Timing of surgery for sciatica

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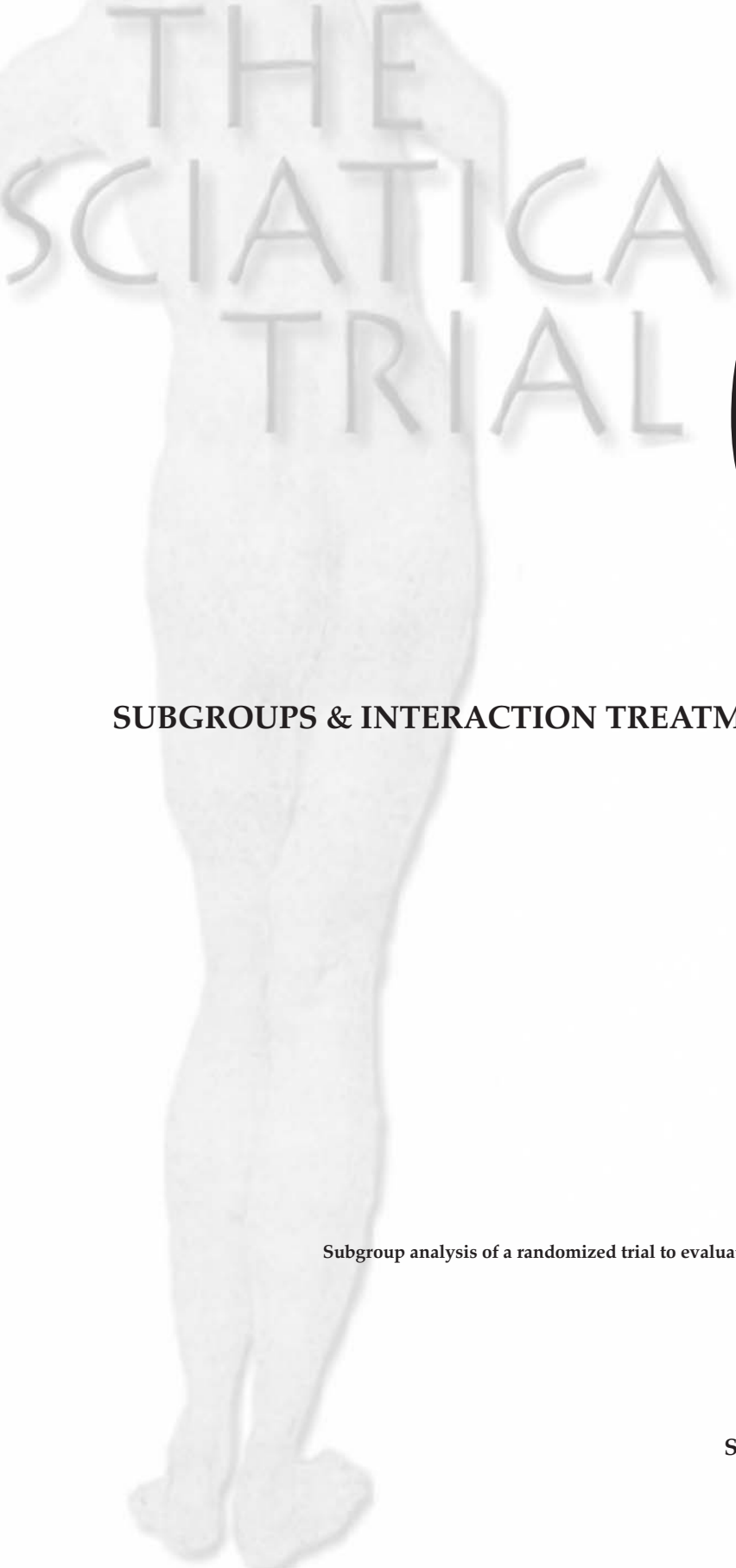

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SUBGROUPS & INTERACTION TREATMENT STRATEGY

Subgroup analysis of a randomized trial to evaluate timing of surgery for sciatica

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ABSTRACT

Context: After 6 to 12 weeks sciatica caused by a lumbar disk herniation, surgery speeds up recovery. Conservative care yields similar results at one year.
Objective: To determine whether baseline variables modify the difference in outcome between these treatment strategies.
Design, Setting and Patients: Baseline data of 283 patients enrolled in a multicenter randomized trial, comparing early surgery with prolonged conservative care, were used to analyze effect modification of the allotted treatment strategy by predefined variables.
Main Outcome measures: Recovery was registered by patients on a 7-point Likert scale, which for this study was dichotomized into "complete recovery" or "no recovery". For predictors shown to modify the effect of the treatment strategy (inferred from a significant interaction effect in a Cox model), repeated measurement analyses with the Roland Disability Questionnaire and VAS pain as continuous outcomes were performed for every level of that predictor (stratification).
Results: Presumed predictive variables did not have any interaction with treatment as far as speed of recovery is concerned, while "sciatica provoked by sitting" could be shown to be a significant effect modifier ($p=0.07$). In a Cox model we estimated a Hazard Ratio (surgery versus conservative) of 2.2 (95 % CI; 1.7 to 3.0) in favor of surgery when sciatica was provoked by sitting, while the HR was 1.3 (95 % CI; 0.8 to 2.2) when this sign was absent. The interaction effect is marginally significant (although interactions are usually tested at the 10 % level) but on the other hand the patterns generated by the repeated measurement analyses of all primary outcomes are completely consistent with the induced pattern in survival analysis.
Conclusions: Classical signs do not help to decide when to operate for sciatica, whereas treatment effects of early surgery are emphasized when sciatica is provoked by sitting and negligible when this symptom is absent.

Sciatica is characterized by radiating pain in an area of the leg typically served by one lumbar or sacral spinal nerve root and is sometimes associated with sensory and motor deficit. Apart from infrequent causes, sciatica is due to a herniated lumbar disk. Because of the high prevalence in general practice and the major impact of low back disorders on society[77], surgery is frequently performed to speed up recovery of sciatica. Probably as a result of socio-cultural circumstances, different timing of surgical removal of the herniated portion of the disk appears to vary greatly in the western countries[46]. Recently the option of surgery was offered to patients after only 6 weeks of unremitting sciatica. The major reason to offer early surgery was the unattractive alternative: the slow natural course of sciatica, occasionally extending over 4 years[40;117]. Globally two options were available: (1) early surgery and (2) prolonged conservative care, possibly with surgery at a later date. Since surgery is economically affordable and relatively safe, most patients in western countries prefer early surgery rather than to wait for months or even years, risking long term work-disability and presence of chronic pain. Recently a randomized trial provided evidence that the prolonged conservative care strategy resulted in complete recovery at one year but it took twice as long compared to early surgery[129]. The one-year effects of the two assigned treatment strategies were similar as far as function and pain were concerned in the randomized cohorts. The contribution to the clinical standard by this study is that patients, opting for surgery, now are able to base their decision on realistic data about the alternative natural course, with similar outcomes at one year compared to early surgery. If fast recovery is warranted individual decisions are still difficult. because both populations were heterogeneous regarding prognostic factors. Moreover surgery could not be avoided for 39 % of patients during prolonged conservative care. Although the complementary 61 % of patients recovered without intervention, they suffered sciatica for a prolonged period. Since treatment effects can differ between subgroups of patients, this might influence the indication for early disk surgery.

Therefore, it would be of great interest to patients and physicians to define determinants which occur early in the course of sciatica and predict the speed of recovery and therefore help in the decision about when to perform surgery. We carried out a subgroup analysis of data from the aforementioned randomized trial to evaluate anamnestic, neurological, and radiological variables which might in theory influence the difference in rate of recovery between the two treatment strategies.

METHODS

A multicenter prospective randomized trial was designed to determine for patients with a short duration of severe sciatica, whether early surgery resulted in a more

effective outcome during the first year, compared to a strategy of prolonged conservative treatment possibly with delayed surgery if indicated. The medical ethics committee at each of the 9 participating hospitals approved the protocol. Written informed consent was obtained from all patients. Details of the design, study protocol and prognostic variables were published previously together with the primary outcomes[118].

Patients

Eligible patients were 18-65 years of age, with radiological confirmation of a clinically expected disk herniation causing an incapacitating lumbosacral radicular syndrome lasting between 6 and 12 weeks as documented by the attending neurologist. At the time of enrolment and randomization an independent research nurse verified persistence of complaints and surgical indication. Patients were excluded if they presented with a cauda equina syndrome or severe paresis (MRC<3). Identical complaints in the past twelve months, a history of spinal surgery, bony stenosis, spondylolisthesis, pregnancy or severe comorbidity also led to exclusion. A computer generated permuted-block scheme was used for randomization, stratified according to center (n=9). The patients were randomized by opening an opaque envelope containing the patient's assigned strategy. Obviously it was not possible to blind patients or their physicians.

Treatment

Early surgery was scheduled within 2 weeks of assignment and only cancelled if spontaneous recovery occurred before the date of surgery. Under either general or spinal anaesthesia the herniated part disk was removed together with as much as possible degenerated nuclear material. Bony removal to gain access to the disk space was minimized and likewise subtotal disk excision was never pursued. The duration of the hospitalization depended on the patient's functional abilities. Since the protocol of the participating surgical departments was not changed, usual care was provided. At home the rehabilitation process was supervised by the physiotherapist on the base of a standardized exercise protocol. Patients were advised to resume their regular jobs from 6 weeks on, depending on the nature of the work. Postoperative care included out-patient control at 8 weeks or earlier if the patient worried about the course and suffered aggravation of symptoms.

Prolonged conservative management was provided by the general practitioner. Ample information was provided about the favorable prognosis. If necessary the prescription of pain medication was adjusted according to existing clinical guidelines. If there was considerable fear of movement, the help of a physiotherapist was recommended. Further on treatment was aimed mainly at resumption of daily activi-

Table 1. Predefined prognostic variables. *

Demographic Variables
• Age < 40 years versus ≥ 40 years,
• Intellectual versus physically demanding job,
• Gender
Anamnestic and Neurological Variables
• Acute start LSRS versus slow start,
• History of back pain versus no history,
• Influence of coughing, sneezing on complaints versus no influence,
• Difficulty to put on shoes and/or socks versus no difficulty,
• Straight leg raising ≤ 30 degrees versus > 30 degrees, †
• Positive crossed straight leg raising sign versus negative sign, †
• VAS-pain > 70 versus < 69 mm, ‡
• Tingling/numbness in pain area versus no tingling,
• Pain leg worse by sitting versus no worsening,
• McGill affective high score versus low score, §
Radiological Variables
• MRI disk sequester versus contained disk herniation, ¶
• MRI circumferential gadolinium enhancement versus no enhancement of disk herniation, ‖
Miscellaneous Variables
• Preference for surgery versus no preference for surgery,
• Disk herniation at L5S1 vs. L4L5.

* During the design of the trial, variables were selected on the physiological assumption to be correlated to speed of recovery

† Lasègue's sign was defined positive if the examiner observed a typically dermatomal area of pain reproduction and pelvic muscle resistance during unilateral provocative straight leg raising below an angle of 60 degrees, and crossed positive if the same experience was noted raising the other leg below 90 degrees.

‡ The intensity of pain was indicated on a horizontal 100 mm visual analogue scale, with 0 representing no pain and 100 the worst pain ever experienced.

§ The McGill affective score measure the qualitative perception of pain by the patient. High affective dimensional scores correlate to a more depressed and anxious individual mood when compared to patients who report low affective scores.

¶ Sequestrated disk herniations are defined by a defect in the annulus fibrosis and loose disk fragments in the epidural space, visualized by MRI scanning.

‖ Enhancement of the rim of disk herniation might correspond to removal of the herniated portion by an inflammatory reaction

ties. However if sciatica was still present at 6 months after randomization, microdiskectomy was offered after a repeat MRI showed the disk herniation again. Increasing drug-resistant leg pain or progressive neurological deficit were reasons for performing surgery even before 6 months.

Outcomes

Functional outcome assessed by means of the Roland Disability Questionnaire for Sciatica (RDQ), intensity of leg or back pain by a 100 mm visual analogue scale for leg pain (VAS-leg and VAS-back) and a questionnaire of patient's global impression

Table 2. Cox model recovery rates of early surgery compared to prolonged conservative care *

Subgroup	Proportion (%)	Lower	Mean	Upper	p-value interaction
Overall	100	1.72	**1.97**	2.22	
Age					**0.12**
< 40 years	41	1.69	**2.50**	3.66	
≥ 40 years	49	1.21	**1.68**	2.32	
Intellectual job					**0.83**
non-intellectual	36	1.21	**1.88**	2.92	
Intellectual	64	1.45	**2.00**	2.76	
Physical demanding work					**0.61**
non-physical	61	1.29	**1.80**	2.51	
physical demanding	39	1.37	**2.06**	3.1	
Sex					**0.64**
Male	66	1.57	**2.12**	2.87	
Female	34	1.20	**1.87**	2.92	
Start Sciatica					**0.91**
acute severe	61	1.40	**1.94**	2.68	
slowly increasing	39	1.27	**1.89**	2.79	
Influence intra-abdominal pressure					**0.45**
Provocation sciatica	73	1.57	**2.10**	2.81	
no provocation	27	1.06	**1.70**	2.74	
Lasègue's sign †					**0.88**
straight leg raising > 60 °	25	1.17	**1.92**	3.15	
straight leg raising ≤ 60 °	75	1.50	**2.01**	2.70	
Crossed straight leg raising †					**0.17**
Negative	41	1.11	**1.61**	2.34	
Positive	59	1.64	**2.28**	3.18	
VAS legpain intensity ‡					**0.98**
> 70	54	1.35	**1.94**	2.79	
≤ 70	46	1.37	**1.93**	2.71	
Sciatica provocation by sitting					**0.07**
no provocation	24	0.80	**1.30**	2.2	
Provocation	76	1.70	**2.24**	2.99	
McGill affective scores §					**0.60**
low score < 3	49	1.34	**2.05**	3.00	
high score	51	1.47	**1.90**	2.46	
MRI Sequester ¶					**0.81**
contained disk herniation	59	1.40	**1.96**	2.74	
Sequester	41	1.23	**1.84**	2.75	
MRI Gadolinium ‖					**0.60**
no enhancement	34	1.425	**2.32**	3.77	
enhancement	66	1.38	**1.97**	2.83	

Table 2. Continued

Subgroup	Proportion (%)	Lower	Mean	Upper	p-value interaction
MRI level disk herniation					**0.75**
L5S1	61	1.39	**1.93**	2.67	
L4L5 or L3L4	39	1.19	**1.77**	2.64	
Preference for surgery					**0.73**
strong preference for surgery	39	1.39	**2.07**	3.09	
some or no preference	61	1.38	**1.90**	2.61	
Tingling/numbness pain area					**0.66**
no sensation	10	1.1	**2.3**	5.1	
Sensation	90	1.5	**1.9**	2.5	

* Time to complete recovery according to baseline patient characteristics. Mean hazard ratios show the effect within each subgroup, with their corresponding 95 % confidence interval by lower and upper scores. Values for the interaction between treatment effect and the predefined subgroup variables for prolonged conservative treatment versus early surgery are shown.

† Lasègue's sign was defined positive if the examiner observed a typically dermatomal area of pain reproduction and pelvic muscle resistance during unilateral provocative straight leg raising below an angle of 60 degrees, and crossed positive if the same experience was noted raising the other leg below 90 degrees.

‡ The intensity of pain was indicated on a horizontal 100 mm visual analogue scale, with 0 representing no pain and 100 the worst pain ever experienced.

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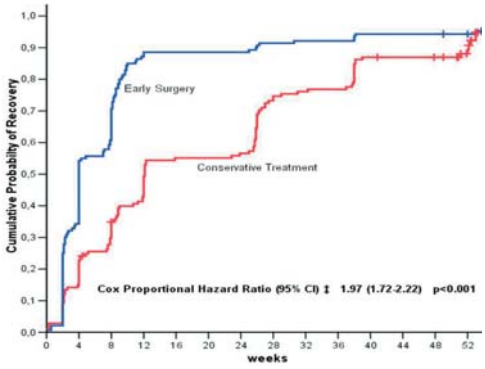
of change questionnaires on a 7-points Likert self-rating scale of recovery were filled out at 2, 4, 8, 12, 26, 38 and 52 weeks[109;114].

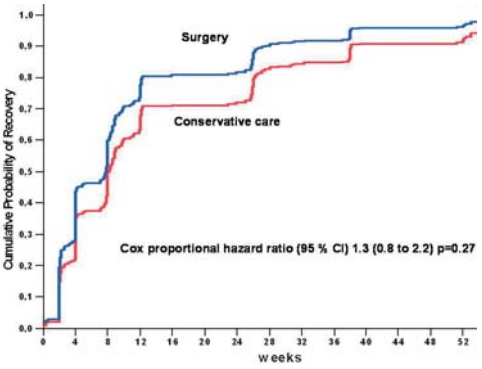
For the current subgroup analyses, the patient's global impression of change (PGIC) was used as dependant variable in dichotomized form. Next to obvious methodological advantages this dichotomized outcome form is easily applicable in general practice. "Very much improved" and "much improved" were coded as recovered, while "minimally improved", "no change", "minimally worse", "much worse" and "very much worse" were coded as not recovered.

Prognostic variables

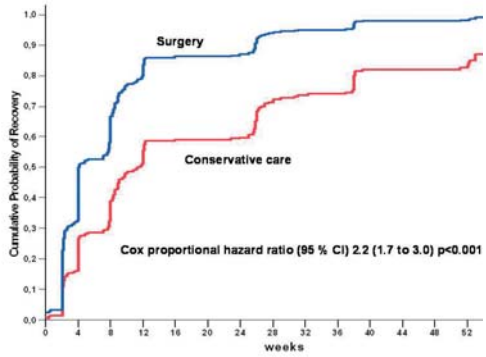
Possibly prognostic determinants were selected on the basis of classical physiological hypotheses or resulted from earlier studies. These socio-demographic, symptom, neurological, and radiological variables (Table 1) were collected before randomization was performed.



Panel A Unadjusted Survival Curves (5)



Panel B Sciatica not provoked by sitting



Panel C Sciatica provoked by sitting

Figure 1 Inverse Kaplan Meier curves.
Panel A presents the original unadjusted curves (5), while panel B and C represent stratified analyses, for sciatica not provoked by sitting and sciatica provoked by sitting, respectively.

Statistical Analysis

Data collection and quality checks were performed using the ProMISe data management system of the Department of Medical Statistics & BioInformatics of the LUMC. All statistical analyses were carried out using SPSS version 14.0.

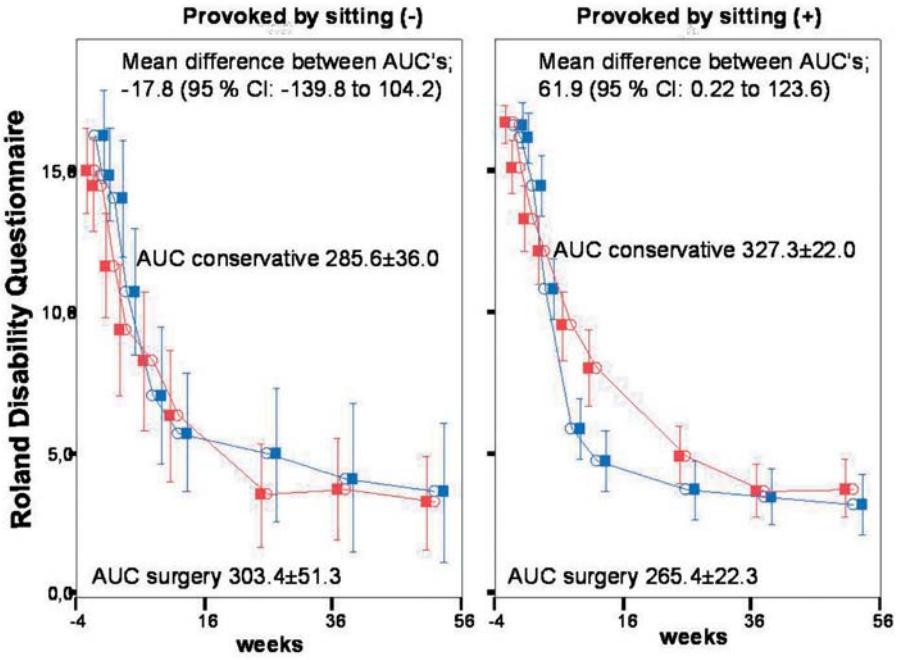
Effect modification of each predictor was first bivariately tested in a model containing the treatment allocation, the predictor and the interaction between them. If the p-value of the interaction term was smaller than 0.10, the predictor and its interaction term was retained for a multivariate model. In the multivariate Cox model, first all these interaction terms were removed by a backward stepwise procedure, also with a threshold of 0.10. The remaining interaction terms determined which predictors were subsequently used in a repeated measurements analysis of variance for continuous

outcomes (RDQ and VAS) where the predictor was used to define the strata in which the repeated effect was estimated. Following the analysis of the interaction effects, explorative Cox regression analyses of other basal demographic, neurological and radiological variables with some plausible relationship to outcome data were carried out.

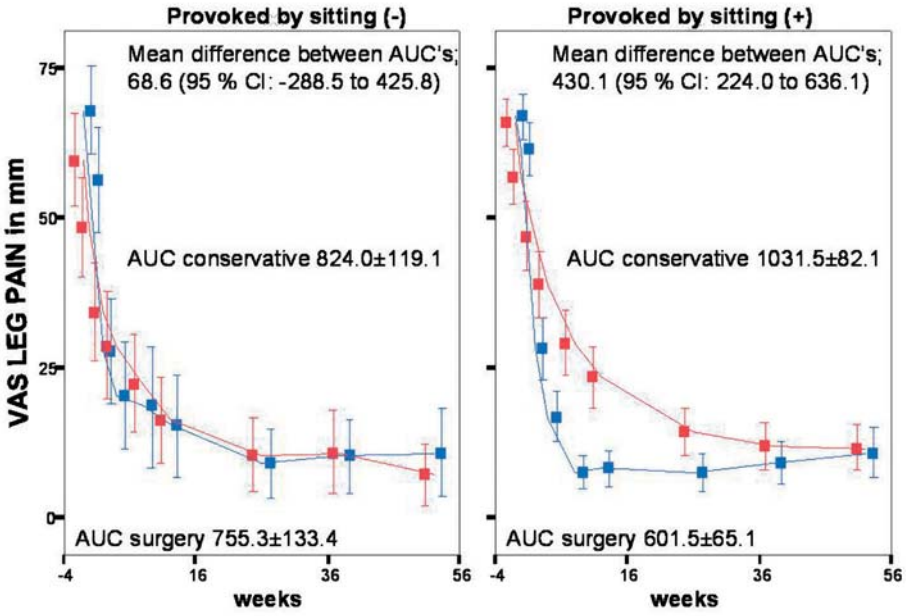
Results

Baseline demographic and neurological variables did not differ between groups[129]. The unadjusted hazard ratio as estimated in a univariable Cox model with recovery as endpoint was 2.0 (95 % CI 1.7 to 2.2), favouring early surgery (Figure 1 panel A). Univariate testing of the predefined prognostic variables showed a significant interaction effect of "sciatica provoked by sitting" with the "treatment strategy" ($p=0.07$), but no significant interaction effect of any of the other predefined variables was found (Table 2). Interestingly the presumed influence of classical neurological tests on speed of recovery could not be confirmed and, in contrast to former medical beliefs interactions were even absent, showing equal recovery rates for different levels of these variables. Treatment preference of patients did not show any interaction with early surgery either.

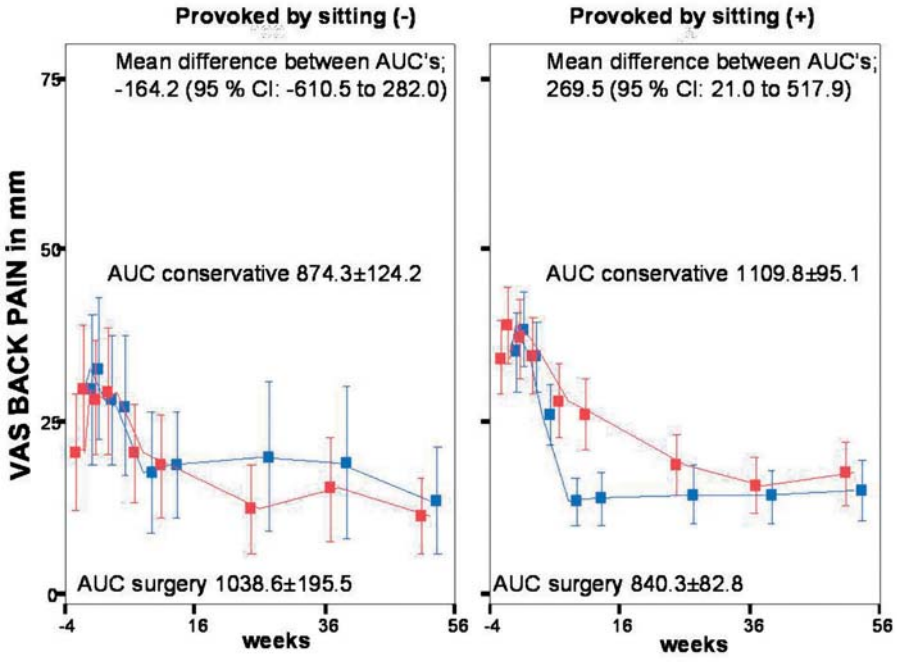
A survival model with "treatment-by-randomization", "sciatica provoked by sitting" as well as their interaction, revealed a differential effect on rate of recovery (Figure 1, panel B and C). Survival models lacking the treatment variable as an independent variable showed that presence or absence of sciatica provoked by sitting in itself did not provide any prognostic value for the speed of recovery rates. Patients with sciatica provoked by sitting did experience a slower rate of recovery when randomized to prolonged conservative treatment while surgery accelerated the rate of recovery with an estimated hazard ratio of 2.2 (95 % CI; 1.7 to 3.0). When patients did not experience leg pain provoked by sitting the survival curves come close together, corresponding with similar average speed of recovery rates: HR 1.3 (95 % CI; 0.8 to 2.2). Repeated measurement analysis, stratified by "sciatica provoked by sitting", gave similar findings with RDQ and VAS pain outcomes showing diverging curves when sitting provoked sciatica. Areas under the RDQ and VAS back pain curves over the first year of early surgery compared to conservative treatment were even statistically different ($p=0.05$ respectively $p=0.03$) in contrast to the original analysis without stratifying variables [129]. These outcomes over the first year between early surgery and conservative treatment did not show relevant differences when sciatica was not provoked by sitting and early surgery even gave less favorable results during the first months compared to conservative treatment in this group (Figure 2).



Panel A †



Panel B ‡



Panel C ‡

*Figure 2 . Repeated Measurement Analysis stratified for "sciatica provoked by sitting.**
Curves of Mean scores for Roland Disability Questionnaire (Panel A) † , Leg Pain (Panel B) ‡ and Back Pain (Panel C) ‡ . All three panels show the 52-week curves with 95 percent confidence intervals represented by vertical bars at consecutive moments of measurement. Red lines represent the conservative treatment group, while the blue lines represent early surgery. Areas under the curve (AUC) are described by their means ± SE.
***Panel A** represents the mean disability scores at consecutive moments of measurement stratified for sciatica provoked by sitting. The overall difference between the areas under the curves over 12 months is not significant for sciatica not provoked by sitting (p=0.77) and significant for provoked by sitting (p=0.05) in favor of early surgery.*
***Panel B** represents mean visual analogue scores for intensity of leg pain in mm. The difference between the mean AUC's is not significant for sciatica not provoked by sitting (p=0.70) and significant for sciatica provoked by sitting (p<0.001) in favor of early surgery.*
***Panel C** represents mean visual analogue scores for intensity low back pain in mm. Starting with a lower intensity score when compared to leg pain, the mean AUC's exhibit no significant difference for sciatica not provoked by sitting (p=0.47) and significant for sciatica provoked by sitting (p=0.03)*

** The mean difference between areas under the curves are expressed by the corresponding 95 percent confidence interval. To enhance visualization of the curves the error bars (95 % confidence intervals) are offset.*
† The Roland Disability Questionnaire for Sciatica is a disease specific disability scale that measures functional status in patients with pain in the leg or back. Scores range from 0 to 23
‡ The intensity of pain was indicated on a horizontal 100 mm visual analogue scale, with 0 representing no pain and 100 the worst pain ever experienced, with higher scores indicating worse functional status.

DISCUSSION

This randomized trial showed that early surgery led to significantly faster recovery compared to prolonged conservative care but failed to show any interaction with classical neurological signs and magnetic resonance imaging findings. Only "sciatica provoked by sitting" showed interaction with timing of surgery, and thus rate of recovery. These results were markedly consistent in stratified analyses of all primary outcomes over the first year.

The finding that classic physical signs and high preference for surgery did not affect the results of treatment strategies was surprising and not expected. Currently most physicians and physiotherapists refer patients for surgery under the near mandatory condition that the straight leg raise test provokes sciatica[45]. The design of this trial made it possible to include enough patients with a negative straight leg raising test. These, however, form a minority which may be due to selection bias. Therefore these results must have to be interpreted very carefully, which also holds true for the findings regarding patient preferences. Earlier prognostic studies suggested a realistic relationship between patient's and doctor's preferences and expectations on the one hand and outcome on the other[151]. These expectations are still likely to play a major role since the patients in this randomized trial were very willing undergo surgery; in fact this was their main motive to visit the outpatient clinic of the participating hospitals. Only a minority of patients did not have a clear preference for surgery and no patient had a preference for the conservative treatment strategy. Therefore the lack of influence of patient preferences on treatment strategies is not unrestrained applicable to general practice.

Sequestrated disk herniations also failed to follow a significantly different course when allotted to early surgery compared to prolonged conservative care. Earlier radiological studies showed strong associations between the type of disk herniation and the natural course or surgical outcome of sciatica[152;153]. According to some authors sequestrated disk fragments were likely to resolve in the spinal epidural space, making surgery an pointless intervention[152;154;155]. Similar conclusions were drawn in the past in favor of MRI gadolinium rim enhancement of the disk herniation, representing neo-vascularization corresponding to macrophage resorption of the disk fragment[156;157]. The current study did not show any relationship between this variable and timing of surgery. Other important effectiveness studies suggested a relationship between spinal level of disk herniation and the surgical timing strategy. This was not confirmed by this analysis, which contains more solid data on duration of sciatica complaints and timing of surgery[49] and sample size[66].

While the scientific value of "sciatica provoked by sitting" as a prognostic variable might be debated, a similar result for this anamnestic variable was found in

the randomized bed rest trial to predict the risk for patients undergoing surgery[153]. Although only a marginally significant different interaction effect was found by univariate Cox proportional hazard analysis, these results appeared consistent when repeated measurement analysis of primary outcomes was performed. Furthermore it is a simple question to ask and physiologically completely understandable that a patient, persistently unable to sit, will gain important relief of pain, quality of life and function with early surgery. On the other hand if patients do not suffer sciatica provoked by sitting, their chances of a beneficial result of early surgery, if any, are reduced. Most of the latter patients might be better off with prolonged conservative care. Since this subgroup, however, was relatively small, one must interpret these results carefully; further investigation in future studies on this subject is needed.

The lack of a prognostic value of physical signs and symptoms for the outcome of sciatica has been reported before, but these studies focussed on the long-term results and not on the short-term rate of recovery[158-160]. It still is important to define neurological deficits[116] when examining a patient but their predictive value, to alter a decision to operate or to advise patients to stay conservative for a prolonged time, is minimal or absent. Nowadays, spine-oriented clinics request magnetic resonance imaging quite early in the course of sciatica to comfort their patients and discuss treatment and prognosis. This study shows evidence of absent predictive and no prognostic value for this diagnostic strategy. Magnetic resonance imaging or a CT-scan is necessary for surgery but is less informative for the patient who must decide whether to undergo surgery or not.

Conclusion

Except for absent "sciatica provoked by sitting" early surgery compared to prolonged conservative care yielded significantly faster rates of recovery for all investigated variables, irrespective of their value. Neurological signs, patient preferences and magnetic resonance imaging findings fail to affect the outcome of early surgery versus prolonged conservative care. But a simple question regarding leg pain provoked by sitting, asked by the family practitioner, might help patients to opt for surgery to speed up recovery rates from sciatica as well as those who prefer to reduce the risk of on back surgery.