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Brief Communication: Tamoxifen Therapy for Nonmalignant Retroperitoneal Fibrosis

Eric F.H. van Bommel, MD, PhD; Tadek R. Hendriksz, MD; Antonius W.L.C. Huiskes, MD; and Antoine G.M. Zeegers, MD

Background: Anecdotal case reports suggest tamoxifen as a possible treatment for retroperitoneal fibrosis, but a systematic assessment of its effect is not available.

Objective: To describe the course and outcomes of patients with nonmalignant retroperitoneal fibrosis treated with tamoxifen.

Design: Prospective, consecutive series.

Setting: Single tertiary care referral center.

Patients: 19 patients with nonmalignant retroperitoneal fibrosis treated with tamoxifen from April 1998 through April 2005.

Intervention: Tamoxifen, 20 mg orally twice daily.

Measurements: Clinical improvement, laboratory variables, and follow-up computed tomography (CT) and gallium scan findings.

Results: Fifteen patients reported substantial resolution of symptoms after a median treatment duration of 2.5 weeks. Erythrocyte sedimentation rate and C-reactive protein also improved. Gallium scanning at follow-up showed incomplete disappearance of pathologic gallium-67 activity. Repeated CT scanning showed slow but steady mass regression in 14 of 15 clinical responders. Five patients failed treatment, including 1 patient who improved clinically. Disease recurred in 1 patient who responded to reintroduction of tamoxifen. One patient developed reversible hepatitis.

Limitations: This small observational study did not have a control group.

Conclusion: Tamoxifen may be a viable therapeutic option in the treatment of retroperitoneal fibrosis.

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For author affiliations, see end of text.

The treatment of retroperitoneal fibrosis is largely empirical, although various surgical and medical treatments have been explored (1–6). Anecdotal case reports suggest tamoxifen as a possible therapy (7–20). In this prospective case series, we describe the clinical course and outcomes, including changes in retroperitoneal masses, of 19 consecutive patients with nonmalignant retroperitoneal fibrosis who were treated with tamoxifen monotherapy.

METHODS

Patients

From April 1998 through April 2005, 19 of 22 consecutive patients with retroperitoneal fibrosis were treated with tamoxifen monotherapy (20 mg twice daily) (**Appendix Figure 1**, available at www.annals.org). Three patients were excluded because of concurrent systemic disease necessitating immunosuppressive therapy (polyarteritis nodosa, acute tubulointerstitial nephritis) or because of concurrent malignant disease (urothelial-cell carcinoma). After careful exclusion of malignant disease, the diagnosis of active nonmalignant retroperitoneal fibrosis was made on the basis of the typical clinical picture and the presence of characteristic findings on computed tomography (CT) (1, 2, 4–6). In 3 patients, the diagnosis was histologically confirmed. Patients provided informed consent at the start of treatment. On the basis of available literature (7–13), it was decided to continue tamoxifen treatment for up to 2 years. If indicated, emergency renal drainage was also done. Follow-up included periodic clinical and laboratory examination (initially, 6- to 8-week intervals; after 6 months, 3-month intervals) and repeated CT scanning (initially, 4-month intervals; after 8 months, 6- to 12-month intervals). Gallium scan studies were done in all recruited patients at baseline and at follow-up if the results of the baseline studies were positive. If there was doubt about the diagnosis during follow-up, CT-guided biopsy was done.

CT Scanning

All CT scans were independently reviewed by 1 experienced radiologist who was unaware of the patients' status. The maximal thickness of the mass was measured in 3 different views (anterior–posterior, left lateral, and transversal directions). The craniocaudal length of the mass was also measured. For follow-up CT scans, measurements were made at the same levels and by using the same method used for the first CT scan. Changes in all of these measurements were used to subsequently categorize regression of a periaortic mass as none, moderate (<50%), significant (≥50%), or complete (that is, no identifiable mass). To further evaluate changes within patients during

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Context

There are few effective treatments for retroperitoneal fibrosis.

Contribution

Of 19 adults with nonmalignant retroperitoneal fibrosis treated with tamoxifen for variable durations of time, 15 reported substantial resolution of symptoms and 14 had computed tomography scans that showed slow regression of retroperitoneal masses. Three men reported minor losses of libido, and 1 patient developed reversible hepatitis.

Caution

There was no control group in this small observational study.

Implications

Tamoxifen is a possible therapy for retroperitoneal fibrosis. It should be compared with other treatments in long-term trials.

—The Editors

follow-up, the largest value of the initial 3 measurements of maximal thickness was compared with the thickness of the mass at the end of follow-up; for this comparison, we used the same measurement direction and the same level from which the largest value was obtained on the first CT scan.

Gallium Scanning

Because of its potential value in assessing disease activity (21–24), gallium-67 imaging was also done. Pathologic gallium-67 uptake in the paravertebral midline at the same position as the periaortic mass, as determined with CT scanning, was considered an indication of the active, inflammatory stage of the disease (positive results) (21–24). Absence of uptake in this region (negative results) did not influence the decision to begin tamoxifen treatment in these patients. In patients with positive results on the baseline gallium scan, follow-up gallium scanning was done after 6 to 12 weeks of tamoxifen treatment. One experienced nuclear radiologist who was unaware of the patients' status independently reviewed all gallium scans and graded them according to the intensity of pathologic activity compared with normal bone marrow gallium activity: grade 0 (no pathologic activity), grade 1 (pathologic activity but less than bone marrow activity), grade 2 (pathologic activity similar to bone marrow activity), and grade 3 (pathologic activity more intense than bone marrow activity).

Adverse Events

At follow-up, we used a checklist of 10 items to ask patients about the presence of the following possible adverse effects of tamoxifen: nausea or indigestion, mood swings, loss of libido, vaginal bleeding, weight gain, visual problems, headache, flushes or sweats, allergic reactions (for example, itching or skin rash), and signs and symptoms of thrombosis (pain, warmth, swelling or tenderness in an arm or leg, or any chest pain). In addition, repeated physical examination and laboratory investigation (including gonadal hormone levels) was done. In female patients with an intact uterus, follow-up vaginal ultrasonography was also scheduled at 1-year intervals.

Measurements

Primary outcome measures, defined a priori, were clinical improvement, changes in acute-phase reactants, and follow-up CT findings. We documented overall subjective improvement as reported by the patient and used a 100-mm horizontal visual analogue scale (VAS) to measure changes of primary symptoms within individuals during follow-up, with pain and discomfort as variables (25). Secondary outcome measures were the findings on the gallium scan and the occurrence of adverse events. All patients were under the care of the first author. Immunohistochemical investigation was done on available biopsy specimens to assess the presence of estrogen and progesterone receptors.

Statistical Analysis

Continuous variables were reported as medians and interquartile ranges (25th to 75th percentile), as appropriate. Differences between baseline and follow-up of continuous and ordinal (gallium score) variables were analyzed by

Table 1. **Demographic and Clinical Characteristics of Study Patients***

Characteristic	Value
Age (range), *y*	63 (54–74)
Men, *n (%)*	16 (84)
First presentation/recurrence, *n/n*†	13/6
Type of retroperitoneal fibrosis, *n (%)*	
Idiopathic	7 (37)
Secondary‡	12 (63)
Duration of symptoms (range), *mo*	6.0 (3.5–13.5)
Presenting symptoms, *n (%)*	
Discomfort§	18 (94)
Abdominal, back, and/or flank pain	16 (84)
Increased urinary frequency	8 (42)
Weight loss	7 (37)
Constipation	6 (32)
Hydrocele, testicular pain	5 (31)
Fever, rigors	3 (16)
Claudication	3 (16)
Retrograde ejaculation	2 (13)
Increased acute-phase reactants, *n (%)*	
Erythrocyte sedimentation rate	15 (79)
C-reactive protein level	14 (74)
Hydronephrosis, *n (%)*‖	9 (47)
Positive results on gallium-67 scan, *n (%)*	13 (68)

* Values are medians and interquartile ranges (25th to 75th percentile) or numbers and percentages.
† Six patients had been treated previously with steroids on first or recurrent presentation.
‡ Secondary to advanced atherosclerosis (chronic periaortitis [$n = 8$] or perianeurysmal fibrosis [$n = 3$]) or recurrent pancreatitis ($n = 1$).
§ Significant loss of subjective well-being because of specific (e.g., pain) and/or nonspecific (e.g., disturbed sleep, malaise, or anorexia) symptoms.
‖ Ureteral stenting with double-J splints was performed in 4 patients.

Table 2. **Clinical, Radiologic, and Laboratory Findings at Baseline and at Follow-Up***

Characteristic	Baseline	End of Follow-up
Visual analogue scale score		
Pain, *mm*	34.0 (16.0–46.0)	5.0 (0.0–15.5)†
Discomfort, *mm*	33.5 (19.0–56.5)	6.5 (0.0–12.5)†
Laboratory findings		
ESR, *mm/h*	33.5 (23.0–69.5)	11.5 (5.5–19.0)†
C-reactive protein level, *mg/L*	23.0 (8.5–41.5)	6.0 (5.0–10.5)‡
Creatinine level		
μmol/L	120 (92–185)	124 (92–158)
mg/dL	1.4 (1.0–2.1)	1.4 (1.0–1.8)
Estradiol level§		
pmol/L	97.5 (87.5–120.5)	99.0 (73.0–142.0)
pg/mL	26.6 (23.8–32.8)	27.0 (19.9–38.7)
Testosterone level§		
nmol/L	15.1 (10.6–21.2)	17.4 (14.7–22.1)
ng/dL	435.2 (305.5–610.9)	501.4 (423.6–636.8)
ALT level, *U/L*	13.5 (9.5–17.5)	16.0 (11.5–24.0)
AST level, *U/L*	13.5 (9.0–24.5)	19.5 (13.5–29.0)
Cholesterol level‖		
mmol/L	4.7 (4.1–5.8)	4.5 (3.8–4.8)
mg/dL	181.4 (158.3–223.9)	173.7 (146.7–185.3)
Hemoglobin level, *g/L*	135 (121–140)	137 (128–145)
Platelet count, $\times 10^9$ *cells/L*	278 (223–329)	238 (208–261)
Leukocyte count, $\times 10^9$ *cells/L*	7.6 (5.6–9.7)	8.1 (6.3–10.1)
Maximal thickness of retroperitoneal mass on CT, *mm*		
Overall (n = 19)	27.5 (16.0–37.0)	14.0 (9.5–26.5)¶
Responders (n = 14)	24.0 (13.5–31.5)	14.0 (8.0–21.0)†
Craniocaudal length of retroperitoneal mass on CT, *mm*		
Overall (n = 19)	130.0 (107.5–168.0)	120.0 (92.0–156.5)**
Responders (n = 14)	125.0 (78.5–149.0)	111.0 (56.0–122.5)†

* Values are medians and interquartile ranges (25th to 75th percentile). ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; ESR = erythrocyte sedimentation rate.
† $P < 0.001$ versus baseline.
‡ $P = 0.002$ versus baseline.
§ Values in men only (n = 16).
‖ Three patients received new statin therapy during follow-up.
¶ $P = 0.003$ versus baseline.
** $P = 0.032$ versus baseline.

using the Wilcoxon signed-rank test. Reported P values are 2-sided and are uncorrected for multiple testing. We performed the calculations with SPSS software, version 11.0.1 (SPSS Inc., Chicago, Illinois).

Role of the Funding Source

No funding was received for this study.

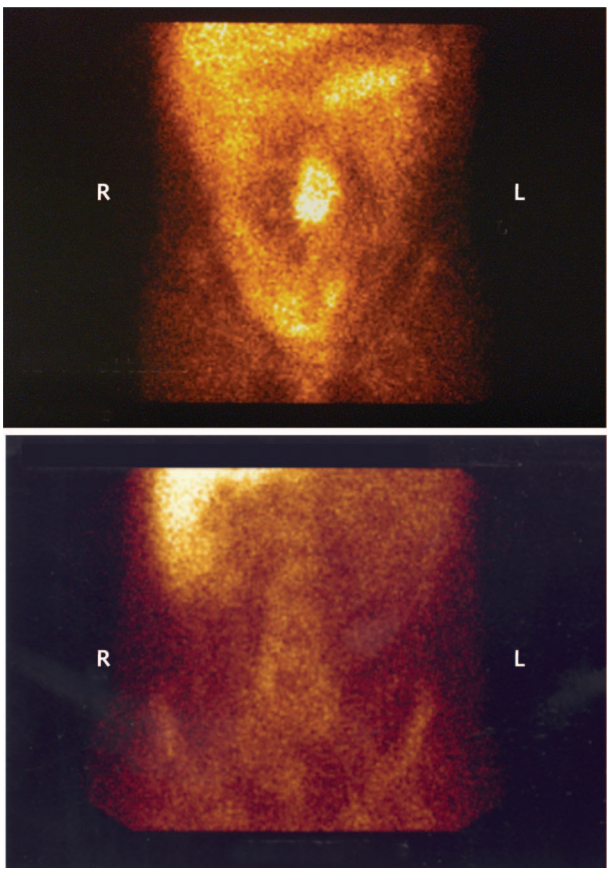
RESULTS

Patient characteristics at presentation are shown in **Table 1**. The median duration of treatment was 8.5 months (range, 5.5 to 15.0 months). Post-treatment follow-up in patients who completed 2 years of tamoxifen treatment was 9 and 59 months in 2 patients and 1 patient, respectively. Follow-up did not reveal other pathologic lesions that could have accounted for the findings at presentation.

Fifteen patients reported substantial resolution of symptoms after a median treatment duration of 2.5 weeks (range, 1.5 to 6.0 weeks). Both erythrocyte sedimentation rate (median, 33.5 mm/h [range, 23.0 to 69.5 mm/h] and 10.0 mm/h [range, 3.0 to 28.0 mm/h], respectively; $P = 0.001$) (**Appendix Figure 2**, available at www.annals.org) and C-reactive protein level (median, 23.0 mg/L [range, 8.5 to 41.5 mg/L] and 7.0 mg/L [range, 5.5 to 16.0 mg/L], respectively; $P = 0.002$) were lower at 4 months of follow-up. Improvement of signs and symptoms persisted until the end of follow-up, as documented by the decrease in VAS score (**Table 2**). Definitive removal of ureteral catheters was possible in 1 patient after 9 months of treatment; in 3 patients, ureteral catheters were still in situ after treatment durations of 4, 8, and 9 months, respectively.

Follow-up CT scanning at 4 months showed moderate to significant mass regression in 9 and 3 patients, respectively. Clinical and laboratory improvement occurred in 2 of 5 patients with stable masses on the first follow-up CT scan at 4 months; these 2 patients subsequently showed mass regression on repeated CT scanning. In 2 patients, an enlarging mass was noted during follow-up. In responders with 2 or more follow-up CT scans (n = 10), continued regression was observed (follow-up, 15.0 months [range, 10.0 to 33.0 months]), including complete regression of

Figure. **Anterior gallium-67 images in a 47-year-old man with retroperitoneal fibrosis before (*top*) and after (*bottom*) 6 weeks of treatment with tamoxifen (20 mg orally twice daily).**



At presentation, there was intense pathologic activity in the prevertebral midabdominal region, which disappeared at follow-up gallium scanning. L = left; R = right.

the mass in 2 patients at 8 months of follow-up; in all other responders, a residual mass was noted at the end of follow-up (moderate regression in 4 patients and significant regression in 4 patients). The mass decreased in thickness and, to a lesser extent, in craniocaudal length (**Table 2**).

Repeated gallium scanning showed incomplete disappearance of pathologic activity at the level of the periaortic mass following initiation of tamoxifen treatment (**Figure**) in 12 of the 13 patients with initial positive results on gallium scans, as documented by a decrease in the gallium score ($P < 0.001$). During follow-up, 5 patients were considered as having had treatment failure because of persistent or recurrent signs and symptoms and/or an enlarging mass on repeated CT scanning. Three of these 5 patients had positive results on baseline gallium scan. Three patients subsequently responded to combined immunosuppressive therapy (prednisone, 60 mg/kg, and azathioprine at 2 mg/kg of body weight). Two patients had only short follow-up after initiation of second-line treatment. One responder developed recurrent disease 48 months after discontinuation of tamoxifen treatment but responded to reintroduction of tamoxifen.

Reported side effects of tamoxifen included transient nausea in 2 men and 1 woman, lightheadedness in 3 men, and minor loss of libido in 3 men. Hormonal changes after treatment in men included transient increases in estradiol level (97.5 pmol/L [range, 87.5 to 120.5 pmol/L] to 148.5 pmol/L [range, 120.5 to 2156.0 pmol/L] or 26.6 pg/mL [range, 23.8 to 32.8 pg/mL] to 40.3 pg/mL [range, 32.8 to 587.3 pg/mL]) and in testosterone level (15.1 nmol/L [range, 10.6 to 21.2 nmol/L] to 22.8 nmol/L [range, 19.5 to 37.3 nmol/L] or 435.2 ng/dL [range, 305.5 to 610.9 ng/dL] to 657.1 ng/dL [range, 561.9 to 1074.9 ng/dL]), which normalized by the end of follow-up (**Table 2**). Levels of follicle-stimulating hormone and luteinizing hormone were unchanged throughout therapy (data not shown). Follow-up laboratory data showed an increase in liver enzyme levels and a decrease in platelet count (**Table 2**). One nonresponder developed reversible hepatitis (alanine aminotransferase level, 123 U/L; aspartate aminotransferase level, 325 U/L) before switching therapies. Follow-up vaginal ultrasonography was unremarkable. No estrogen or progesterone receptors were found in retroperitoneal fibrosis tissue on immunohistochemical investigation in 5 patients.

Table 3. **Previously Published Case Reports of Patients Treated with Tamoxifen***

Characteristic	Value
Patients, *n*	14
Age (range), *y*	51 (42–63)
Men, *n (%)*	6 (43)
Tamoxifen treatment	
Dosage (range), *mg/d*	20 (20–30)
Duration (range), *mo*	12.5 (9.0–22.5)
Radiologic regression	
All patients with radiologic regression, *n (%)*	14 (100)
Time to first documentation of radiologic regression (range), *mo*	4.0 (3.0–8.5)
Patients with complete regression, *n*	6
Time to complete regression (range), *mo*†	12.5 (6.0–24.0)
Double-J splint	
Patients, *n (%)*	7 (50)
Time to definitive removal (range), *mo*	9.0 (6.0–13.5)
Follow-up	
Overall duration (range), *mo*	15.0 (9.0–32.5)
Patients still receiving treatment, *n*	11
Duration of treatment (range), *mo*	10.0 (9.0–27.0)
Post-treatment follow-up	
Patients, *n*	3
Duration, *mo*	21
Patients with recurrent disease, *n (%)*	1 (33)‡
Time to recurrence, *mo*	2

* Values are medians and interquartile ranges (25th to 75th percentile) or numbers and percentages, unless otherwise noted. Data are from references 7 to 19. Seven patients (50%) had exploratory laparotomy, including ureterolysis ($n = 3$) or gastroenterostomy ($n = 1$).
† 6 patients.
‡ Responded to reintroduction of tamoxifen.

DISCUSSION

This study suggests that tamoxifen may be a viable therapeutic option for patients with retroperitoneal fibrosis. We observed a gradual improvement of signs and symptoms over several weeks to months in most patients. Repeated CT scanning showed slow but steady mass regression, albeit with the usual persistence of some residual periaortic mass. Searching English-, German-, and French-language literature through June 2005 using MEDLINE, we identified several other case reports of patients treated with tamoxifen (**Table 3**) (7–19). Our radiologic findings were less impressive than the findings reported in many of those cases, which may be explained by the longer overall treatment duration at the end of follow-up in previously published case reports or by positive reporting bias of previous cases.

Irrespective of the results of the gallium scan at presentation, most patients in our study responded to tamoxifen, so the potential success of this treatment cannot be definitively determined on the basis of gallium scan results. Our findings may also suggest the potential efficacy of tamoxifen in both early and later stages of the disease (21–23). Of note, repeated gallium scanning in patients with initial positive results showed incomplete disappearance of the pathologic gallium-67 uptake, suggesting suppression of the inflammatory process by tamoxifen.

No major side effects were noted in our study other than 1 case of reversible hepatitis. Serum hormone levels in men were not affected at the end of follow-up. These findings underline the potential of tamoxifen as a safe alternative therapy in both men and women. Unlike corticosteroids, tamoxifen probably will not promote or mask tumor growth in cases where the retroperitoneal mass is caused by unrecognized malignant disease.

The pathophysiologic pathway by which tamoxifen exerts its effects is unknown, but we suggest a hormone-independent mode of action. Immunohistochemical studies of biopsy material did not reveal estrogen or progesterone receptors. Other studies have noted very low or undetectable levels of serum estrogen receptors (7, 11, 12). Tamoxifen may alter the balance of growth factors in such a way that fibroblast proliferation is inhibited (26–28). The antiangiogenic properties of tamoxifen may also contribute to its efficacy (29, 30). Because tamoxifen is an antiestrogen drug, it may also act as anti-inflammatory or immunosuppressive therapy in retroperitoneal fibrosis (31, 32), which would explain the observed decrease in acute-phase reactants and disappearance of the pathologic gallium-67 activity in our study.

Some patients who did not respond to tamoxifen therapy did respond to combined immunosuppressive therapy. Another study reported successful tamoxifen treatment in a patient with steroid resistance (20). Therefore, corticosteroids and tamoxifen therapy may be considered viable medical options for patients with tamoxifen or steroid resistance, respectively, either alone or combined. Sequential therapy may also be considered (33).

With corticosteroid therapy, pain and constitutional symptoms may disappear within days and erythrocyte sedimentation rate may decrease more rapidly (1, 4, 5); the retroperitoneal mass may also regress more rapidly (1, 5, 34). The response to tamoxifen, therefore, differs from that seen with steroids. However, a residual mass is also noted in most patients after steroid treatment (6, 7, 35). Reported success rates with combined immunosuppressive treatment vary from 50% to more than 90% (2, 3, 6, 35, 36). Our results seem to fall within this category.

Our study is limited because of the absence of a control group and the small sample size. However, because of the low estimated incidence of retroperitoneal fibrosis (1 in 200 000 to 1 in 500 000 persons), a controlled, therapeutic trial would be very difficult to perform (1). To our knowledge, this is the first report on a substantial number of patients followed in a standardized fashion after initiation of tamoxifen therapy. Another concern may be the long-term outcome of patients treated with tamoxifen. As in most case reports (**Table 3**), most of our patients were still receiving tamoxifen at the end of follow-up. Some authors choose to administer long-term tamoxifen treatment to their patients (12, 14, 17). In our study, disease recurred in 1 of 3 patients who completed 2 years of tamoxifen treatment, and data from the literature revealed similar results (**Table 3**). All of these patients responded to reintroduction of tamoxifen. Of note, recurrent disease with combined immunosuppressive treatment may also occur in as many as 30% of patients (2, 3, 6, 35, 36). Nevertheless, more studies are needed to establish the long-term efficacy of tamoxifen.

In conclusion, this study suggests the viability of tamoxifen as a therapeutic option for some patients with retroperitoneal fibrosis. Optimum duration of therapy, efficacy compared with other potential treatments, and long-term efficacy remain to be determined.

From Albert Schweitzer Hospital, Dordrecht, the Netherlands.

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Requests for Single Reprints: Eric F.H. van Bommel, MD, PhD, Department of Internal Medicine, Albert Schweitzer Hospital, Dordrecht, P.O. Box 444, NL-3300 AK Dordrecht, the Netherlands; e-mail, e.f.h.vanbommel@asz.nl.

Current author addresses and author contributions are available at www.annals.org.

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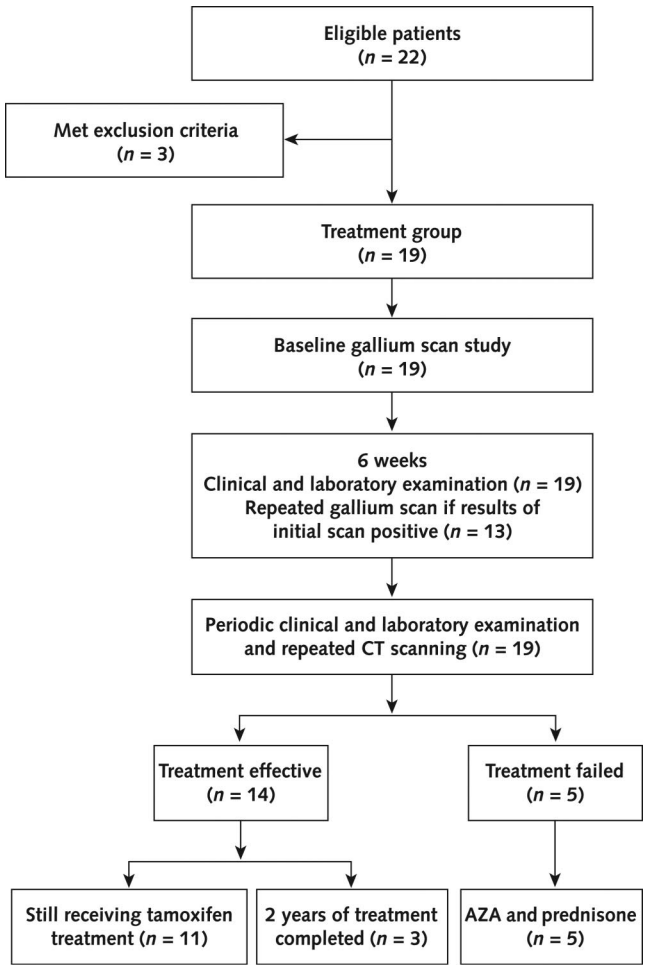
Current Author Addresses: Dr. van Bommel and Drs. Hendriksz, Huiskes, and Zeegers: Albert Schweitzer Hospital, P.O. Box 444, NL-3300 AK Dordrecht, the Netherlands.

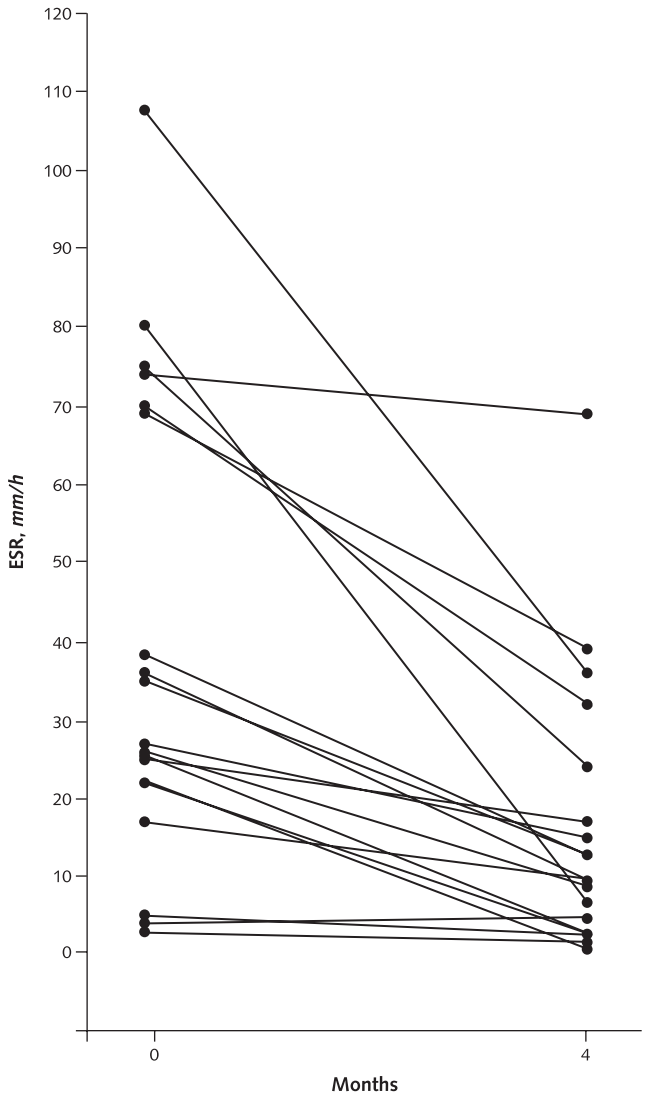
Author Contributions: Conception and design: E.F.H. van Bommel.
Analysis and interpretation of the data: E.F.H. van Bommel, T.R. Hendriksz, A.W.L.C. Huiskes, A.G.M. Zeegers.
Drafting of the article: E.F.H. van Bommel.
Critical revision of the article for important intellectual content: E.F.H. van Bommel, T.R. Hendriksz, A.W.L.C. Huiskes, A.G.M. Zeegers.
Final approval of the article: E.F.H. van Bommel, T.R. Hendriksz, A.W.L.C. Huiskes, A.G.M. Zeegers.
Statistical expertise: E.F.H. van Bommel.
Collection and assembly of data: E.F.H. van Bommel, T.R. Hendriksz, A.W.L.C. Huiskes.

Appendix Figure 1. **Flow of patients through the study.**



AZA = azathioprine; CT = computed tomography.

Appendix Figure 2. **Erythrocyte sedimentation rate (*ESR*) at presentation and after 4 months of tamoxifen therapy.**



$P = 0.001$.