

Watchful waiting versus surgery of mildly symptomatic or asymptomatic inguinal hernia in men aged 50 years and older: A randomized controlled trial

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ABSTRACT

Objective: To compare if watchful waiting is non-inferior to elective repair in men aged 50 years and older with mildly symptomatic or asymptomatic inguinal hernia.

Background: The role of watchful waiting in elderly male patients with mildly symptomatic or asymptomatic inguinal hernia is still not well established.

Methods: In this non-inferiority trial we randomly assigned men aged 50 years and older with mildly symptomatic or asymptomatic inguinal hernia to either elective inguinal hernia repair or watchful waiting. Primary endpoint was the mean difference in a 4-point pain/discomfort score at 24 months of follow-up. Using a 0.20-point difference as a clinically relevant margin, it was hypothesized that watchful waiting was non-inferior to elective repair. Secondary endpoints included quality of life, event-free survival and crossover rates.

Results: Between January 2006 and August 2012, 528 patients were enrolled of whom 496 met the inclusion criteria: 234 were assigned to elective repair and 262 to watchful waiting. The mean pain/discomfort score at 24 months was 0.35 (95% CI 0.28 to 0.41) in the elective repair group and 0.58 (95% CI 0.52 to 0.64) in the watchful waiting group. The difference of these means (MD) was -0.23 (95% CI -0.32 to -0.14). In the watchful waiting group 93 patients (35.4%) eventually underwent elective surgery and 6 patients (2.3%) received emergent surgery for strangulation/incarceration. Postoperative complication rates and recurrence rates in these 99 operated individuals were comparable to individuals originally assigned to the elective repair group (8.1% vs. 15.0%; $P = 0.106$; 7.1% vs. 8.9%; $P = 0.668$, respectively).

Conclusions: Our data could not rule out a relevant difference in favor of elective repair with regard to the primary endpoint. Nevertheless, in view of all other findings, we feel that our results justify watchful waiting as a reasonable alternative compared to surgery in men aged 50 years and older.

INTRODUCTION

Inguinal hernia repair is one of the most frequently performed surgical procedures worldwide constituting a major economic burden on the healthcare sector.^{1,2} The incidence of inguinal hernia increases with age, especially in men from the fifth to the seventh decade of life.^{3,4} Interestingly, in this population more than one-third of inguinal hernia is reported to be mildly symptomatic or asymptomatic at first presentation.⁵⁻⁷

Surgical tradition advocated that inguinal hernia should be repaired to prevent a hernia complication, even if presented as asymptomatic.^{5,8} To date, the general consensus states that prevention of incarceration of inguinal hernia per se is not a proper indication to perform surgery. Chronic postoperative inguinal pain has become an increasingly important issue after inguinal hernia repair with reported incidences of approximately 12% after open tension-free repair.^{9,10}

Until now 2 randomized clinical trials have been published, comparing a watchful waiting strategy and surgical approach in treatment of mildly symptomatic and asymptomatic inguinal hernia. Both trials reported that no superiority could be found for elective repair over watchful waiting with regard to pain/discomfort, concluding that watchful waiting is an acceptable strategy for men with minimally symptomatic hernia.^{11,12} The long-term results, however, showed crossover rates to 72% in patients who were initially treated conservatively, even rising to 79% in patients over 65 years old.^{5,13} The authors concluded that most patients will develop symptoms over time and recommend surgical repair for medically fit patients with a painless inguinal hernia.

The objective of this study was to determine the non-inferiority of watchful waiting to elective repair in men aged 50 years and older with mildly symptomatic or asymptomatic inguinal hernia.

METHODS

Eligibility criteria

Men aged 50 years and older with a mildly symptomatic or asymptomatic inguinal hernia (pain/discomfort score 1 or 0) were eligible for inclusion. We utilized a 4-point pain/discomfort score that was also used in the trial by Fitzgibbons et al.¹¹ The level of pain/discomfort was determined by the selection of one of the following 4 options:

0) no pain or discomfort due to the hernia when working, exercising or performing any of a patient's usual activities;

1) mild pain or discomfort due to the hernia when working and exercising that does not prevent a patient from performing his usual activities;

2) moderate pain or discomfort due to the hernia when working, exercising, and performing any of a patient's usual activities;

3) severe pain or discomfort due to the hernia when working, exercising, and performing any of a patient's usual activities.

Excluded were those with a bilateral, scrotal or femoral hernia or those classified as American Society of Anaesthesiologist (ASA) class 4. We have only included men in the present study because the incidence of inguinal hernia exceeds that of women by far. Men with a first recurrent inguinal hernia were not excluded. An inguinal hernia was confirmed on physical examination. Confirmation of the diagnosis with the use of ultrasonography was optional, not mandatory. Patients were recruited from 29 community and academic centers in the Netherlands and two Belgian centers. Study enrolment commenced on January 1, 2006. The last patients were included on August 31, 2012. All included patients provided written informed consent. Detailed information on the randomization procedure, data collected during follow-up, and ethical considerations and monitoring can be found in the Supplementary Appendix II.

Follow-up

Patients assigned to surgery underwent repair as soon as possible after randomization (preferably within 4 to 8 weeks). Patients in both treatment groups were invited for follow-up at 3, 12, 24, and 36 months at the outpatient clinic of each participating center. During these follow-up visits patients underwent physical examination. Independent trial coordinators conducted the follow-up visits at 3, 12, 24, and 36 months. Surgery was performed at the surgical department of the involved center. In consultation of the patient, the surgeon determined the operation technique used for inguinal hernia repair. Patients who were randomly assigned to watchful waiting were given written instructions to recognize a hernia complication (incarceration or strangulation) after randomization.

Primary and secondary endpoints

The primary endpoint was the mean difference in the 4-point pain/discomfort score between patients assigned to watchful waiting and elective repair after a follow-up

period of 24 months. Secondary endpoints were: 1) health-related quality of life measured at baseline, 3, 12, 24 and 36 months, 2) the overall 3-year crossover rate in patients assigned to watchful waiting and 3) the overall 3-year event-free survival between the two treatment groups, defined as survival free from moderate or severe pain (pain/discomfort score of 2 or higher), hernia complication (incarceration or strangulation), ischemic orchitis and recurrent hernia. Health-related quality of life was assessed by the Short-Form 36 (SF-36) questionnaire, from which we have used the mean physical component scores (PCS) and the mean mental component scores (MCS) between the treatment groups at the different points in time; the EuroQoL-5D (EQ-5D) questionnaire was also assessed at baseline, 3, 12, 24, and 36 months of follow-up.^{14,15} The EQ-5D included a visual analogue scale (VAS) to rate overall health status on a scale of 0 (worst imaginable health state) to 100 (best imaginable health state).

Sample size calculation and statistical analysis

The power calculation was based on the difference in mean pain/discomfort score between groups after a 24-month follow-up period. To show non-inferiority, the lower limit of the two-sided 95% CI for the difference (elective repair minus watchful waiting) should not exceed the pre-specified non-inferiority margin. The determination of the non-inferiority margin was based on clinical and statistical considerations, for which a margin of 0.20 points after 24 months was chosen. This required the accrual of 528 patients ($2 \times 220 + 20\%$) at a power of 80% to take into account a potential loss to follow-up of 20%.

Percentages were compared between groups using the chi-square test or Fisher's exact test. Comparison of continuous data was done with use of the Mann-Whitney test. Time to event was calculated from the date of randomization until an event occurred; patients were considered censored if they died, were lost to follow-up or completed follow-up without any event with a maximum of 36 months (length of the study period). Overall 3-year event-free survival was calculated and compared with the use of Kaplan-Meier curves. The Kaplan-Meier method was also used to estimate the overall 3-year crossover rate among patients assigned to watchful waiting. The log-rank test was used for the univariate comparisons. For the differences in the 4-point pain/discomfort score a mixed model with an unstructured covariance matrix was used to allow for correlations within individuals over time. In addition, the analysis for the primary endpoint was stratified for men aged 50 to 65 years and 65 years and older, participating centers, and duration of inguinal hernia present at baseline. Statistical analysis was performed with SPSS software, version 20.0 (IBM Corp. 2011, Armonk, NY) and SAS software (PROC MIXED), version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

Study population

From January 2006 through August 2012, 528 patients were enrolled in the study of whom 258 were assigned to elective repair and 270 to watchful waiting. Study follow-up ended in August 2014. A total of 24 patients who were assigned to surgery were not included in the analysis: 21 patients withdrew consent immediately after randomization and 3 patients did not meet the inclusion criteria including 1 patient with a femoral hernia, 1 with a bilateral hernia, and 1 patient with a lipoma. A total of 8 patients who were assigned to watchful waiting were not included in the analysis: 4 patients withdrew consent and 4 patients did not meet the inclusion criteria including 1 patient with a femoral hernia, 1 with a lipoma, and 2 patients were excluded because they were younger than 50 years of age (Figure 1).

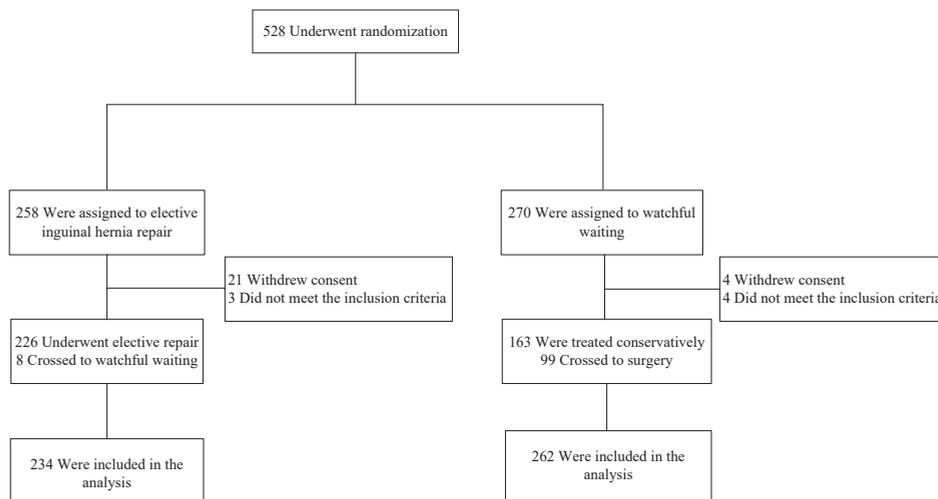


Figure 1. Study enrollment.¹⁸

Baseline characteristics and hernia details were balanced between the two groups (Table 1, 2). The mean age of the population was 65.1 years (SD 8.3) and the mean BMI was 24.9 kg/m² (SD 2.7). A total of 463 out of 496 men (93.3%) with mildly symptomatic or asymptomatic inguinal hernia were referred to the hospital by their general practitioner; 473 of 496 men (95.4%) presented with a primary inguinal hernia and 23 men (4.6%) had a first recurrence. An ultrasound was performed in 267 of 496 (53.8%) of the study population, and a radiologist was able to confirm the diagnosis in 241 (90.3%) of ultrasonographies.

Table 1. Baseline characteristics of patients aged 50 years and older with mildly symptomatic or asymptomatic inguinal hernia, according to treatment group.

Characteristic	Watchful waiting (n = 262)	Elective repair (n = 234)
Age – yr (mean, SD)	65.2 (8.3)	65.0 (8.2)
BMI* – kg/m ² (mean, SD)	24.8 (2.7)	25.0 (2.7)
Smoking – n (%)		
Current	50 (19.1)	47 (20.1)
Former	112 (42.7)	104 (44.4)
None	83 (31.7)	73 (31.2)
Not reported	17 (6.5)	10 (4.3)
Packyears – yr (median, range)	5.0 (90.0)	7.3 (90.0)
ASA* classification – n (%)		
1	152 (58.0)	139 (59.4)
2	92 (35.1)	79 (33.8)
3	15 (5.7)	12 (5.1)
Not reported	3 (1.2)	4 (1.7)
Cardiovascular system – n (%)		
Angina	4 (1.5)	4 (1.7)
Hypertension	47 (17.9)	38 (16.2)
MI†	8 (3.1)	8 (3.4)
Cardiac arrhythmia	12 (4.6)	10 (4.3)
Other	5 (1.9)	7 (3.0)
Not reported	2 (0.8)	3 (1.3)
TIA* or stroke – n (%)	10 (3.8)	5 (2.1)
Not reported	2 (0.8)	3 (1.3)
Diabetes Mellitus – n (%)	16 (6.1)	17 (7.3)
Not reported	2 (0.8)	3 (1.3)
Medication – n (%)		
Aspirin	33 (12.6)	28 (12.0)
Anticoagulants	33 (12.6)	22 (9.4)
Not reported	3 (1.2)	6 (2.7)
Pulmonary system – n (%)		
COPD†	13 (5.0)	9 (3.8)
Chronic cough	2 (0.8)	2 (0.9)
Other	3 (1.2)	5 (2.1)
Not reported	2 (0.8)	3 (1.3)
Gastro-intestinal system – n (%)		
Liver cirrhosis	2 (0.8)	-
Constipation	4 (1.5)	1 (0.4)
Not reported	2 (0.8)	3 (1.3)
Back problems – n (%)	12 (4.6)	16 (6.8)
Not reported	2 (0.8)	3 (1.3)
Urinary tract – n (%)		
Prostate cancer	5 (1.9)	3 (1.3)
BPH†	15 (5.7)	17 (7.3)
Urinary complaints	6 (2.3)	2 (0.9)
Other	2 (0.8)	2 (0.9)
Not reported	2 (0.8)	3 (1.3)

Table 1. Baseline characteristics of patients aged 50 years and older with mildly symptomatic or asymptomatic inguinal hernia, according to treatment group. (continued)

Characteristic	Watchful waiting (n = 262)	Elective repair (n = 234)
Health status – n (%)		
Independent	252 (96.2)	228 (97.4)
Partly dependent	4 (1.5)	2 (0.9)
Totally dependent	2 (0.8)	-
Not reported	4 (1.5)	4 (1.7)
Education – n (%)		
Not reported	245 (93.5)	220
	15 (5.7)	13 (5.6)
Employment – n (%)		
Paid work	93 (35.5)	82 (35.0)
Retirement	143 (54.6)	123 (52.6)
Unemployed	1 (0.4)	4 (1.7)
Unfit for work	8 (3.1)	5 (2.1)
Volunteer work	6 (2.3)	3 (1.3)
Domestic chores	5 (1.9)	4 (1.7)
Not reported	6 (2.3)	13 (5.6)

*BMI = body mass index, ASA = American Society of Anesthesiologists, MI = myocardial infarction, TIA = transient ischemic attack, COPD = chronic obstructive pulmonary disease, BPH = benign prostate hyperplasia.

Primary and secondary endpoints

The mean 4-point scale pain/discomfort scores at baseline, 3, 12, 24, and 36 months for the two treatment groups are presented in Figure 2; the changes from baseline are shown in table 3. The mean pain/discomfort score at months 3, 12 and 24, i.e. the primary endpoint according to the protocol, was 0.35 (95% CI 0.28 to 0.41) in the elective repair group and 0.58 (95% CI 0.52 to 0.64) in the watchful waiting group. The difference of these means (MD) was -0.23 (95% CI -0.32 to -0.14). Similar results were found after adjustment for the stratification factors at randomization (men aged 50 to 65 years or 65 years and older, participating centers, duration of inguinal hernia present at baseline), 0.29 vs 0.51 (MD -0.22, 95%CI -0.31 to -0.13). The widths of these 95% CIs indicate that a difference of means greater than 0.20 in favor of elective repair cannot be excluded.

In the subgroups of men aged 50 to 65 years and men aged 65 years and older similar results were found: in men aged 50 to 65 years the mean 4-point pain/discomfort score was 0.57 for patients assigned to watchful waiting and 0.34 for patients assigned to elective repair (MD, -0.23; 95% CI, -0.36 to -0.11); in men aged 65 years and older the adjusted mean 4-point pain/discomfort score was 0.58 for patients assigned to watchful waiting and 0.36 for patients assigned to elective repair (MD, -0.22; 95% CI, -0.36 to -0.09).

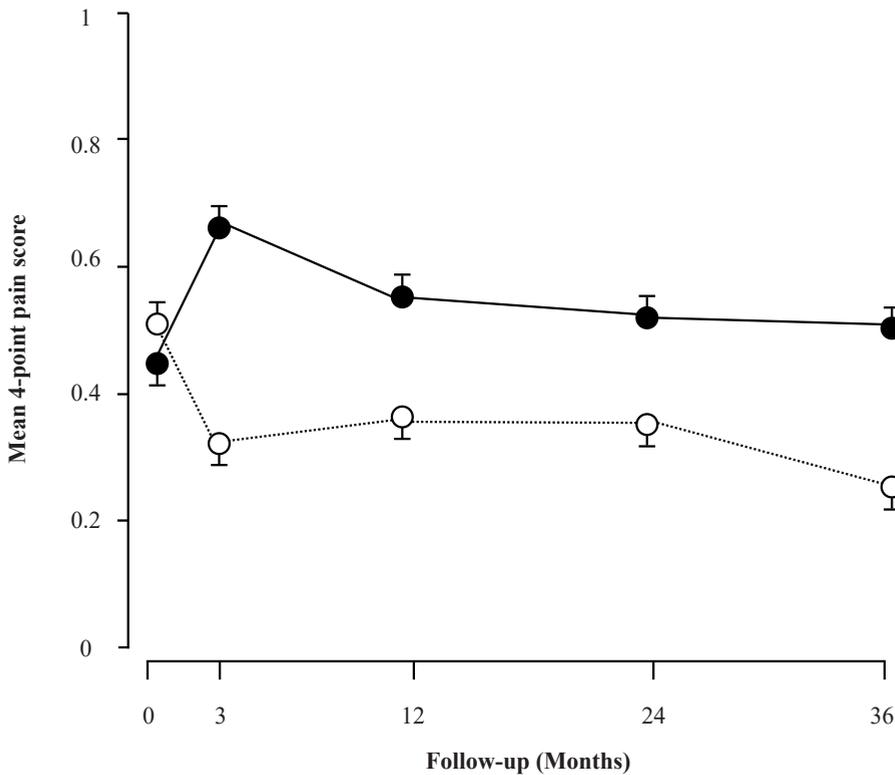


Figure 2. Mean 4-point pain score (error bars represent standard error of the mean) at various time points after inclusion according to treatment arm (closed circles: watchful waiting, open circles: elective hernia repair).

For the secondary endpoints, mean changes compared to baseline and mean differences between treatment groups for different measures of quality of life are presented in Table 3. At 3 months of follow-up the mean PCS score showed better results in the group assigned to watchful waiting compared with the group assigned to surgery (51.37 vs. 49.05; $P < 0.001$). However, at 12 and 24 months the mean difference in PCS scores of the SF-36 were in favor of the elective repair group.

The mean EQ5D scores at 24 months were slightly higher in patients assigned to elective repair compared with patients assigned to watchful waiting (0.91 vs. 0.90; MD, 0.04, 95% CI; 0.01 to 0.07; $P = 0.009$). At 3 months the mean VAS score rating overall health status was 87.02 in the elective repair group and 80.97 in the group assigned to watchful waiting (MD, 5.59, 95% CI; 3.78 to 7.40; $P < 0.001$).

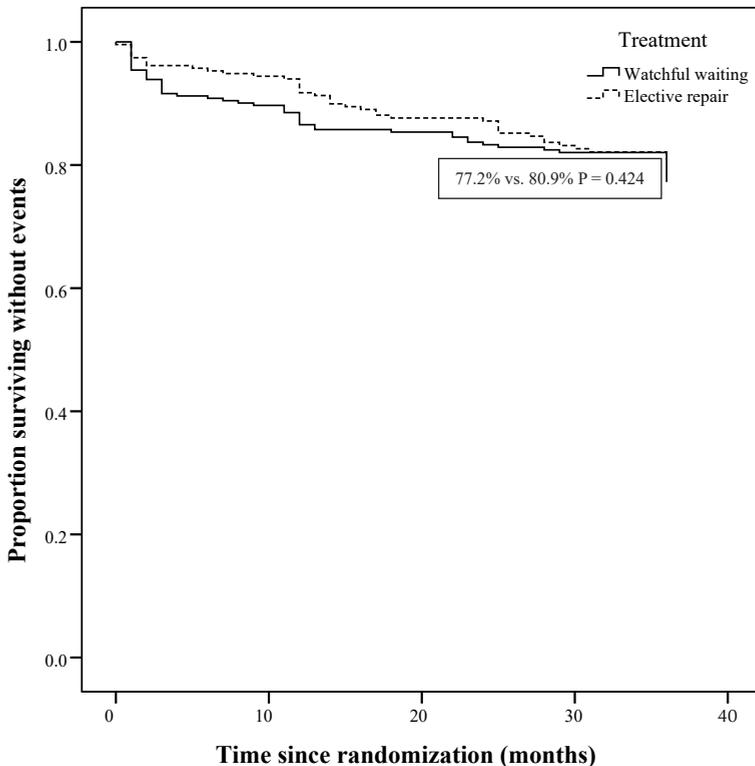
Table 2. Hernia details of patients aged 50 years and older with mildly symptomatic or asymptomatic inguinal hernia, according to treatment group.

Characteristic	Watchful waiting (n = 262)	Elective repair (n = 234)
Referral – n (%)		
General practitioner	244 (93.1)	219 (93.6)
Other specialist	9 (3.4)	8 (3.4)
No referral	-	1 (0.4)
Not reported	9 (3.4)	6 (2.7)
Time of presence at inclusion – n (%)		
≤ 3 months	133 (50.8)	118 (50.4)
> 3 months	129 (49.2)	116 (49.6)
Inguinal hernia – n (%)		
Primary	249 (95.0)	224 (95.7)
1 st Recurrence	13 (5.0)	10 (4.3)
Side – n (%)		
Left	123 (46.9)	108 (46.2)
Right	138 (52.7)	126 (53.8)
Not reported	1 (0.4)	-
Enlargement – n (%)	47 (17.9)	42 (17.9)
Not reported	14 (5.3)	10 (4.3)
Reducibility – n (%)		
Spontaneously	171 (65.3)	159 (67.9)
Easy	82 (31.3)	67 (28.6)
With difficulty	3 (1.2)	2 (0.9)
Not reported	6 (2.3)	6 (2.7)
Positive family history* – n (%)	26 (9.9)	25 (10.7)
Not reported	2 (0.8)	3 (1.3)
Ultrasonography – n (%)	150 (57.3)	117 (50.0)
Diagnosis confirmed – n (%)	134/150 (89.3)	107/117 (91.5%)
Type – n (%)		
Medial	72/150 (48.0)	58/117 (49.6)
Lateral	43/150 (28.7)	29/117 (24.8)
Unclear	22/150 (14.7)	23/117 (19.7)
Not reported	13/150 (8.7)	7/117 (6.0)
Diameter – mm (mean, SD)		
Sagittal	17.9 (11.4)	18.9 (11.7)
Transverse	19.2 (9.4)	20.5 (11.3)

* Positive family history of abdominal wall hernia (i.e. inguinal, umbilical and epigastric hernia).

Intention-to-treat analysis showed a mean follow-up of 32.5 months (SD 7.5) for the elective repair group and 32.9 months (SD 6.7) for the group assigned to watchful waiting ($P = 0.558$). The 3-year cumulative incidence of patients with 1 or more event was 17.5% (41/234) in the elective repair group (25 individuals reported moderate or severe pain, 1 hernia complication, 1 ischemic orchitis, 20 recurrent hernias) compared with 20.6% (54/262) in the group assigned to watchful waiting (69 individuals reported moderate or severe pain, 7 hernia complications occurred in 6 individuals, 7 recurrent hernias);

the overall 3-year Kaplan Meier (KM) event-free survival was 80.9% after elective repair compared to 77.2% after watchful waiting (hazard ratio (HR), 1.20; 95% CI, 0.80 to 1.80; $P = 0.377$), which is presented in Supplementary Figure 3. The 3-year cumulative (KM estimate of 39.5%) crossover rate to hernia repair in patients who were initially assigned to watchful waiting was 37.8% (99/262); The crossover rate did not differ between the groups stratified for men aged 50 to 65 years or men aged 65 years and older (38.2% vs. 37.0%). The 3-year cumulative incidence (KM of estimates 9.9% and 7.8%; HR, 1.25; 95% CI, 0.53 to 2.96; $P = 0.610$) of a recurrent inguinal hernia was 8.9% (20/226) in the elective repair group compared with 7.1% (7 out of 99) in the group assigned to watchful waiting and crossed to surgery ($P = 0.668$). Recurrence rates were comparable between different surgical techniques, type of mesh, and participating centers.



No. at risk

WW	262	225	203	137
ER	234	210	180	133

Figure 3. The estimated overall 3-year event-free survival among patients aged ≥ 50 years with mildly symptomatic or asymptomatic inguinal hernia assigned to watchful waiting (WW) and elective repair (ER), according to intention-to-treat analysis.

Table 3. Mean baseline values and mean changes from baseline according to treatment group for measures of quality of life.

Measure of Pain/ Quality of Life	Watchful waiting (n = 262)	Elective repair (n = 234)	Mean Difference	P Value ^a
4-point pain/discomfort score^c				
Baseline	0.44 (0.38 ; 0.50)	0.51 (0.44 ; 0.58)		
3 months	+0.21 (0.11; 0.31) ^b	-0.19 (-0.30 ; -0.09) ^b	-0.41 (-0.55 ; -0.26)	<0.001
12 months	+0.11 (0.01 ; 0.21) ^b	-0.15 (-0.24 ; -0.06) ^b	-0.26 (-0.40 ; -0.13)	<0.001
24 months	+0.07 (-0.03 ; 0.17)	-0.16 (-0.26 ; -0.06) ^b	-0.23 (-0.37 ; -0.09)	0.001
36 months	+0.06 (-0.04 ; 0.16)	-0.26 (-0.36 ; -0.16) ^b	-0.33 (-0.47 ; -0.18)	<0.001
EQ-5D^d				
Baseline	0.92 (0.89 ; 0.94)	0.90 (0.87 ; 0.93)		
3 months	-0.02 (-0.03 ; 0.00)	0.04 (0.03 ; 0.07) ^b	0.06 (0.04 ; 0.09)	<0.001
12 months	-0.02 (-0.04 ; 0.00) ^b	0.03 (0.01 ; 0.05) ^b	0.05 (0.02 ; 0.08)	<0.001
24 months	-0.02 (-0.04 ; 0.00)	0.01 (0.00 ; 0.04)	0.04 (0.01 ; 0.07)	0.009
36 months	-0.01 (-0.03 ; 0.00)	0.01 (0.00 ; 0.04)	0.03 (0.00 ; 0.05)	0.055
VAS^e				
Baseline	83.52 (81.34 ; 85.70)	83.98 (81.95 ; 86.01)		
3 months	-2.55 (-3.76 ; -1.34) ^b	3.04 (1.65 ; 4.43) ^b	5.59 (3.78 ; 7.40)	<0.001
12 months	-2.36 (-4.89 ; -1.05) ^b	-0.36 (-1.95 ; 1.22)	1.99 (-0.16 ; 4.14)	0.069
24 months	-2.25 (-4.92 ; -0.75) ^b	-0.82 (-2.49 ; 0.85)	1.43 (-1.78 ; 3.63)	0.203
36 months	-1.72 (-4.69 ; -0.23) ^b	-0.67 (-2.28 ; 0.94)	1.05 (-1.10 ; 3.19)	0.339
SF-36 PCS^e				
Baseline	51.28 (50.06 ; 52.50)	51.27 (50.16 ; 52.38)		
3 months	0.09 (-0.79 ; 0.97)	-2.22 (-3.27 ; -1.18) ^b	-2.31 (-3.66 ; -0.96)	<0.001
12 months	-0.86 (-1.58 ; -0.15) ^b	1.44 (0.62 ; 2.25) ^b	2.29 (1.24 ; 3.36)	<0.001
24 months	-0.98 (-1.85 ; -0.12) ^b	0.79 (-0.12 ; 1.71)	1.77 (0.53 ; 3.02)	0.005
36 months	-0.43 (-1.31 ; 0.45)	-0.05 (-0.99 ; 0.90)	0.38 (-0.89 ; 1.065)	0.555
SF-36 MCS^e				
Baseline	55.96 (54.79 ; 57.13)	56.56 (55.37 ; 57.75)		
3 months	0.17 (-0.68 ; 1.02)	-0.10 (-1.10 ; 0.89)	-0.27 (-1.56 ; 1.02)	0.679
12 months	0.03 (-0.77 ; 0.84)	-0.22 (-1.15 ; 0.70)	-0.26 (-1.47 ; 0.96)	0.676
24 months	-0.17 (-0.99 ; 0.64)	-1.15 (-2.01 ; -0.29) ^b	-0.98 (-2.16 ; 0.21)	0.106
36 months	-1.16 (-1.99 ; -0.33) ^b	-0.02 (-0.92 ; 0.87)	1.14 (-0.08 ; 2.35)	0.067

Abbreviations: EQ-5D, the EuroQol-5D questionnaire; VAS, Visual Analogue Scale; SF-36, the 36-item short form health survey score; PCS, physical component score; MCS, mental component score.

Values between parentheses represent 95% CIs.

a: P values represent the difference between the two treatment groups for pain or measures of quality of life;

b: Mean change compared to baseline is statistically significant ($P < 0.05$);

c: Expressed on a 0 (no pain) to 3 (severe pain) point scale;

d: Expressed on a 0 (worst) to 1 (best) point scale;

e: Expressed on a 0 (worst) to 100 (best) point scale.

The 3-year cumulative incidence of death was comparable between the two treatment groups; 3.0% (7/234) of patients died who were assigned to elective repair and 3.1% (8/262) of patients who were assigned to watchful waiting ($P = 1.000$). None of the deaths was hernia-related.

Inguinal hernia repair

In men assigned to elective repair 8 out of 234 patients (3.4%) did not undergo surgery; 7 patients decided immediately after randomization that they did not want to be operated on, and 1 patient was considered to be medically unfit for surgery due to progression of his comorbidities prior to the operation. In men assigned to watchful waiting 99 out of 262 patients (37.8%) crossed to hernia repair during the 36-month study period; 90 because of some degree of pain or discomfort, 6 because of a hernia complication, 1 because of cosmetic reasons and 2 for reasons unknown. Of the 6 patients who had a hernia complication, 5 men (1.9%) had an acutely painful groin without bowel obstruction due to an incarcerated hernia for which they underwent emergency surgery. In 1 patient (0.4%) an acute repair was performed because of a strangulated hernia. In none of those patients a resection of the bowel had to be performed. The median time between randomization and surgery was 7.0 weeks (range 67.0) for patients assigned to elective repair and 41.0 weeks (range 158.0) for patients assigned to watchful waiting and crossed to surgery.

Perioperative data of patients assigned to elective repair and patients assigned to watchful waiting who crossed to surgery were comparable and are provided in Table 4. The mean operation time was 45.7 minutes (SD 15.3) in the elective repair group, as compared to 47.4 minutes (SD 20.2) in the crossover group. Most surgeons performed Lichtenstein open tension-free repairs: 176 out of 226 repairs (77.9%) in patients who were assigned to elective repair and 69 out of 99 repairs (69.7%) in patients assigned to watchful waiting and crossed to surgery. In both groups more than half of patients were treated in day-care; one morbidly obese patient of the crossover group was admitted for observation at the intensive care unit due to respiratory distress and was discharged from the hospital after two days.

The total number of peri- and postoperative complications that occurred within one month are summarized in Table 5. A total of 66 peri- and postoperative complications were reported in 42 patients; the total number of patients with 1 or more postoperative complications was 34 out of 226 patients (15.0%) assigned to elective repair compared with 8 out of 99 patients (8.1%) assigned to watchful waiting and crossed to hernia repair ($P = 0.106$). In the elective repair group 1 patient was converted during surgery from laparoscopic to open repair and one patient needed a reoperation because of testicular ischemia; in the crossover group 1 patient had a cardiac arrest before surgery during the anaesthetic induction. During follow-up a reoperation was performed in 7 out of 226 patients (3.1%) assigned to elective repair: 2 because of continuing pain/

discomfort, 1 because of ischemic orchitis and 4 because of a recurrent hernia of which 1 patient underwent emergency surgery because of incarceration. In the cross-over group 5 out of 99 patients (5.0%) underwent a reoperation because of a recurrent hernia of which one was preceded by incarceration necessitating emergency repair.

Table 4. Perioperative data of patients aged 50 years and older assigned to elective repair and patients who crossed to surgery after initial watchful waiting strategy.

	Crossed to surgery (n = 99)	Elective repair (n = 226)
Operation time – min (mean, SD)	47.4 (20.2)	45.7 (15.3)
Operation technique – n (%)		
<i>Lichtenstein</i>	69 (69.7)	176 (77.9)
<i>TEP</i> [*]	11 (11.1)	24 (10.6)
<i>TAPP</i> [*]	2 (2.0)	9 (4.0)
<i>Plug and Patch</i>	4 (4.0)	3 (1.3)
<i>PHS</i>	1 (1.0)	3 (1.3)
<i>Pre-peritoneal mesh repair</i>	9 (9.1)	10 (4.4)
Type of repair not reported	3 (3.0)	1 (0.4)
Type of mesh – n (%)		
<i>Flat mesh</i>	64 (64.6)	180 (79.6)
<i>Three-dimensional mesh</i>	9 (9.1)	14 (6.2)
Mesh type not reported	26 (26.3)	32 (14.2)
Experience, procedures – n (%)		
<10	3 (3.0)	16 (7.1)
10-25	3 (3.0)	18 (8.0)
>25	40 (40.4)	116 (51.3)
Not reported	53 (53.5)	76 (33.6)
Type of anesthesia – n (%)		
<i>Local</i>	13 (13.1)	20 (8.8)
<i>Spinal</i>	36 (36.4)	107 (47.3)
<i>General</i>	30 (30.3)	91 (40.3)
Not reported	20 (20.2)	8 (3.5)
Nyhus classification [*] – n (%)		
<i>Type I</i>	8 (8.1)	38 (16.8)
<i>Type II</i>	14 (14.1)	46 (20.4)
<i>Type III</i>	38 (38.4)	111 (49.1)
<i>Type IV</i>	4 (4.0)	10 (4.4)
<i>No hernia (lipoma)</i>	1 (1.0)	1 (0.4)
Not reported	34 (34.3)	20 (8.8)
Nerve identification – n (%)		
<i>No identification</i>	7 (7.1)	8 (3.5)
<i>1) Ilioinguinal nerve</i>	20 (20.2)	59 (26.1)
<i>2) Iliohypogastric nerve</i>	1 (1.0)	2 (0.9)
<i>3) Branch of genitofemoral nerve</i>	-	2 (0.9)
<i>Nerve 1 & 2</i>	6 (6.1)	21 (9.3)
<i>Nerve 1 & 3</i>	6 (6.1)	14 (6.2)
<i>Nerve 2 & 3</i>	-	2 (0.9)
<i>Nerve 1, 2 & 3</i>	6 (6.1)	34 (15.0)
Not reported	46 (46.5)	76 (33.6)

Table 4. Perioperative data of patients aged 50 years and older assigned to elective repair and patients who crossed to surgery after initial watchful waiting strategy. (continued)

	Crossed to surgery (n = 99)	Elective repair (n = 226)
Transsection of the nerve – n (%)		
No transsection	35 (35.4)	126 (48.1)
1) Ilioinguinal nerve	12 (12.1)	19 (8.4)
2) Iliohypogastric nerve	2 (2.0)	4 (1.8)
3) Branch of genitofemoral nerve	-	3 (1.3)
Nerve 1 & 2	4 (4.0)	2 (0.9)
Nerve 1 & 3	-	2 (0.9)
Nerve 2 & 3	-	1 (0.4)
Nerve 1, 2 & 3	-	1 (0.4)
Not reported	46 (46.5)	68 (30.1)
Closure of subcutis – n (%)	70 (70.7)	163 (72.1)
Not reported	19 (19.2)	32 (14.2)
Closure of skin – n (%)		
Staples	-	5 (2.2)
Intra-cutaneous	81 (81.8)	180 (79.6)
Continuous	2 (2.0)	11 (4.7)
Interrupted	-	2 (0.9)
Continuous, intra-cutaneous	1 (1.0)	11 (4.9)
Strips	-	1 (0.4)
Not reported	15 (15.2)	16 (7.1)
Level of operation difficulty – n (%)		
Easy	31 (31.3)	94 (41.6)
Moderate	50 (50.5)	111 (49.1)
Hard	4 (4.0)	5 (2.2)
Not reported	14 (14.1)	16 (7.1)
Hospital admission – n (%)		
None	57 (57.6)	150 (66.4)
Surgical department	10 (10.1)	33 (14.6)
Intensive care unit	1 (1.0)	-
Not reported	31 (31.3)	43 (19.0)
Peri-operative antibiotics – n (%)	12 (12.1)	42 (18.6)
Not reported	51 (51.5)	53 (23.5)

*TEP = total extra-peritoneal repair, TAPP = trans-abdominal pre-peritoneal repair, PHS = prolene hernia system, Nyhus classification¹⁹: I) indirect inguinal hernia with normal internal ring, II) indirect inguinal hernia with dilated internal ring, III) direct inguinal hernia/posterior wall defect, and IV) recurrent hernia.

Table 5. Total number of perioperative complications in patients aged 50 years and older assigned to elective repair and patients who crossed to surgery after initial watchful waiting strategy.

Event	Elective repair (n= 226)	Crossed to surgery (n= 99)
Complications during surgery – n (%)		
Damage to epigastric or testicular vessels	2 (0.9)	3 (3.0)
Unintended nerve damage	2 (0.9)	1 (1.0)
Conversion to open repair	1 (0.4)	-
Peritoneal defect	3 (1.3)	-
Bradycardia during surgery	1 (0.4)	-
Cardiac arrest during anesthetic induction	-	1 (1.0)
Direct postoperative complications – n (%)		
Bleeding	2 (0.9)	2 (2.0)
Reoperation: <i>Testicular ischemia</i>	1 (0.4)	-
Urinary retention requiring catheterization	2 (0.9)	-
Infection	2 (0.9)	1 (1.0)
Seroma	1 (0.4)	-
Post-operative complications (≤ 1 month) – n (%)		
Wound infection	2 (0.9)	-
Hematoma		
<i>Wound</i>	10 (4.4)	-
<i>Scrotal</i>	8 (3.5)	1 (1.0)
<i>Femoral</i>	2 (0.9)	-
Seroma	10 (4.4)	1 (1.0)
Urinary tract infection	3 (1.4)	-
Urinary retention requiring catheterization	2 (0.9)	-
Pain during ejaculation	2 (0.9)	-

DISCUSSION

This multicenter randomized trial in men aged 50 years and older with mildly symptomatic or asymptomatic inguinal hernia could not rule out a relevant difference in favor of elective repair for the pain/discomfort scores after a follow-up of 24 months. The 95% CI of the difference of means ranged from -0.32 to -0.14. A difference of 0.20 or greater cannot be excluded and, therefore, our trial is inconclusive in this respect. For secondary endpoints the different measures of quality of life and the mean changes over time compared to baseline and study groups were slightly in favor of surgery.

The differences, however, were too small to be clinically relevant. With regard to the crossover rate approximately 60% of men assigned to watchful waiting did not need surgery during follow-up. In the group who did cross to surgery this was mostly driven by an increase in symptoms – only in 2.3% of the patients crossed over it was due to an emergency setting such as incarceration. However, even these acutely performed procedures were without any negative sequelae. For example, no bowel resection had to be performed due to a prolonged state of ischemia. Although the difference in complication rate between the two groups is not significant, our study was not powered to find a relevant difference in complication rate. We feel that it should be communicated with the patient however, that watchful waiting could result in the necessity of an emergent repair later on, and that there is currently no evidence that an emergency procedure puts one at risk for permanent health disadvantages.

Similar results were reported by two earlier published trials.^{5,13} No differences were found in postoperative complication rates and recurrence rates for patients assigned to elective repair and patients initially assigned to watchful waiting and crossed over to surgery. The recurrence rates reported in our study were high. About 9% in patients assigned to elective repair and 7% in operated patients initially assigned to watchful waiting. However, no difference in recurrence rates could be found between different surgical techniques, types of mesh, and participating centers. In both groups one reoperation was performed because of a hernia complication in a recurrent hernia. This shows that not only patients who were treated conservatively but also patients with a failed hernia repair are at risk for emergency surgery. As such these results justify watchful waiting as a reasonable alternative compared to surgery in the treatment of mildly symptomatic or asymptomatic inguinal hernia in men aged 50 years older.

Our results contribute to earlier published trials as the outcome measure and size of our study allowed for the detection of smaller but perhaps clinically relevant differences in pain/discomfort and quality of life during a certain period of time. It enables surgeons to discuss the potential benefits of inguinal hernia repair in men aged 50 years and older who are actually burdened by pain/discomfort preoperatively. Even if inguinal hernia were corrected, it would still not completely eliminate the risk of emergent repair owing to recurrent hernias. For patients who are too frail for surgery it can be argued that watchful waiting is a valid option as it rarely leads to an emergency operation.

In 2006 Fitzgibbons et al.¹¹ randomly assigned men aged 18 years and older with minimally symptomatic hernia to either open tension-free repair or watchful waiting. Similar to our study a 4-point scale was used as primary endpoint to measure the

mean difference in pain/discomfort score at 24 months, which was presented as a dichotomous variable. In contrast, we decided to use a more comprehensive manner by presenting pain/discomfort over time as a continuous variable enabling us to provide more detailed data between the two treatment groups and compared to baseline. Moreover, as Fitzgibbons et al.¹¹ included men aged 18 years and older, we focussed on men aged 50 years and older allowing us to draw more definite conclusions for this clinically relevant subgroup. The Fitzgibbons trial showed no significant difference in pain/discomfort and change in PCS from baseline between groups at two years of follow-up, concluding that watchful waiting is as an acceptable option for men with minimally symptomatic inguinal hernia.

In 2006 a second trial was published by 'O Dwyer et al.¹², in which male patients aged 55 years and older with asymptomatic hernia were randomized to either operation or observation. The primary endpoint was the mean difference in VAS scores rating pain/discomfort between treatment groups at 12 months of follow-up. No difference was observed between operation and observation with regard to the primary endpoint. Although this study did focus on patients aged 55 years and older, the sample size was small and the follow-up was limited.

Recently both studies published long-term results that showed crossover rates of 72% and 68% in patients who were initially treated conservatively after 7.5 and 10-years of follow-up respectively. It was also found that older men crossed over to surgery at a considerably higher rate than younger men.^{5,13} Although we still have to wait for long-term data, subgroup analysis of our data found no differences in crossover rates between men aged 50 to 65 years or men aged 65 years and older.

This study has to be interpreted in light of limitations. This study allowed surgeons to use different operation techniques, which might have hampered the comparability between groups. In contrast this provided us with a better reflection of daily practice as both endoscopic and open repairs were allowed. Analytical adjustments were made for participating centers in the comparison of mean pain/discomfort scores over time to eliminate hospital preferences for different operation techniques. Secondly, less endoscopic repair and more spinal anesthesia were used compared to the general Dutch population who underwent inguinal hernia repair in 2005.¹⁶ Nowadays endoscopic hernia repair is increasingly used and associated with less postoperative pain compared to open techniques, which perhaps makes surgical repair more appealing.¹⁷ Furthermore local or regional anesthetics can be advantageous in treatment of older patients with multiple comorbidities.¹⁶ Thirdly, Fitzgibbons et al.⁵ and Chung et al.¹³ already mentioned in their discussion that the answer to the high crossover rates in

both trials were to be explained by the recruitment process and the fact that elderly patients might have a tendency to minimize their symptoms more than younger patients. Because of this, elderly patients become eligible for the trial more easily despite having more advanced disease. This not only affects the generalizability, it also explains for the higher crossover rates in those studies. As in the trial by Fitzgibbons et al.^{5,11} the majority of our patients were referred to the clinic by their general practitioner because of concern about the hernia after which they were invited to participate in the trial. Therefore it may not be valid to extrapolate the results of our trial to the entire population of men aged 50 years and older with mildly and asymptomatic inguinal hernia. Long-term follow-up will be needed to confirm these hypotheses stated by our colleagues. Finally from a policy maker perspective, it is not immediately clear if a relatively small reduction in pain scores over time is worth the potentially extra costs of performing surgery, especially when pain is minimal.

Our data could not rule out a relevant difference in favor of elective repair with regard to the primary endpoint. Nevertheless, in view of all other findings, we feel that our results justify watchful waiting as a reasonable alternative compared to surgery in male patients aged 50 years and older.

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to all the data in the study and had final responsibility for the decision to submit for publication.

CONFLICTS OF INTERESTS

All authors have seen and approved this manuscript. The authors of this manuscript have no conflicts of interest to disclose. Funding has been reported.

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THE SUPPLEMENTARY APPENDIX I

INCA (Inguinal Hernia: Conservative or Operative Approach) Trialists' Collaboration:

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THE SUPPLEMENTARY APPENDIX II

Randomization procedure

Patients were registered in an online database (Trial Online Process (TOP), designed and managed by HOVON data center, Rotterdam, The Netherlands) in which each patient received a unique trial code. The randomization process was performed during the first visit at the outpatient clinic of each participating center by telephone (block randomization) and later on by a computer-based randomization service in TOP. Patients were randomly assigned to watchful waiting or elective repair. Randomization was stratified for participating centers, age (men aged 50 to 65 years or 65 years and older) and for the duration the inguinal hernia was present at baseline (3 months or less and more than 3 months).

Data collected during follow-up

- § Patient's characteristics at baseline: body mass index (BMI), smoking status, health status, ASA classification, education level, and type of employment.
- § Comorbidities at baseline: The cardiovascular system (i.e., history of angina, hypertension requiring medication, history of myocardial infarction, history of cardiac arrhythmia, diabetes mellitus, history of transient ischemic attack (TIA) or stroke, medication usage (i.e., aspirin, anticoagulants), history of other cardiovascular disease (i.e., history of valve insufficiencies, abdominal aortic aneurysm (AAA), coronary artery bypass graft surgery (CABG))); The pulmonary system (i.e., chronic obstructive pulmonary disease (COPD), chronic cough, other pulmonary disease (i.e., history of lung embolism, sarcoidosis)); The digestive system (i.e., constipation, cirrhotic liver disease with ascites) and urinary tract (i.e., prostate cancer, benign prostate hyperplasia (BPH), urinary complaints, history of other diseases of the urinary tract (i.e., cancer of the bladder, history of prostatitis, or nephritic diseases)); musculoskeletal system (back problems: rheumatic diseases, herniated disc, back pain).

- § Hernia details at baseline: inguinal hernia (primary or recurrence), hernia side, hernia enlargement (past 6 weeks), reducibility, referent physician, the duration of inguinal hernia present at baseline (3 months or less and more than 3 months), positive family history of abdominal wall hernia, ultrasonography at baseline (i.e., hernia type, diameter of the defect).
- § Perioperative data: operation time, operation technique (i.e., Lichtenstein repair, total extra-peritoneal (TEP) repair, trans-abdominal pre-peritoneal (TAPP) repair, plug and patch repair, prolene hernia system (PHS), pre-peritoneal mesh repair (Kugel or Ugahary hernia repair)), type of mesh (flat mesh (i.e., polypropylene, polyester, large pore lightweight mesh), three-dimensional mesh (i.e. plug&patch repair, bilayered mesh, memory-ring patch)), surgical experience (less than 10, 10 to 25 and more than 25 procedures), type of anaesthesia, Nyhus classification¹⁹, identification of the nerves (i.e., iliohypogastric nerve, ilioinguinal nerve, and/or the genital branch of the genitofemoral nerve), nerve handling, closure of the subcutis, closure of the skin, difficulty of the procedure, perioperative complications (i.e., damage to the vas deferens, epigastric or testicular vessels, nerve injury, peritoneal/hernia sac defects, cardiovascular or anesthetic complications), perioperative use of antibiotics, post-operative complications (i.e., wound infection, hematoma, seroma, ischemic orchitis, urinary retention requiring catheterization, urinary tract infection requiring antibiotics, epididymitis requiring antibiotics, reoperation, pain during ejaculation), hospitalization.
- § Long-term complications (i.e., hernia complication (incarceration, strangulation), hernia complication requiring intervention, moderate or severe pain (pain/discomfort score of 2 or higher), recurrence, reoperation, crossover rates).

Ethical considerations and monitoring

The study protocol was approved by the institutional review board (IRB) of Erasmus University Medical Center, Rotterdam (MEC-2004-298) and by the IRBs of each study center before local start of inclusion. An independent data and safety monitoring board (DSMB) was constituted before the start of the trial. This DSMB consisted of three independent surgeons and one statistician. All serious adverse events (SAEs), defined as incarceration and/ or strangulation, were to be reported to the IRB of each participating center by the local investigators. The progress of the trial and all serious adverse events were reported to the DSMB and the safety of the trial was examined. The trial was registered at the Dutch Trial Registry, recognized by the World Health Organisation, before enrollment began, and assigned to ID number: NTR629.