CHAPTER 8

GENERAL DISCUSSION

General discussion

The aim of this thesis was to investigate the value of ultrasound (US) for the measurement and prediction of progression in patients with Dupuytren's disease.

First, the available literature was reviewed, to investigate the different possible applications of US for Dupuytren's disease. Next, we assessed the inter- and intra-observer reliability of this relatively newly introduced device. Subsequently, we investigated the role of the US-image as predictor of disease activity and progression, and the representativeness of the actual US-image for the constitution of nodules. Finally, we evaluated the clinical value of US for Dupuytren's disease patients undergoing percutaneous needle fasciotomy (PNF), by assessing the efficacy of ultrasound-guided PNF, as well as the role of US in the prediction of recurrence after PNF.

In this chapter, the primary findings of this thesis are summarized and placed in perspective. Also, suggestions for future studies are made.

Applications of imaging for Dupuytren's disease

Because the field of imaging for Dupuytren's disease is relatively new, we decided to start with a systematic review in **Chapter 2**. As expected, we found that currently, imaging has no standard place in the diagnosis of Dupuytren's disease, since the diagnosis is usually clinically evident. Also, with respect to the costs, the added value of US to monitor disease severity seems to be too limited, because currently the right moment to intervene is still primarily based on severity of contractures, which is measured best by physical examination, since US cannot measure a whole cord at once or assess degree of contracture.

Imaging does seem to have additional value in the monitoring of disease activity, since imaging may be able to assess cellularity of nodules and cords. However, no study was found that did evaluate this theory statistically. Furthermore, imaging may be able to improve safety and outcomes of (minimally invasive) surgical procedures such as PNF, because it can prepare the surgeon for altered anatomy, like digital nerve displacement by a Dupuytren's cord. However, outcomes of non-imaging-guided procedures have also proven to be excellent (1-3), which is why the exact benefit needs to be further explored. Finally, there seems to be a role for imaging in the follow-up of non-surgical and minimally invasive procedures. Especially in the follow-up of nodule size of patients without contractures, undergoing treatment aiming at disease control, imaging could be of additional value.

The main limitation of this review was that the amount of papers on the subject was small, while the described applications for imaging varied widely. The overall level of evidence of the included papers was low. We chose also to include other imaging modalities than US, because we wanted to give an overview of all possible applications for which imaging was used. Only studies on US and magnetic resonance imaging (MRI) were found, probably because these are the preferred modalities to assess soft tissue diseases (4,5). A stronghold of these imaging modalities is that they do not cause unnecessary radiation exposure for patients.

The greatest value of imaging seems to lie in the monitoring of disease activity and outcome of non-surgical treatments for patients with early disease. For this purpose, MRI is probably most accurate, since a detailed 3D image can be made and different signal intensities can be detected (6,7). However, currently it is not feasible to add MRI to the standard follow-up of Dupuytren's patients, since MRI is time consuming, expensive and cannot be easily conducted by the physician "at bedside" yet, although small hand MRIs are emerging. Therefore, US is most interesting, since it has low costs and is easy to access. An advantage of US compared to MRI, is that it is dynamic (4). Also, three-dimensional (3D) US is available and already widely used by other specialists (e.g. obstetricians/gynaecologists) (8). However, it is not known if 3D US is also valuable for Dupuytren's disease.

For the examination of hand diseases, a high frequency linear array US-transducer is required, preferably with a range of 15-18 mHz (9). Because US is a relatively new measurement instrument for Dupuytren's disease, it would have been interesting to find out more about technical aspects of US for Dupuytren's disease specifically (US pre-settings, learning curve and reliability). Unfortunately, in the studies included in our systematic review, we did not find many useful technical recommendations for sonographic evaluation of Dupuytren's patients.

US has been used by urologists for years to detect and measure penile plaques in patients with Peyronie, which is an associated disease of Dupuytren's disease (10,11). Recently, the use of sonoelastography has been introduced in the field of Peyronie (12). This technique is able to measure tissue stiffness by assessing the response of tissue to acoustic energy (13). In Peyronie patients, sonoelastography is able to detect areas with relatively increased stiffness in the area of maximum penile curvature. In our systematic review, we also found one article that describes the use of sonoelastography in a Dupuytren's patient (14). According to the authors, sonoelastography could be a potential diagnostic for the differentiation between active and inactive Dupuytren's disease. Unfortunately, only one Dupuytren's disease case evaluated with sonoelastography has been described in the literature so far. More research is needed to define its place.

Reliability and interpretability of ultrasound for Dupuytren's disease

Because ultrasound is a new measurement instrument for the assessment of Dupuytren's disease, reliability and interpretability had to be determined. In **Chapter 3** we performed a study on this subject and found that the reliability of measurement of nodule size is good when repeated measurements are performed by the same observer. When using multiple observers, reliability was evidently lower. Furthermore, although the reliability of measurements performed by a single observer was good, we found that there still is a relatively large dispersion in the measurements.

In **Chapter 4** we found that the intra-observer reliability of the subjective assessment of echogenicity (hypo-echogenic vs. hyper-echogenic) of 91 Dupuytren's nodules was excellent and the inter-observer reliability was fairly good but imprecise, because of the wide confidence intervals.

Our results show that measurements of nodule size, even when only one observer is involved, have a large dispersion. We made several suggestions for future researchers to reduce variability of the measurements, such as using the previous US image of a nodule to compare a new measurement to and by marking and subsequently photographing the exact location of the obtained US images. This study was somewhat hampered by being the first to assess reliability of this new measurement instrument for Dupuytren's disease. Nonetheless, we are of the opinion that the method we used for this particular study, was justified. In the future, it may also be interesting to investigate if the use of 3D US instead of the conventional 2D US, improves reliability and interpretability of sonographic measurements of Dupuytren's nodules. Instead of measurement of cross-sectional area in multiple planes, 3D US may make it possible to assess nodule volume with a single measurement. 3D US is already used to measure volume of small organs. For example, studies have shown that the use of 3D US to measure organs of the male and female reproductive system is highly reliable (15-17). Unfortunately, at the writing of this chapter, not much is known about the reliability of 3D US for musculoskeletal disorders like Dupuytren's disease.

When using US to subjectively measure echogenicity (or grey-value) of the US-image of a Dupuytren's nodule, it turned out that a single observer is able to consistently judge this. Especially the judging of nodules that have a homogenous dark (hypoechogenic) or light (hyperechogenic) aspect, was consistent. The nodules with a 'mixed' aspect on the other hand were sometimes more difficult to classify. This is demonstrated by the 'fairly' good inter-observer reliability. After this study, we decided to add another category to the subjective measurement of grey-value, namely 'mixed echogenicity'. Also, we concluded that it may have been better to use an objective scale for grey-value, which was further explored in chapter 5.

The use of US is operator dependent. The operator should be aware of possible artefacts or differences in echogenicity that can occur when using US (18,19). For Dupuytren's disease, hypo-echogenic areas can wrongfully be interpreted as (parts of) a nodule, when in fact they are artefacts. Also, echogenicity of a nodule can change during one measurement, when changing probe angle . This is why we tried to standardize our US protocol as much as possible. We have debated whether measurements should have been performed by (expert) musculoskeletal radiologists. However, this would have made US less easy to access, which was of key importance to us, since our ultimate goal is to implement US in the standard monitoring of Dupuytren's patients at the outpatient clinic. It is questionable if reliability would have improved substantially if US was performed by radiologists, since Dupuytren's disease is a disease that sometimes has no clear borders and shows mixed echogenicity, which complicates repeatability of measurements. In a previous study in which cord-thickness and nodularity of Dupuytren's cords was assessed by two radiologists, a moderate intraclass correlation coefficient (0.63) was found for the assessment of cord-thickness and a low Cohen's Kappa (0.38) was found for nodularity, which shows the complexity of repeated measurements of Dupuytren's disease by different operators and, moreover, shows that the inter-observer reliabilities that we obtained, which we felt were somewhat disappointing, were very much in line with those found by others (20). This is also illustrated by the fact that literature shows that sonography of other/comparable structures of the hand and foot is subject to variation when performed by multiple observers. A study on the reliability of sonographic measurement of plantar fascia thickness showed a moderate inter-observer reliability of 0.62 (21). Another study on sonographic measurement of the median nerve at the carpal tunnel in*let al*so showed a moderate inter-observer reliability of 0.59 (22). This illustrates that sonography structures of the hand and foot is subject to variation when performed by multiple (expert) observers.

The use of US by non-radiologists is not new; hand surgeons all over the world use ultrasound in their practice to assess traumatic and non-traumatic hand conditions other than Dupuytren's disease (23). There is a learning curve, but once it is mastered, US provides the operator with an internal image of the involved anatomical structure in the axial, coronal, and transversal planes (9,23). Numerous courses are available for learning how to apply US in the field of hand surgery. Unfortunately since US is not widely used for Dupuytren's disease, specific US-courses for Dupuytren's disease do not exist. However, since Dupuytren's disease is a palpable disease and the anatomical location of nodules (palmar to the flexor tendons) is clear on US, it is quite easy to visualise the disease in our experience. For these reasons we decided to perform US ourselves.

In both reliability studies we tried to provide researchers with advice on the learning curve of sonographic measurement and judgement of Dupuytren's nodules. Since the use of US for Dupuytren's disease is not part of standard care, no guidelines were available. We found

that, after evaluating palmar nodules in 30 Dupuytren's disease patients, sonographic measurements became consistent, which is why we used this number as a minimum. However, this number is merely based on experience and not on research. Further work is needed to assess the exact learning curve of sonographic measurement of Dupuytren's patients.

Ideally, if US becomes a part of standard care for Dupuytren's patients, residents in the field of hand surgery should all be trained in US assessment of the hand. Especially since US can be of value for a variety of hand disorders (9). In other specialisms like emergency medicine and general surgery, training residents how to perform US has already been more widely studied and has proven to be of value (24,25).

The use of ultrasound to measure disease activity in Dupuytren's patients

An important subject of this thesis was to investigate the ability of ultrasound to measure disease activity and predict progression based on echogenicity. Hypoechogenic (dark) nodules are thought to consist of a high level of cells, presumably myofibroblasts, and hyperechogenic (light) nodules are thought to consist mainly of collagen (26). Over the past decades, researchers have been trying to find non-surgical therapies that aim to stop progression or even cause regression in patients with Dupuytren's disease (27-29). Since not all patients are at risk of developing contractures, for such treatment to be cost-effective, we have to be able to select those patients with mild symptoms that are at risk of developing severe contractures. If ultrasound can indeed investigate the amount of cells in a nodule, presumably myofibroblasts, than it would be of great value in the selection process of patients undergoing non-surgical therapy aiming at the control of activity of myofibroblasts (30-32).

In **Chapter 4,** echogenicity (hypoechogenic vs hyperechogenic) of nodules of patients with early Dupuytren's disease was related to progression, defined as increase in nodule size measured by physical examination one year later. We found 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.

In **Chapter 5** we assessed if echogenicity (measured as average grey-value) of 38 Dupuytren's nodules of patients undergoing limited fasciectomy was correlated to average myofibroblast density (measured by histopathology). We found a significant, but moderate, correlation between average grey-value of nodules and myofibroblast load. The lower the grey-value (darker), the higher the myofibroblast load and vice versa. Furthermore, echogenicity was subjectively assessed (hypoechogenic/mixed echogenicity/hyperechogenic) and compared

to myofibroblast load. The subjective measurements matched the objective measurements. We also investigated in this chapter if nodule hardness, measured with a tonometer, was correlated to average grey-value. We again found a significant, but moderate, correlation. The lower the grey-value (darker), the higher the nodule hardness and vice versa.

In these chapters we assessed the possible relation between echogenicity of Dupuytren's tissue and disease activity in different ways. We started in the least complex way, by following patients of an existing longitudinal cohort study over time and investigating whether patients with hypo-echogenic nodules have a higher risk of progression, measured as growth of a nodule. Unfortunately it turned out that, overall, Dupuytren's nodules did not grow in terms of increase of surface area in the palm of the hand during the period of 1 year. Since nodules did not seem to grow in this coronal plane during this period, it is not surprising that we were not able to find a significant difference in growth of hypo- and hyper-echogenic nodules. Possibly we should have lengthened our follow-up period or we should have used different outcome measures to monitor disease progression. Measurement of extension deficit was not an option, since patients all had early stage Dupuytren's disease without significant contractures. For future studies, researchers should consider the use of US to also follow-up nodules instead of only using it to assess echogenicity. This would enable the measurement of nodules in other dimensions than only the coronal plane, which is measured with physical examination. This is important since possibly, while Dupuytren's disease progresses and nodules contract, they do become thicker, which can only be observed in the transverse and/or sagittal plane. The use of 3D US, which has been mentioned before, may be an interesting addition for the follow-up of volume of Dupuytren's nodules. A possible alternative is the measurement of tissue hardness, using a tonometer (33). In chapter 5, we found that echogenicity of nodules is correlated to tissue hardness, measured with a tonometer. In this same chapter we found that echogenicity is also correlated to myofibroblast load, which suggests that tissue hardness may also be correlated to myofibroblast load and changes in tissue hardness may be a reflection of disease progression. This is an interesting finding, since tonometry is easy to access and to execute. However, no data are available on reliability and measurement error of tonometry for Dupuytren's disease. Also, tissue hardness itself has not been directly related to myofibroblast load yet, so the value of this new measurement instrument for Dupuytren's disease has to be further explored. Sonoelastopgraphy, which has been discussed previously, may also be a valuable addition for monitoring disease activity of Dupuytren's disease, because it also focuses on differences in stiffness of soft tissues (13).The fact that echogenicity of Dupuytren's nodules was correlated to myofibroblast load, substantiates the hypothesis that ultrasound can measure disease activity.

Because we experienced difficulties in assessment of nodules with mixed type echogenicity at the beginning (chapter 4), we added mixed echogenicity as a third category to our measurements later on (chapter 5&7). Still, dividing nodules in these three categories remained subjective, which is why in chapter 5 we used average grey-value to assess echogenicity objectively. We compared our objective and subjective findings, which corresponded to each other. Also we showed average grey-value of nodules for each subjective echogenicity group and the corresponding average myofibroblast load. Future studies have to confirm that these numbers correspond with myofibroblast load, so a classification can be created that is easy to use in the clinical practice. This is an essential step before US can be implemented in a Dupuytren's disease monitoring and treatment algorithm.

The clinical value of ultrasound for patients undergoing minimal invasive surgery for Dupuytren's disease

In both **Chapter 6 and 7**, we aimed to show the clinical value of US for Dupuytren's patients undergoing PNF, by assessing if US can be used to prepare the investigator for possible anatomical abnormalities, that could increase the risk of post-operative complications. Moreover, we aimed to show the clinical implications of our previous finding that echogenicity is related to myofibroblast load (chapter 5), by investigating if pre-operative echogenicity of a Dupuytren's cord is a predictor of early recurrence.

In both chapters the outcomes of US guided PNF were excellent and the complication rate was low. In addition to this, in **Chapter 6** we found that PNF is especially an effective treatment modality for patients with mild to moderate Dupuytren's disease, that the procedure is most effective for MCP-contractures and that PNF was effective for patients with recurrent disease.

In **Chapter 7** we found that the Kaplan-Meier failure curve of early recurrence following percutaneous needle fasciotomy (PNF) for Dupuytren's disease was evidently steeper for patients with hypoechogenic cords, followed by mixed cords, followed by hyperechogenic cords. This could indicate that the time to recurrence is shortest in patients with hypo-echogenic cords, which would confirm that hypo-echogenicity reflects disease activity. Unfortunately, survival analysis showed that this difference in time to recurrence was not statistically significant.

The main limitation of chapter 6, is that we have not been able to compare our findings to outcomes of PNF in Dupuytren's disease patients not undergoing pre-operative US. When looking at numbers of non-US-guided PNF in literature, our results are comparable (1-3,34). So based on this study, it is not possible to draw any conclusions about increased safety

and better outcomes when using US. A randomized controlled trial would be the next step. However, it is questionable if adding US to PNF patients is really efficient, since PNF also seems to be safe and effective without US. Especially, since sonography of Dupuytren's cords with contractures is a lot more difficult than sonography of a simple isolated palmar nodule. In our experience it is not possible to see the different layers of the palmar fascia, with the currently available US probes. Also the course of the digital nerves is easiest to see by following the Doppler signal of the artery (35,36). However, when the nerve and artery do not run parallel to each other, which is sometimes the case in patients with recurrent Dupuytren's disease, US may actually be misleading. Perhaps the introduction of ultra-high frequency (30-70 mHz) US probes, will provide more precise information about altered anatomy and lead to better identification of pathology (37). This may improve outcomes and enhance safety of surgical procedures for Dupuytren's disease, especially for patients with recurrent Dupuytren's disease (9).

Throughout this thesis, we hypothesized that echogenicity of Dupuytren's tissue, which turns out to be a reflection of myofibroblast load (chapter 5), can be used to assess disease activity. In chapter 7, we showed what these presumed differences in activity most likely mean clinically. The fact that our Kaplan-Meier failure curve showed a very clear gradient between hypo-, mixed and hyperechogenic cords, shows us that there are differences in recurrence between patients with different types of echogenicity. The darker the cord appears on the US-image (and the more myofibroblasts it contains), the higher the risk of early recurrence. Unfortunately, the survival analysis that accompanied this Kaplan-Meier failure curve, was not significant. We think that the main limitation of our study was lack of power. A prospective study, using the data of our results to calculate power, should be conducted in the future. The follow-up period should be the same for all patients, which was not the case in our study due to its retrospective nature. Whether a different definition of recurrence should be used is debatable. Our definition (recurrent intervention) is very clear and does not lead to any discussion whether the doctors perception of recurrence is inconsistent with the patients perception of recurrence. On the other hand, another definition of recurrence (i.e. TPED > 30 degrees) would lead to a higher number of events.

Besides the fact that we showed what increased disease activity measured with US, means in terms of disease progression, our findings could be used to manage patient expectations. Also, it could be possibly used as part of a treatment algorithm. For patients with a high risk of recurrence, limited fasciectomy (LF) may be preferred instead of PNF, since the 5-year recurrence rate of LF is much lower (38).

In chapter 6 we also aimed to emphasize the importance of the use of statistical tests that can account for a multi-level data structure when performing studies in the field of hand surgery, since hands, rays and joints are correlated (39). In both chapter 6 and 7 we were challenged by the analysis of multi-level data (multiple rays of one patient). Since we did not want to reduce our numbers, by randomly selecting only one ray per patient, the only way to account for this, was by conducting multilevel analyses. Many previous studies failed to use appropriate statistical techniques. With these studies we hope to motivate researchers in the field of hand surgery to select the appropriate statistical test or to exclude data until there is no risk of correlation within patients.

Conclusions

The studies in this thesis were designed to acquire knowledge regarding the value of US for Dupuytren's disease. We hope that they will form the basis for further investigations using this recently introduced measurement instrument. We found that US is reliable in the measurement of nodule size and echogenicity and that measurements should preferably be performed by the same observer at subsequent occasions. Furthermore we found that echogenicity of Dupuytren's nodules is correlated to myofibroblast load. We attempted to show that this myofibroblast load is a reflection of disease activity in terms of progression, by relating echogenicity of Dupuytren's cords to time to recurrence after PNF. Unfortunately, our findings were non-significant. Finally, we found that US guided procedures are safe and effective, with a side note that we did not investigate if these results are superior to that of non-US guided procedures. When, in the future, a validated individualized monitoring and treatment algorithm is created for patients with Dupuytren's disease, US may be able to assist in the follow-up of nodule size and in the selection of the most appropriate treatment regimen (ranging from wait and see, to non-operative to operative).

US techniques are evolving, and the possible value of 3D US, sonoelastography, ultra-high frequency US for Dupuytren's disease has to be further investigated. Furthermore, since US is operator dependent and has a certain learning curve, we have to keep exploring the feasibility of the implementation of US in the standard care of Dupuytren's disease patients, and we also have to keep looking into other options, like tissue hardness.

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