High-Dosage Tamoxifen as Neoadjuvant Treatment in Minimally Invasive Surgery for Dupuytren Disease in Patients with a Strong Predisposition Toward Fibrosis

A Randomized Controlled Trial

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Background: Tamoxifen, a synthetic nonsteroidal anti-estrogen known to modulate the production of transforming growth factor-beta (TGF-β), has demonstrated effectiveness on fibroblast activity in vitro and in vivo. The main purpose of this study was to investigate the effect of tamoxifen on the outcome of surgery for Dupuytren contractures in patients with a strong predisposition toward fibrosis.

Methods: We used a prospective, randomized, double-blind study protocol (conforming to the CONSORT standards) to investigate the influence of tamoxifen compared with placebo on the total passive extension deficit in the finger and patient satisfaction after subtotal fasciectomy in thirty patients with a strong predisposition toward fibrosis (grade, >4 according to the Abe scale). High-dosage tamoxifen (80 mg/day) was administered from six weeks prior until twelve weeks after surgery, and patients were monitored for two years.

Results: Three months after surgery, patients in the tamoxifen group had a smaller total passive extension deficit and higher satisfaction compared with the placebo group. This positive effect was lost over the two years following cessation of the medication.

Conclusions: This study demonstrated that the short-term outcome of Dupuytren disease treatment could be influenced by use of tamoxifen as a neoadjuvant from six weeks prior to three months after subtotal fasciectomy in patients with a strong predisposition toward fibrosis. However, the beneficial effect disappeared within two years after surgery, with worsening of the contractures after the medication was discontinued. Thus, tamoxifen may have a short-term effect on the outcome of surgery for Dupuytren disease.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Peer Review: This article was reviewed by the Editor-in-Chief and one Deputy Editor, and it underwent blinded review by two or more outside experts. It was also reviewed by an expert in methodology and statistics. The Deputy Editor reviewed each revision of the article, and it underwent a final review by the Editor-in-Chief prior to publication. Final corrections and clarifications occurred during one or more exchanges between the author(s) and copyeditors.

Finger contractures in patients with Dupuytren disease are currently treated symptomatically with enzymatic or surgical fascia interruption or removal, skin replacement, or, in select cases, even amputation[1-3]. The disease is incurable; treatment is restricted to reversing contractures and reported recurrence rates are 39% to 71%[4-6]. Bulstrode et al. claimed that disease recurrence may be inevitable if the patient lives long enough[7]. Studies utilizing a variety of surgical techniques have not clearly defined the recurrence risk[8-10]. No surgical technique guarantees permanent results and less invasive surgery, such as

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TABLE I Outcomes Within Two Years of Surgery on the Most Affected Ray*

Variable	Follow-up *(mo)*	Mean	Median	Min.	Max.	P Value Between Groups
MCP improvement *(deg)*						
Placebo	3	26.4 ± 20.4	22.0	−5.0	62.0	
	12	26.0 ± 20.3	22.0	−5.0	62.0	
	24	23.9 ± 23.3	22.0	−24.0	62.0	
Tamoxifen	3	29.5 ± 31.8	20.0	0.0	90.0	0.7631
	12	29.5 ± 31.8	20.0	0.0	90.0	0.7368
	24	28.3 ± 31.8	15.0	0.0	90.0	0.6931
PIP improvement *(deg)*						
Placebo	3	21.4 ± 18.7	19.0	−12.0	60.0	
	12	16.4 ± 38.0	20.0	−80.0	78.0	
	24	14.5 ± 24.2	17.0	−20.0	70.0	
Tamoxifen	3	54.4 ± 22.0	54.5	13.0	95.0	0.0004†
	12	47.0 ± 19.2	43.5	20.0	75.0	0.0187†
	24	28.3 ± 32.5	29.0	−31.0	75.0	0.2262
Tubiana index						
Placebo	3	61.0 ± 26.8	65.5	17.0	100.0	
	12	44.8 ± 77.4	65.5	−200.0	100.0	
	24	49.4 ± 37.7	57.6	−40.0	100.0	
Tamoxifen	3	92.8 ± 13.2	100.0	67.0	100.0	0.0010†
	12	83.4 ± 22.9	100.0	41.7	100.0	0.1092
	24	64.1 ± 38.4	74.7	7.4	100.0	0.3366
DASH						
Placebo	12	11.9 ± 15.6	9.0	0.0	57.0	
	24	16.5 ± 18.5	12.5	0.0	57.0	
Tamoxifen	12	11.0 ± 18.3	2.0	0.0	50.0	0.8985
	24	13.2 ± 16.1	8.0	0.0	54.0	0.6321
VAS satisfaction						
Placebo	3	8.2 ± 2.0	8.5	4.0	10.0	
	12	8.2 ± 2.5	9.0	2.0	10.0	
	24	8.2 ± 1.7	9.0	5.0	10.0	
Tamoxifen	3	9.7 ± 0.9	10.0	7.0	10.0	0.0319†
	12	8.5 ± 1.7	9.0	5.0	10.0	0.7366
	24	8.2 ± 1.8	8.5	4.0	10.0	0.9456

*N = 14 in the placebo group and 12 in the tamoxifen group. MCP = metacarpophalangeal joint motion, and PIP = proximal interphalangeal joint motion. †Significant.

minimally invasive subtotal fasciectomy, requires less rehabilitation compared with radical fasciectomy[5,9,10].

Recurrence is dependent on the predisposition toward fibrosis, but research to predict recurrence on the basis of tissue biopsies remains inconclusive[6,11,12]. Abe et al. established a risk evaluation method based on clinical variables, with predictable recurrence rates ranging from 5% in patients with high risk to 85% in low-risk patients[4]. Our group confirmed these findings in previous studies; the Abe score correlated well with patient-reported recurrence rates ($p = 0.006$) of 34% in patients with a low predisposition toward fibrosis and 94% in those with a strong predisposition[4,11,13,14].

The activated fibroblast is the major component of the involved tissue in Dupuytren disease. Transforming growth factor-beta (TGF-β) is a key cytokine in the pathobiology of the disease, acting as a potent modulator of myofibroblast activation, proliferation, and differentiation[12,15-19]. Kuhn et al. found that tamoxifen, a synthetic nonsteroidal anti-estrogen drug known to

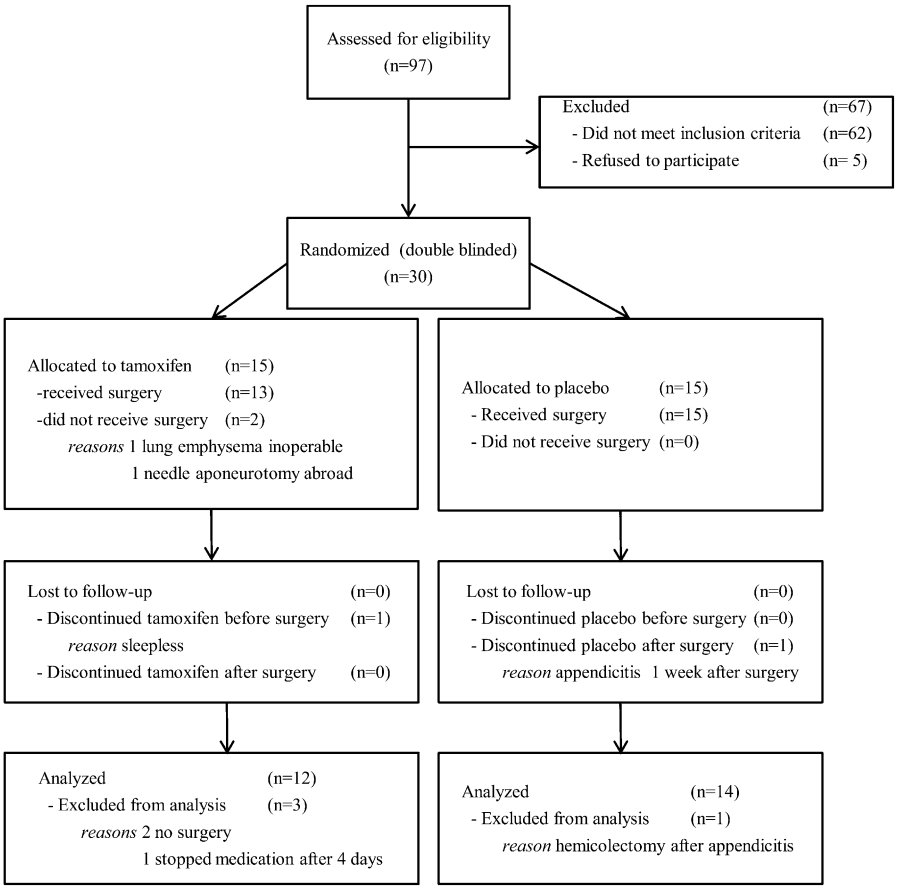

Fig. 1

CONSORT diagram showing the flow of participants through the trial.

modulate the production of TGF-β, reduced the contraction rate and TGF- 2 expression in myofibroblast cultures from patients with Dupuytren disease[20]. Tamoxifen is commonly used as an anti-estrogen therapy in breast cancer treatment, acting to suppress estrogen-dependent cancer cells. Because of its fibroblast-repressing effects, possibly involving TGF-β expression, it is also used in aggressive fibrotic diseases such as idiopathic retroperitoneal fibrosis and desmoid tumors[21-23]. Although it is used mostly in women, men with breast cancer, gynecomasty, prostate cancer, or acromegaly tolerate tamoxifen well[23-25].

These findings led us to conduct a prospective, randomized double-blind trial according to CONSORT (Consolidated Standards of Reporting Trials) standards to investigate the possible adjuvant effect of tamoxifen on the outcome of subtotal fasciectomy in patients with Dupuytren disease with a predisposition toward fibrosis[24,26-28].

Materials and Methods

The randomized controlled trial was registered in the European Clinical Trials Database (EudraCT 2006-006400-11). The trial was double-blinded and conducted at a single center. Patients with a strong predisposition toward fibrosis were randomly allocated (in a 1:1 ratio) to receive placebo or high-dosage tamoxifen as a neoadjuvant. An 80-mg dose of tamoxifen was given once daily; this is similar to the dose used to treat desmoid tumors (up to 120 mg, compared with 20 mg to treat breast cancer). The neoadjuvant drug treatment was started six weeks prior to surgery because of the known latency period of tamoxifen treatment[1-24,29,30]. After six weeks, standard minimally invasive segmental fasciectomy was performed as described by Moermans to address the contractures[31]. Tamoxifen was continued for twelve weeks after surgery as this is the estimated time interval for the most active scar tissue formation, after which the involution or remodeling stage is reached and postoperative splinting is usually discontinued[29]. The predisposition toward Dupuytren disease was evaluated with the D (diathesis) score formulated by Abe et al. (see Appendix)[4] to ensure that high-risk patients were included.

Participants

Adult patients scheduled for subtotal fasciectomy to treat Dupuytren disease were eligible for inclusion if they had a D score of >4. The sample size, based on an expected mean difference of 20° in the total passive extension deficit per ray between the placebo and tamoxifen groups, was set at thirty patients (fifteen per treatment arm), with the possibility for expansion if needed. Patients undergoing a reintervention due to recurrent contractures were excluded to avoid mixing the effects of scar tissue and primary disease. Patients with a need for skin grafts or flaps, premenopausal women, patients using anti-inflammatory drugs, patients with a history of malignancy, and patients with a known allergy to tamoxifen were also excluded. Potential reasons for withdrawal were a request by the patient, a decision by the investigator based on a suspicion of complications due to tamoxifen, an unexpected event such as serious illness, and a decision by the data monitor (Fig. 1).

Intervention

The patients underwent minimally invasive subtotal fasciectomy performed by the first author[31]. This surgical procedure involves correction of the contractures

without the intention to remove all affected tissue, allowing for easy rehabilitation. Placebo or 80 mg/day of tamoxifen was given for a total of eighteen weeks, starting six weeks before surgery and ending twelve weeks after surgery. Tablets were provided by the hospital pharmacist, and both items looked exactly alike.

A strict postoperative protocol was followed; clinical follow-up was performed at ten days for wound inspection and a bandage change, and a dynamic extension splint was worn at night for eight weeks. Patients were well instructed by the surgeon regarding active finger mobilization and splinting[32]. Further follow-up data were collected at three months and one and two years.

Outcomes

One of the two primary quantitative outcome parameters was the total passive extension deficit of the metacarpophalangeal and proximal interphalangeal joints of the most affected ray, as documented with digital photography and measured with goniometry by two independent surgeons. As only patients with a strong predisposition toward fibrosis were included, all showed multiple affected digits. However, in every case, the contracture was most pronounced in one digit (most often the fifth digit, in some cases the fourth), with the other digits being less involved. In some cases, an additional ray required surgical treatment for a minor contracture of the metacarpophalangeal joint. The study focused on individual rays rather than on patients, especially for the data analysis. The other primary outcome parameter was the Tubiana index, a relative correction coefficient comparing the final contracture with the initial one, was calculated to evaluate relative motion gain[33]. This allowed determining whether tamoxifen was more effective in, for instance, less affected fingers. The secondary qualitative outcome parameters were a VAS (visual analog scale) score for satisfaction with the outcome, which was graded from 1 to 10 points at every visit, and the DASH (Disabilities of the Arm, Shoulder and Hand) score to evaluate disability.

Recurrence was defined as the development of a recurring contracture, as true disease recurrence is difficult to define in segmental fasciectomy, in which the affected tissue is never completely removed.

In addition, abnormal wound-healing, scar formation, and complications were noted. Possible side effects of tamoxifen are flushing, edema, thrombocytopenia, nausea and vomiting, vaginal bleeding, impotence, and very rarely dizziness, venous thrombosis and embolism, vaginal infection, and malignancy. Extremely rare side effects are headache, allergy, leucopoenia, anemia, alopecia, erythema multiforme, liver steatosis, cholestasis, hepatitis, and vision problems. If complications occurred in a patient in the study, the tamoxifen was stopped, rather than reduced in dosage as is the practice in breast cancer treatment.

Tissue samples obtained during surgery were used to confirm the diagnosis and were archived for potential later research.

Sample Size

A common standard deviation of 15° and a two-sided significance level of 5% were assumed. Thus, it was calculated that a sample size of thirty patients (fifteen per treatment arm) would provide 95% power to detect an overall difference of 20° per ray.

Randomization and Blinding

After providing informed consent and completing a clinical data questionnaire, patients received one of thirty numbered boxes (according to their order of enrollment) designating treatment with either placebo or tamoxifen for eighteen weeks.

The boxes had been numbered at random by the data monitor beforehand, and the investigator used the boxes in the given order without knowledge of their content. Blocking and stratification was not done. The investigator who enrolled the participants assigned them blindly to the tamoxifen or placebo groups. Box numbers were noted on the consent form and on all other forms pertaining to a given patient. A sealed envelope stating the actual content of the given boxes was prepared by the data monitor and was kept in his office, to be opened only in case of emergency.

Thus, patients, surgeon-investigators, and pathologist-investigators were blinded with regard to the treatment (double-blinding). The data monitor was the only person with knowledge of the group to which each patient belonged. The success of blinding was evaluated at the end of the study by asking the investigator and the patient to guess the group to which the patient had been allotted, then comparing the answers with the actual allotment.

Statistical Methodology

Linear models were used to analyze the effects of time, treatment, and the interaction between time and treatment on the four outcomes of interest. An unstructured residual covariance matrix was modeled to account for correlation in the data due to repeated measurements. The initial analysis was a complete-case analysis (analysis of all patients with outcome data), excluding the dropouts. To assess the effect of the dropouts, we performed a second analysis including all patients. Missing observations were dealt with by means of multiple imputation (ten iterations) with a parametric regression method, assuming multivariate normality.

Source of Funding

No external funding was received for this study. The Belgian Orthopaedic Society paid for the medication and placebo so that there would be no additional cost to the patients.

Results

The recruitment period lasted twelve months, and all surgical interventions were performed within fourteen months of the start of the recruitment period; unblinding was performed at each patient's two-year follow-up visit. The mean patient age was sixty-four years in the placebo group and sixty-two years in the tamoxifen group; the mean D score was 6 in both groups (see Appendix). The placebo group included three female patients and the tamoxifen group included one. Finger extension deficits did not differ significantly between the groups at baseline ($p = 0.4213$, Student t test), although there was a tendency for the proximal interphalangeal joint to be slightly more affected in the tamoxifen group ($p = 0.1871$). The mean DASH score was 19 in the placebo group and 21 in the tamoxifen group. Only one patient failed to achieve full finger extension during surgery; that patient, in the tamoxifen group, had incomplete correction of the proximal interphalangeal joint even after check-rein ligament release.

Number of Patients Analyzed (Fig. 1)

The placebo group had one dropout, who discontinued medication after complicated appendicitis requiring hemicolectomy one week after surgery. His hand healed uneventfully. Three patients in the tamoxifen group were not included in the final analysis; one cancelled the surgery because of deteriorating lung emphysema, one stopped the medication after four days because of insomnia that he attributed to stress associated with the medication and study participation, and the third patient went abroad for needle aponeurotomy after three weeks.

Outcomes and Estimation

Outcome data are shown in Table I, Figures 2-A, 2-B, and 2-C, and the Appendix. In the complete-case analysis of the two groups, there were significant differences in both the VAS score for satisfaction and the total passive extension deficit at three months in favor of the tamoxifen group ($p = 0.0319$ and $p = 0.0176$, respectively; Table I). The difference in total passive extension deficit was significant only for the proximal interphalangeal joints ($p = 0.0004$ for these joints, $p = 0.7631$ for the metacarpophalangeal

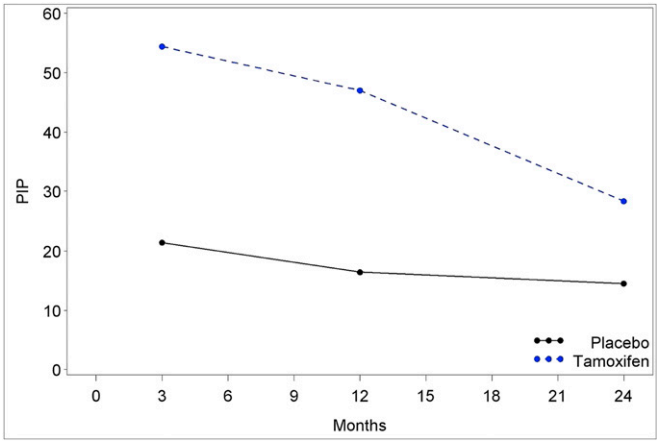

Fig. 2-A

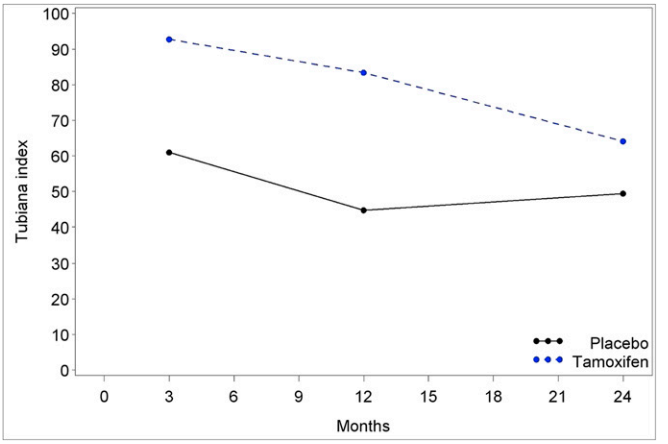

Fig. 2-B

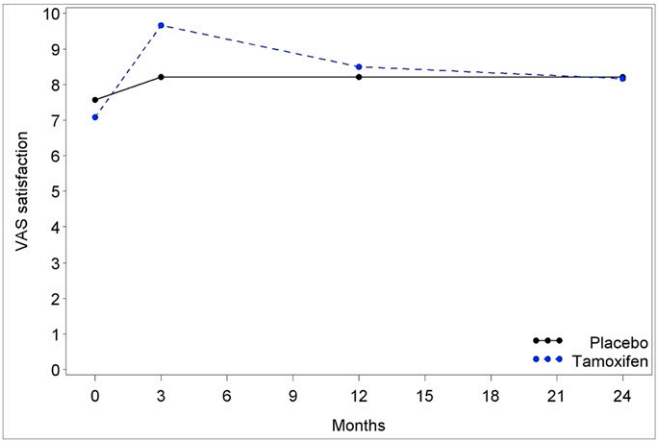

Fig. 2-C

Figs. 2-A, 2-B, and 2-C The evolution of the significantly improved parameters after surgery. Improvement in proximal interphalangeal (PIP) joint motion (in degrees, **Fig. 2-A**) was significantly greater in the tamoxifen group than in the placebo group through one year. This difference is also reflected in the Tubiana index (**Fig. 2-B**) and satisfaction (**Fig. 2-C**), which were significantly better at three months. After two years without tamoxifen, all effects were lost.

joints). The relative improvement in finger extension, as measured with the Tubiana index, was also significantly better in the tamoxifen group ($p = 0.0010$). At one year of follow-up, the difference only remained significant in the proximal interphalangeal joints ($p = 0.0187$). At two years, the difference was no longer significant for any of the parameters. Multiple imputation analysis of all patients including the dropouts yielded similar results; after correction for dropouts, the difference in proximal interphalangeal joint correction remained significant ($p = 0.0366$), although the treatment difference at three months no longer reached significance for the VAS score for satisfaction ($p = 0.0628$). Summary statistics showed that the VAS score was lower for the dropouts compared with the rest of the sample. Given that more dropouts occurred in the treatment group, it is possible that the complete-case analysis overestimated the VAS satisfaction scores in the treatment group. This may explain the lack of significance of the effect after correction for dropouts. No treatment effect was observed with regard to the DASH score ($p = 0.8985$ at one year in the complete-case analysis).

The day before unblinding, 86% of the placebo group guessed correctly that they had received the placebo and 33% of the tamoxifen group guessed that they had received the active substance. The observing surgeon guessed correctly in 64% and 83% of the cases, respectively.

Adverse Events

No life-threatening complications were seen. Possible milder side effects never led to withdrawal from the study. In the placebo group, carpal tunnel syndrome was observed in three patients (two male and one female). The female patient underwent carpal tunnel surgery six months later; the symptoms subsided spontaneously in the male patients. Although not a known side effect of tamoxifen, the carpal tunnel symptoms did draw attention because a recent study demonstrated fluid accumulation and tenosynovial changes, which may induce secondary nerve compression, with tamoxifen use[34]. The remaining symptoms also all occurred in the placebo group and consisted of four cases of impotence (three transient and one continuing after two years), weight increases (in one male and two female patients), and one case of severe gastroenteritis (in a female patient).

Wounds healed uneventfully except in one patient in the tamoxifen group who had a granuloma lasting for three weeks.

Although the patient's finger could be fully extended, active finger flexion was limited, necessitating flexor tendon adhesiolysis three months later. One patient in the tamoxifen group had an excellent result until three months after surgery followed by rapid recurrence and extension loss within three months after cessation of the tamoxifen; finger extension stabilized over the remainder of the two years.

Discussion

This study demonstrated a significantly improved short-term outcome of segmental fasciectomy in patients with a predisposition toward fibrosis and Dupuytren disease treated with high-dosage tamoxifen. The observed improvements in both contractures and satisfaction reflect a probable influence of tamoxifen on the healing process. Tamoxifen primarily improved the motion of the proximal interphalangeal joint, which is the most challenging joint to treat in Dupuytren disease. The metacarpophalangeal joints improved well in both groups, as is the case with most treatment modalities[35].

Unfortunately, most of the short-term outcome improvements were lost within a year after tamoxifen cessation. A disease rebound in the affected finger of one patient shortly after tamoxifen cessation may indicate a necessity to either continue the medication for longer periods (if not indefinitely) at lower dosages or at least avoid discontinuing it so abruptly. The long-term effects of high-dosage tamoxifen are not known; thus, even though no life-threatening complications were encountered in this study, caution is imperative in long-term high-dosage drug therapy. Risks of thrombosis, liver necrosis, and malignancy may become relevant in long-term use. In this study, side effects were seen only in the placebo group. The occurrence of a single wound problem is inconclusive, but monitoring of future tamoxifen use in surgically treated patients is imperative to assess its influence on wound-healing. Although the surgeons correctly guessed which treatment the majority of subjects had received, the patients were less likely to be correct when asked whether they thought they had received tamoxifen or placebo. For the patients, this may have been due to the lack of side-effects and to the recurrence of contractures within the two years. However, the surgeon focused solely on clinical outcome, and the large difference in outcomes within the first months led to better identification of the active group.

Strengths of the study are the double blinding, adherence to the CONSORT standards[27,28,36], strict randomization, use of a single surgical technique performed by a single surgeon, and similar populations with a high risk for a poor outcome without treatment (which potentially increases the magnitude of any treatment effect). Weaknesses are the limited size of the patient groups and the dropout rate, which was greater in the tamoxifen group. However, the results remained significant after multiple-imputation analysis with correction for dropouts. Another general weakness of studies on the outcome of Dupuytren disease is the limited availability of outcome measures. Goniometry to measure joint motion was the most important objective quantitative parameter, given that hands have unique contractures that are never completely similar. More subjective parameters, the DASH score and the VAS score for satisfaction, were also used. Although often used as a simple method of preference measurement, use of VAS scores raises some concerns regarding validity; the anchors may not be well defined, and biases (e.g., context and end-aversion) may occur. However, there is evidence that limited and cautious use of the VAS score is valuable and appropriate, and it was included in this study to add an easy subjective patient-reported outcome score[37]. On the other hand, the relation of the DASH score to the severity of Dupuytren disease is equivocal, which may explain the fact that outcome improvement was not reflected in significantly improved DASH scores[10,38,39].

Although tamoxifen use should not be considered in every patient with Dupuytren disease, this study does support the development of neoadjuvant pharmacotherapy in patients with a predisposition toward fibrosis. Continued research may lead to the development of adequate adjuvant pharmacotherapy for patients with a history of unsuccessful surgery (poor outcome and rapid recurrence). To develop drugs for control of the disease in severely affected patients, translational research with strong attention to the system biology of Dupuytren disease is required[16]. The pathobiology of phenotype modulation of fibroblasts into myofibroblasts is the subject of numerous research projects, and the understanding of its function and molecular regulation will have a major influence on future medicine[18].

If adjuvant pharmacotherapy is to be considered some day to improve the outcome of surgical treatment in patients with Dupuytren disease, prevent disease recurrence, and avoid the need for high-risk reoperations that carry an increased risk for amputation, it is essential to identify patients with an elevated risk of recurrence or severe progression[2,13]. Patients with a strong predisposition toward Dupuytren disease often show other features of a general predisposition toward fibrosis[40]. Therefore, similar "Dupuytren-like" diseases such as frozen shoulder (which is often associated with Dupuytren disease) or arthrofibrosis in patients with a predisposition toward fibrosis may also one day benefit from the continued research on inclusion of disease-modifying drugs as a part of their treatment algorithms[16,40,41].

Tamoxifen is used primarily in patients with breast cancer because of its anti-estrogen effect. Long-term use has been confirmed to be efficacious and safe at a low 20-mg/day dosage in the overall female population[30]. Some experience with long-term use of higher tamoxifen dosages, as high as 120 mg/day, is available in patients with rare desmoids tumors who were given tamoxifen for its fibroblast-repressing effect; however, we are aware of no reports of large case series, and some controversy regarding its effectiveness remains[23]. Positive effects of tamoxifen have been reported in patients with retroperitoneal fibrosis[21,22]. In vitro studies of myofibroblasts from patients with Dupuytren disease did suggest a positive effect of tamoxifen on their cellular activity, and the present study has now confirmed a clinical effect of tamoxifen on the outcome of surgery, possibly due to the suppression of myofibroblasts[30].

In conclusion, neoadjuvant use of high-dosage tamoxifen for four months (with discontinuation three months postoperatively)

improved the short-term outcome after surgical treatment of Dupuytren disease in patients with a strong predisposition toward fibrosis, but the effect disappeared within two years after surgery. Although the effect of extended use is unproven, long-term administration of high-dosage tamoxifen may carry risks. Therefore, although a positive short-term effect on surgical outcome was found, the risks of using tamoxifen may outweigh the possible benefits in patients with Dupuytren disease.

Appendix

(eA) Tables showing the Abe scoring system, patient demographics, and details of the outcome analyses as well as figures showing the DASH score, joint motion, and Tubiana index over time are available with the online version of this article as a data supplement at jbjs.org. ■

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