 year later using linear regression analysis. Sensitivity analysis was performed using data obtained 1 year before ultrasound. The interobserver and intraobserver reliability was calculated using the intraclass correlation coefficient.

Results: Hypoechoogenicity was not a predictor of growth 1 year later (beta = -0.019, $p = 0.748$). Sensitivity analysis looking at the year before ultrasonographic measurement showed that hypoechoogenic nodules were more likely to have grown in the past year (beta = 0.173, $p = 0.011$). However, these data were influenced by nodules that developed in the year before ultrasound. The intraobserver reliability of echogenicity of Dupuytren's nodules was excellent (intraclass correlation coefficient, 0.996; 95 percent CI, 0.993 to 0.998) and the interobserver reliability was fairly good but imprecise (intraclass correlation coefficient, 0.688; 95 percent CI, 0.329 to 0.977).

Conclusions: Hypoechoogenicity is not a predictor of progression in terms of increase in nodule size measured by physical examination 1 year later. When using ultrasound to assess echogenicity of Dupuytren's nodules, the use of a single observer leads to more consistent results. (*Plast. Reconstr. Surg.* 143: 814, 2019.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Risk III.

Clinical evaluation and treatment of patients with Dupuytren's disease is evolving toward a more individualistic approach based on patient history, genetics, and disease stage, instead of treatment based on surgical relief of symptoms for patients with advanced stage disease.¹ Recent studies on the disease indicate that ultrasound may facilitate preoperative, perioperative, and postoperative assessment of patients with Dupuytren's disease.²⁻⁶ An interesting purpose of ultrasound for Dupuytren's disease was described by Créteur et al. in 2010.⁷ They examined Dupuytren patients using ultrasound and found that early nodules were hypoechoogenic and older nodules isoechoogenic

to hyperechoogenic, relative to the underlying tendons, which appear hyperechoogenic because of their composition of longitudinally oriented collagen fibers.⁸ The difference in ultrasonographic aspect of Dupuytren's nodules was attributed to the cellularity of the nodules, which can best be described according to the three histologic phases first described by Luck: proliferative, involutional (contracting), and residual.⁹⁻¹³ During the proliferative and involutional phases, a nodule contains myofibroblasts. Because of this high cellularity, a nodule is most likely hypoechoogenic when

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assessing it with ultrasound.⁷ During the residual phase, the nodules become almost acellular and a fibrous structure consisting mainly of collagen persists, which on ultrasound resembles tendon and appears isoechogenic/hyperechogenic.¹² Yacoe et al. conducted an analogous study using magnetic resonance imaging.¹⁴ They also found a difference in signal of new versus older nodules. To support their hypothesis, a histologic analysis of the nodules was conducted. They concluded that magnetic resonance imaging signal characteristics are correlated to the degree of cellularity.¹⁴ The findings of these studies indicate that the degree of Dupuytren's disease activity may be visualized with ultrasound and magnetic resonance imaging, and therefore it might be possible to predict the disease course using these methods.^{7,14} Unfortunately, both studies based their conclusion on only a few cases and disease progression was not monitored over time. Compared with magnetic resonance imaging, ultrasound is less expensive and easier to access and use. It can be performed in the outpatient clinic by the attending clinician and is less time consuming than magnetic resonance imaging. Therefore, if ultrasound is indeed a good method with which to monitor disease progression, this would be the first choice. Furthermore, if ultrasound enables us to predict the natural course of Dupuytren's disease, this will help us in further optimizing treatment. It could, for example, be of great value for studies focusing on slowing down progression in patients who present with early-stage but active disease.^{15,16} Ultrasound may be of help in objectifying the stage of the disease. However, as the volume of the literature on this topic is limited, further research is necessary to define the exact role of ultrasonographic assessment of patients with Dupuytren's disease.

Our primary aim was to further investigate the hypothesis that the echogenicity of Dupuytren's nodules is a measure of disease activity. A secondary aim of this study was to evaluate the interobserver and intraobserver agreement of judging the echogenicity of the ultrasound images.

PATIENTS AND METHODS

Participants

This cohort study was part of an ongoing longitudinal cohort study on the disease course of Dupuytren's disease,¹⁷ in which patients with various stages of Dupuytren's disease are included. For the current study, we asked patients with Dupuytren's nodules to participate and to have

one ultrasound measurement added to their regular measurements. The study was approved by the local medical ethics committee (2011.397) and all participants gave informed consent.

Procedures and Outcome Measures

The first investigator (S.M.) had already acquired experience with ultrasound for Dupuytren's disease before the start of this study. The second investigator (D.C.B.) was trained by the first investigator. An ultrasound protocol was created while assessing multiple Dupuytren's disease patients together (S.M. and D.C.B.). This enabled us to assess each nodule in the same way during the study. It also minimized the risk of the ultrasonographic aspect of a nodule being influenced by other parameters than the echogenicity of the nodule itself (ultrasound settings, probe direction, pressure, and the amount of ultrasound gel used). Each investigator had examined at least 30 Dupuytren's disease patients with ultrasound, before including patients for this study.

Transverse and sagittal ultrasound images (MyLab One 18 mHz; Esaote, Genova, Italy) of one randomly selected palmar Dupuytren's nodule from every participant were obtained by the second investigator (D.C.B.). The ultrasound images were reviewed for echogenicity of the nodules, which was compared to that of the underlying flexor tendons (hypoechoic or isoechoic/hyperechoic) by both investigators. While assessing the images for echogenicity, the investigators were blinded to each other's findings. For the intraobserver reliability, the first investigator (S.M.) reviewed the images twice, with a period of 2 weeks in between. For the interobserver agreement, the second investigator (D.C.B.) reviewed the images 4 weeks after assessing the participants with ultrasound. This period was chosen so the second investigator would not be able to remember the course of the disease of the participants, thus preventing confirmation bias.

We included only participants who had primary disease nodules. The selected nodules were either isolated or easy to distinguish from a cord, to facilitate the measurement of echogenicity and area. Rays that were previously operated on were excluded a priori, to prevent scar tissue formation from interfering with the ultrasound image. Digital nodules were also excluded a priori because the images had previously been found to be more difficult to interpret, because of the probe not fully making contact with the skin. For the analysis of echogenicity versus growth, we excluded

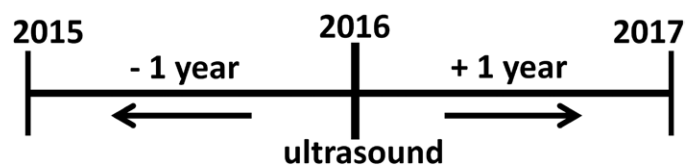


Fig. 1. Timeline of conducted measurements (including sensitivity analysis).

nodules (a posteriori) that were inconsistent in the intraobserver reliability because they had a “mixed” aspect. These nodules were not excluded from the calculation of the interobserver and intraobserver reliability, because this would lead to positive bias.

One year after ultrasound, progression was measured and correlated to echogenicity. Progression was defined as growth of the projection of a nodule on the overlying skin in square centimeters and determined by physical examination using a Tumormeter (Cancer Technologies, Inc., Tucson, Ariz.).¹⁸ The surface area of a nodule was calculated using the length and width of the nodule ($\pi \times \frac{1}{2} \text{ length} \times \frac{1}{2} \text{ width}$). The investigators were unaware of the ultrasound results when calculating nodule size 1 year later.

Statistical Analysis

Patient characteristics and mean growth were calculated using descriptive statistics in IBM SPSS Version 23 (IBM Corp., Armonk, N.Y.). To analyze whether echogenicity of a Dupuytren’s nodule was associated with growth, a linear regression model was chosen, with growth as a dependent variable and echogenicity as an independent variable. Growth was distributed normally. Sex and age were included in the analysis as possible confounding factors. Because it is possible that a nodule had already progressed in size at the time of the ultrasonographic measurement, we chose to perform a sensitivity analysis with data on growth of the year before (2015 to 2016) (Fig. 1). These analyses were performed using IBM SPSS Version 23. Significance was defined as $p < 0.05$.

An intraobserver reliability (S.M.1/S.M.2) and an interobserver reliability (S.M./D.C.B.) were calculated for echogenicity of Dupuytren’s nodules. As a measure of reliability on the echogenicity of the nodule, the intraclass correlation coefficient was chosen. The intraclass correlation coefficient was calculated using a generalized linear mixed model with a binomial distribution and logit link function, in which a latent variable for participant was laid underneath the binary outcome. The rptR package (Version 0.9.2) in R was used for this.¹⁹

Confidence intervals were obtained by bootstrapping with 1000 samples. Intraclass correlation coefficients can range from 0 to 1. A high value means better reliability.

Several rating scales for the intraclass correlation coefficient have been described. Often, 0.70 is recommended as a minimum standard for reliability, which is why we defined an intraclass correlation coefficient of greater than or equal to 0.70 as good reliability.²⁰

RESULTS

Of 117 patients with palmar nodules, 91 were included in the analysis. In 14 patients, the nodule was more cordlike during follow-up in 2017 or the nodule was part of a cord and it was not possible to distinguish the nodule clearly from the cord, complicating the measurement of nodule length and width used for calculating area. For seven patients, data were missing or incorrect, and five patients were lost to follow-up. Patient characteristics are listed in Table 1.

Echogenicity versus Progression

Linear regression analysis, excluding two nodules that were inconsistent in the intraobserver agreement, showed that growth of both isoechogenic/hyperechogenic and hypoechogenic nodules was negligible in the period 2016 to 2017. Average growth of all 89 nodules was -0.006 cm^2 . Isoechogenic/hyperechogenic nodules exhibited a mean growth of 0.0002 cm^2 and hypoechogenic nodules exhibited a mean growth of -0.019 cm^2 . This difference was not significant ($p = 0.748$).

Table 1. Patient Characteristics

	Value (%)
Mean age \pm SD, yr	66.4 \pm 9.8
Male sex	60 (65.9)
Right hand	47 (51.6)
Ray	
Thumb	5 (5.5)
Index	7 (7.7)
Long finger	32 (35.2)
Ring finger	34 (37.4)
Little finger	13 (14.3)

Table 2. Multivariate Linear Regression Evaluating the Association between Echogenicity and Progression

	Beta*	95% CI	<i>p</i>
Growth 2016–2017			
Crude analysis			
Hypoechoogenic	−0.019	−0.134–0.097	0.748
Adjusted analysis†			
Hypoechoogenic	−0.021	−0.138–0.095	0.717
Growth 2015–2016			
Crude analysis			
Hypoechoogenic	0.173	0.040–0.306	0.011
Adjusted analysis†			
Hypoechoogenic	0.172	0.037–0.307	0.013

*Mean difference in growth between hypoechoogenic and isoecho-genic/hyperechoogenic nodules.

†Adjusted for possible confounders: age and sex.

Adjustment for confounders (i.e., age and sex) did not influence the result (Table 2).

These results indicate that nodules on average did not grow over time in 2016 to 2017. Also, there was no significant difference in growth between hypoechoogenic and isoechoogenic/hyperechoogenic nodules.

When performing the sensitivity analysis using data from 2015 to 2016, linear regression analysis showed that hypoechoogenic nodules on average grew more than isoechoogenic/hyperechoogenic nodules in the period 2015 to 2016. Average growth of all 89 nodules was 0.23 cm². Growth was 0.35 cm² for hypoechoogenic nodules and 0.18 cm² for isoechoogenic/hyperechoogenic nodules. This difference in growth was significant (*p* = 0.011). When adjusting for confounders (i.e., age and sex), the results remained the same (Table 2). These results indicate that both hypoechoogenic and hyperechoogenic/isoechoogenic nodules grew over time in the period 2015 to 2016, but that the growth in hypoechoogenic nodules was significantly larger.

Interobserver and Intraobserver Reliability

Of the 91 nodules that were analyzed for intraobserver and interobserver reliability, 29 (31.9 percent) were defined as hypoechoogenic by the first observer (S.M.). During the second round 2 weeks later, again 29 nodules were defined as hypoechoogenic (Figs. 2 and 3). There were two discrepancies, as shown in Table 3.

The second observer (D.C.B.) defined 38 nodules (41.8 percent) as being hypoechoogenic, with 17 discrepancies (Table 4). The intraobserver reliability had an intraclass correlation coefficient of 0.996 (95 percent CI, 0.993 to 0.998), and the interobserver reliability had an

intraclass correlation coefficient of 0.688 (95 percent CI, 0.329 to 0.977).

DISCUSSION

Recently, there has been a growing interest in the use of imaging for Dupuytren's disease to measure disease activity.^{7,14} However, these studies had small populations, and no follow-up study has yet been performed. In our study, a group of 89 patients with Dupuytren's disease was followed for 1 year to evaluate whether echogenicity of a Dupuytren's nodule is related to disease activity, reflected as growth of a Dupuytren's nodule.

Créteur et al. found that Dupuytren's nodules early on have high cellularity and are hypoechoogenic.⁷ Our hypothesis was that these new (hypoechoogenic) nodules are more likely to grow than older (isoechoogenic/hyperechoogenic) nodules. The results of our study do not confirm this theory when looking at increase in nodule size 1 year after ultrasonographic measurement. This means that, based on our results, echogenicity of a Dupuytren's nodule is not a predictor of progression in terms of growth measured as surface area with physical examination. Still, as we do not know exactly how Dupuytren's tissue behaves over time, this finding does not mean that the disease does not progress. As mentioned previously, the development of Dupuytren's tissue is often described according to the three histologic phases defined by Luck.⁹ However, Verjee et al. state that the picture might be more heterogeneous than these histologic phases imply.²¹ Older nodules that are in the residual phase are expected to be isoechoogenic/hyperechoogenic. It has been reported that small clusters of cells including myofibroblasts are present in advanced, tendon-like cords.²¹ This might be the same for the older nodules in our study. Several nodules were predominantly isoechoogenic/hyperechoogenic, and thus were defined as isoechoogenic/hyperechoogenic, but had small parts with a hypoechoogenic aspect. The parts that were hypoechoogenic are likely to contain myofibroblasts, as described above. If this is the case, this may explain why there is no significant difference in growth of hypoechoogenic nodules and isoechoogenic/hyperechoogenic nodules. However, in our study, average growth of all nodules was −0.006 cm² between 2016 and 2017, which means that on average a nodule did not grow during the period of 1 year. There was no significant difference in growth between hypoechoogenic and isoechoogenic/hyperechoogenic nodules. This

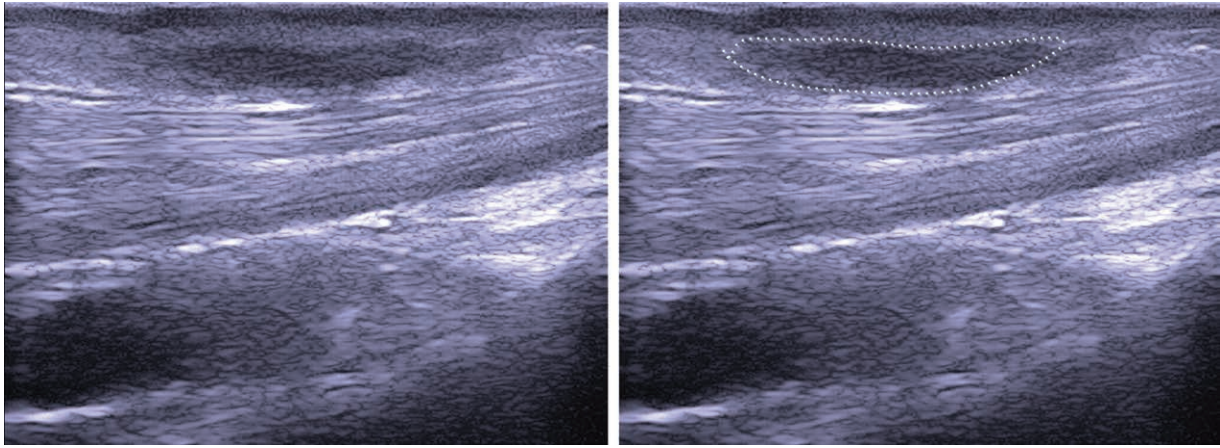


Fig. 2. Sagittal image of a hypoechoic nodule (with and without nodule border indicated by *dashed line*).

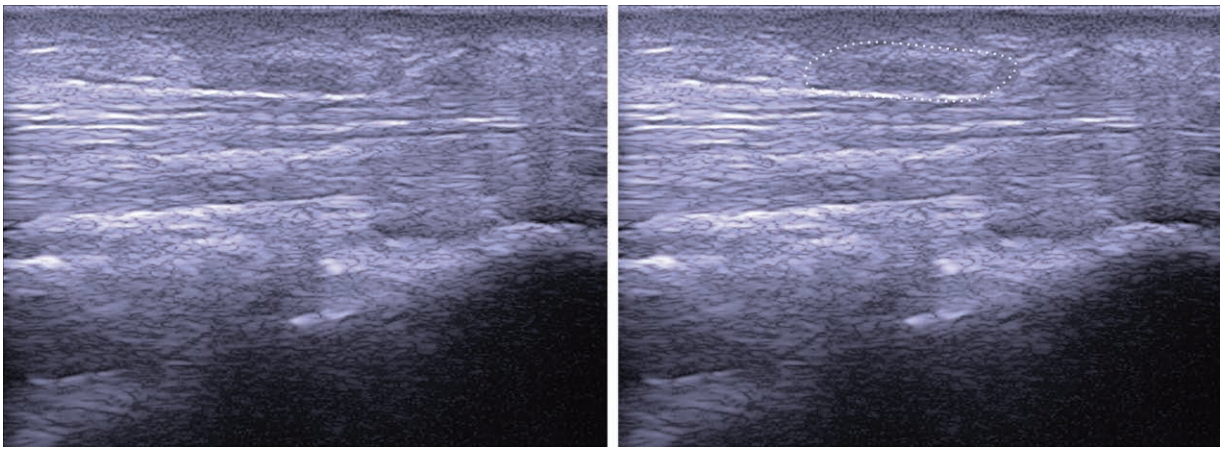


Fig. 3. Sagittal image of an isoechoic/hyperechoic nodule (with and without nodule border indicated by *dashed line*).

Table 3. Intraobserver Reliability

Measurement 1	Measurement 2		Total
	Hypoechoic	Isoechoic/ hyperechoic	
Hypoechoic	28	1	29
Isoechoic/ hyperechoic	1	61	62
Total	29	62	91

Table 4. Interobserver Reliability

Observer 1	Observer 2		Total
	Hypoechoic	Isoechoic/ Hyperechoic	
Hypoechoic	25	4	29
Isoechoic/ hyperechoic	13	49	62
Total	38	53	91

might indicate that activity of a nodule does not necessarily imply growth of the nodule itself. It is known that during the proliferative phase, myofibroblasts are arranged randomly and during the

involutional phase they align along certain lines of tension, and this process coincides with the start of contracture formation and finally progresses to a cordlike (residual) phase. Because of this contraction, nodules might become smaller while they progress into cords.⁹

When looking at the sensitivity analysis in which we analyzed the relation between growth in the year before the ultrasonographic measurement and echogenicity of nodules, hypoechoic nodules were more likely to grow than isoechoic/hyperechoic nodules. Average growth of all nodules was evidently higher in the period 2015 to 2016 than in the period 2016 to 2017 (0.23 cm² versus -0.006 cm²). This might be explained by the fact that 18 nodules that we investigated in 2016 by ultrasound were not present at the time of measurement in 2015. These 18 nodules were predominantly responsible for an average growth of 0.23 cm² between 2015 and 2016. When removing these 18 nodules from our regression analysis, there was no longer a significant difference

in growth of hypoechogenic and isoechogenic/hyperechogenic nodules ($\beta = 0.096$, $p = 0.089$). However, when looking at these 18 nodules separately, there was no significant difference in growth between the eight hypoechogenic nodules with an average growth of 0.75 cm^2 and the 10 isoechogenic/hyperechogenic nodules with an average growth of 0.59 cm^2 ($p = 0.101$). This means that the 18 nodules that were not present in 2015 influenced our regression analysis to such an extent that it led to significance, but it does not mean that hypoechogenicity was a predictor of growth of a nodule.

In our study, the border of a nodule was outlined by physical examination and subsequently its surface was measured using a Tumorimeter. Most studies quantify progression using measurements of passive extension deficits of joints. This is a relatively late event in the natural disease course of Dupuytren's disease. In our cohort, hardly any (6 percent) of the selected rays had contractures (yet). As we were most interested in early progression of disease, we defined progression as growth of a nodule itself. The use of surface area was, in our view, the most accurate measure. Also, we wanted to eliminate the risk of potential activity in surrounding tissue being accountable for progression in the same ray.

Based on our results, it seems that a nodule itself does not necessarily grow in the period of 1 year when measuring its surface area. As it can still progress into cordlike tissue, which in the beginning is hard to define with physical examination, it might even be better to add ultrasound to measure the borders of a nodule during follow-up. With physical examination, only two dimensions can be measured. With ultrasound, it is possible to add depth and to assess transformation of a

nodule in a more cordlike structure. Also, the use of tonometry to assess skin pliability may be of additional value, as hardness of a nodule possibly is a better indicator of progression of a nodule.¹⁵

Because ultrasound is a relatively new measuring device for Dupuytren's disease, the intraobserver reliability and the interobserver reliability of echogenicity of nodules were calculated. The intraobserver reliability was excellent (intraclass correlation coefficient, 0.996; 95 percent CI, 0.993 to 0.998). The interobserver reliability was fairly good (intraclass correlation coefficient, 0.688; 95 percent CI, 0.329 to 0.977), but the confidence interval is very wide. It can therefore be argued that the ultrasound measurements should preferably be performed by one and the same observer. The fact that the intraobserver reliability was evidently higher can, however, be explained by the fact that some nodules were difficult to interpret, because of a mixed aspect (Fig. 4). With two observers, interpretation of these "mixed" nodules becomes less consistent. This is why the results of one observer (S.M.) were used for the regression analyses in this study. For future studies on echogenicity of nodules, we would advise researchers to consider mixed nodules to be hypoechogenic. As these nodules consist of both hypoechogenic and isoechogenic/hyperechogenic areas, they might still be able to cause progression.

We conclude that ultrasound cannot be used to predict the course of Dupuytren's disease in terms of growth of a nodule in the first year following the ultrasound measurement, when measuring growth as an increase in surface area by physical examination. Ultrasound might still be useful to get an indication of the stage a nodule is in. As the literature on the value of ultrasound

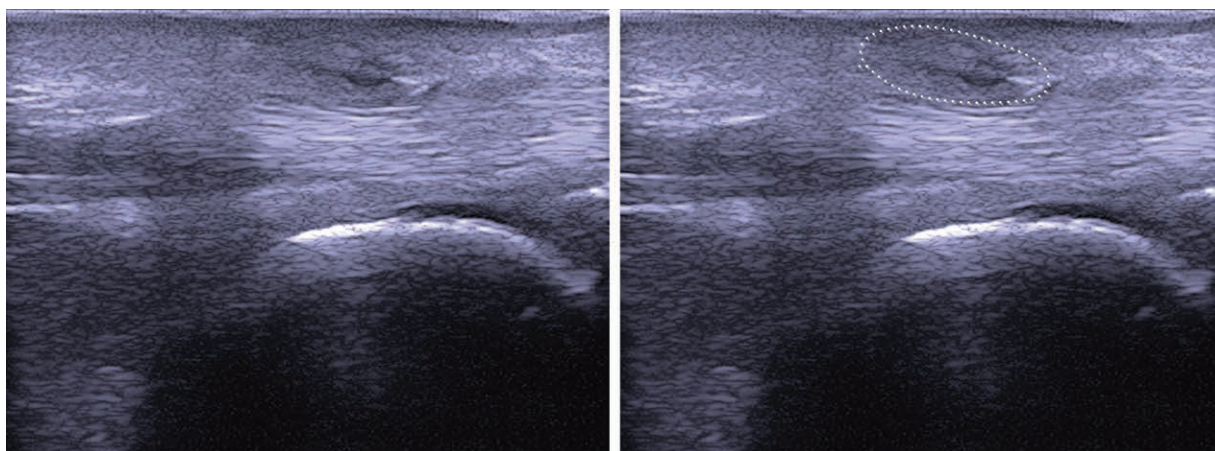


Fig. 4. Sagittal image of a "mixed" nodule (with and without a nodule border indicated by the dashed line).

to measure disease activity in patients with Dupuytren's disease is very limited, our study design was exploratory and lays the foundation for further research. The interobserver reliability of echogenicity was fairly good, but the knowledge that was acquired with this study enables us to make adjustments to the ultrasound protocol, which will increase reliability. As echogenicity of Dupuytren's nodules might add valuable information to the clinical evaluation of Dupuytren's patients, we are of the opinion that it should be further explored.

The assumption that hypoechogenicity is related to hypercellularity seems logical. However, to confirm this hypothesis, a histologic study should be performed. Also, in the future, it might be better to add ultrasound to physical examination when following progression, to have a more multidimensional idea of the behavior of a Dupuytren's nodule.

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