A Randomized Controlled Trial of Postthoracotomy Pulmonary Rehabilitation in Patients with Resectable Lung Cancer

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Introduction: Little is known about the effects of rehabilitation for patients with lung cancer after thoracotomy. The primary objective of this study was to evaluate the effect of a multidisciplinary rehabilitation program on quality of life (QOL) and secondary objectives were to determine its effects on pain and exercise capacity and the feasibility of combining rehabilitation with adjuvant chemotherapy.

Methods: Patients who had undergone a thoracotomy for lung cancer were randomized between rehabilitation and usual care. Rehabilitation consisted of twice-weekly training for 12 weeks starting 1 month after hospital discharge, scheduled visits to pain specialists, and medical social work. QOL and pain were measured with validated questionnaires at baseline and after 1, 3, 6, and 12 months. Exercise tolerance was assessed at baseline and after 3 months with a 6-minute walking distance test.

Results: The study closed prematurely because of the introduction of video-assisted thoracoscopic surgery. Of 57 randomized patients, 49 patients (23 active and 26 control) were analyzed. QOL was not significantly different between groups, although, the active group reported more pain after 3 and 6 months and more limitations because of physical problems after 3 months. In the active group, 6-minute walking distance improved by 35 m from preoperative baseline, as opposed to the control group that showed a decline by 59 m (p = 0.024 for difference). Patients treated with adjuvant chemotherapy showed decreased attendance at training sessions.

Conclusion: Rehabilitation did not result in a better QOL. Exercise tolerance improved at the cost of more pain and more limitations because of physical problems. We suggest that rehabilitation is better postponed for 3 to 4 months after hospital discharge.

Key Words: Rehabilitation, Lung cancer, Thoracotomy, Quality of life, Exercise training.

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Although thoracoscopic surgery for lung cancer has been gaining ground rapidly over the last years, in many patients thoracotomy is still performed. Postoperative morbidity after thoracotomy is characterized by a deterioration of existing preoperative impaired parameters, like physical, social, and mental state and thoracic pain.[1] Decreased exercise tolerance is repeatedly described, particularly in patients after pneumonectomy measured after 3 to 6 months.[2–4]

Pain and a diminished exercise tolerance definitely influence daily activities and quality of life (QOL). A few studies demonstrated a decrease in QOL but a return to normal after 3 to 6 months postoperatively.[5–8]

It has been shown that rehabilitation after coronary artery bypass surgery improves QOL and mortality and decreases the hospital admission rate.[9] We surmised that a similar program of pulmonary rehabilitation could be beneficial for patients with lung cancer after thoracotomy. These patients share similarities with postoperative cardiac patients in characteristics such as health status and age, although pain is less of a problem after sternotomy compared with thoracotomy.

Literature on postthoracotomy rehabilitation is minimal. Two nonrandomized trials in 10 and 25 patients showed improvements in exercise tolerance measured with 6-minute walking distance (6MWD) test after an 8- and 4-week rehabilitation program, respectively.[10,11] The only randomized controlled trial performed on 53 patients failed to demonstrate an effect of rehabilitation on exercise tolerance (6MWD) and QOL.[12] This randomized study focused on physical parameters and QOL as outcome measures but special attention to pain management and psychosocial aspects was lacking. It seems obvious that optimization of pain treatment and psychosocial care improves patients well-being and improves the circumstances for exercise training.

None of the studies reported on the feasibility of integrating rehabilitation with adjuvant chemotherapy (ACT). Chemotherapy with subsequent toxicity may limit the possibilities of rehabilitation to a great extent, especially of an intensive training program.

For the current study, a multidisciplinary rehabilitation program was designed for postthoracotomy patients with resectable lung cancer. The program contained intensive exercise and muscle training, specialized pain treatment, and scheduled visits to a medical social worker.

The primary objective of this randomized controlled trial was to evaluate the effect of this concise multidisciplinary rehabilitation program on QOL. Secondary objectives were to evaluate the effects of rehabilitation on exercise tolerance and pain sensation and also to explore the feasibility of a rehabilitation program in patients with ACT.

PATIENTS AND METHODS

Study Design and Patients

This study is a prospective parallel group randomized (1:1 ratio) controlled trial with 1-year follow-up carried out in the Isala Clinics, a large teaching hospital in Zwolle, The Netherlands. The design of the study is depicted in Fig. 1.

Resectable patients (aged 18–80 years) with non–small-cell lung cancer were randomized before surgery to the active (rehabilitation) group or control (usual care) group. ACT was not an exclusion criterion and was administered according to national guidelines starting within 1 month after surgery.

Four weeks after discharge, active patients entered the 12-week rehabilitation program with exercise training by physiotherapists and scheduled visits to a specialized pain team and medical social worker.Twice a week, patients exercised between 60% and 80% of their peak cycling load (determined by a postoperative incremental cycling ergometer test) and performed muscle training. A dedicated anesthesiologist adjusted pain treatment during the study according to the World Health Organization analgesic ladder.[13]

Before discharge, patients consulted a medical social worker who assessed psychosocial problems and arranged a second visit during rehabilitation. In case of problems, direct help was provided or referral to a specialized facility was offered.

Patients in the control group received usual care consisting of routine outpatient appointments, scheduled 1, 3, 6, and 12 months after discharge. Pain medication was prescribed by their pulmonologist or general practitioner. Referrals to physiotherapy or social work occurred on a personalized base.

The study was approved by the local medical ethics committee (NL14089.075.06). All patients provided written informed consent.

Assessments

Change in QOL was measured with the St. George's respiratory questionnaire (SGRQ)[14] before thoracotomy and 1, 3, 6, and 12 months after discharge. During these timepoints, generic QOL was assessed with the Short Form health survey (SF-36),[15] and pain with the Dutch version of the McGill Pain Questionnaire (MPQ-DLV)[16] and use of analgesics was recorded.

Pulmonary function tests (PFT) and exercise capacity (6MWD) were measured before surgery and 3 months after discharge, corresponding to 2 months of exercise training. Attendance rates at planned rehabilitation sessions were determined to assess the feasibility of rehabilitation in patients with ACT.

Statistics

Sample size calculation was based on the SGRQ outcomes in a trial on chronic obstructive pulmonary diseases rehabilitation described by Rossi et al.[17]To demonstrate a two-sided ($\alpha = 0.05$) difference between the study groups in mean change of the SGRQ total score of at least 4 (SD = 6.4) points (considered as the minimal clinically important difference)[14,18] after 12 months, 44 patients are needed in each group (with a dropout rate of 10%).

After surgery, patients were randomized to the active (rehabilitation) group or control group, using a computer minimization system, initiated by the treating chest physician. The minimization program balanced patients for the following factors: age (< 70 or ≥ 70 years), sex (male or female), baseline 6MWD (< 100 m or ≥ 100 m), the forced expiratory volume in 1 second (FEV1) (FEV1< 40% or ≥ FEV1 40 %) and type of surgery (pneumonectomy versus other).

Primary analysis was based on an intention-to-treat. Differences between the two groups in mean change scores of the SGRQ total after 1, 3, 6, and 12 months were tested using analysis of covariance (ANCOVA). In contrast to the generally used *t* test, ANCOVA is able to control for baseline imbalances.[19] ANCOVA was also used to test differences in MPQ-DLV, SF-36, 6MWD and PFT. The χ^2 test was used to test differences in proportions from these assessments. Difference

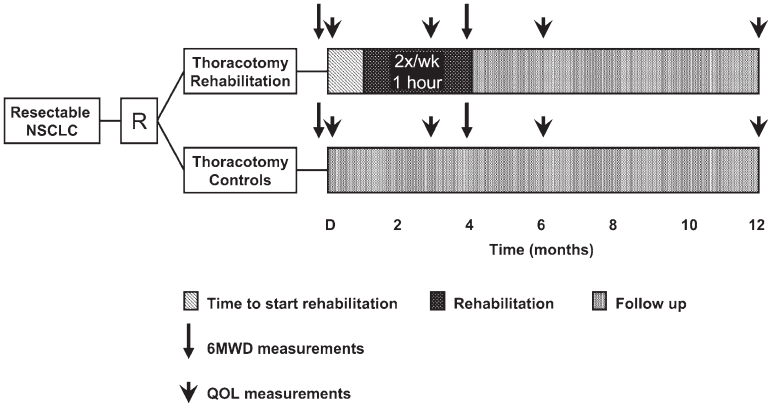


FIGURE 1. Study design. NSCLC, non–small-cell lung cancer; R, randomization; 6MWD, 6-minute walking distance; QOL, quality of life; D, discharge from hospital.

in attendance rate in the active group between patients with and without ACT was analyzed with Mann–Whitney *U* test.

p Values less than 0.05 were considered significant. Analyses were performed using SPSS-Statistics version 19.0 (IBM corporation, Armonk, NY).

RESULTS

Patients

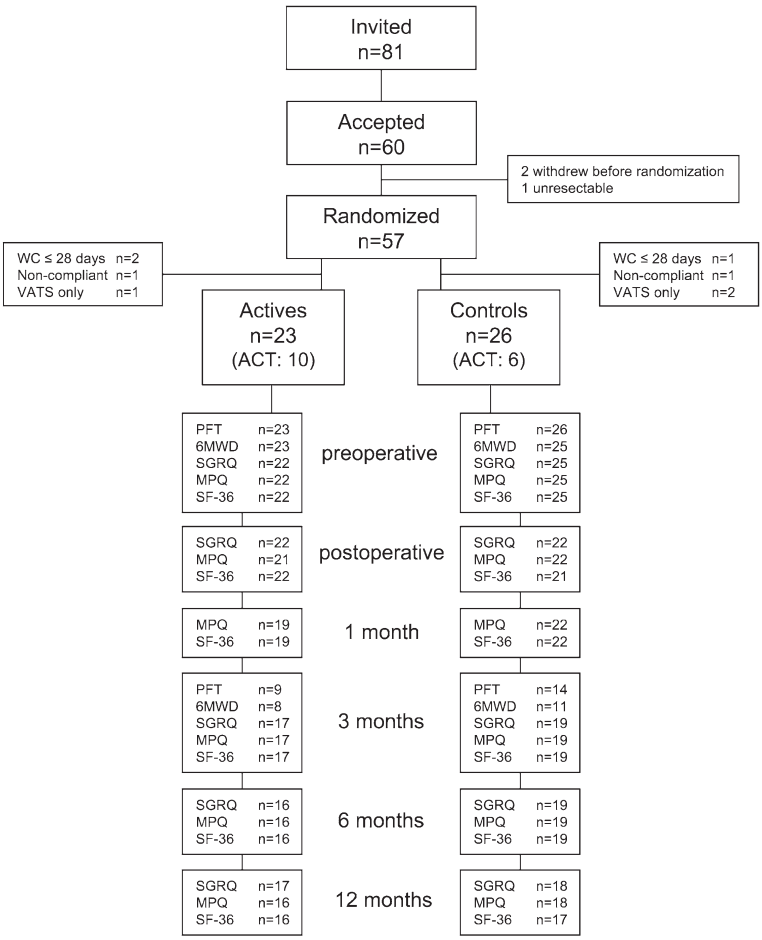
From May 2007 to September 2010, a total of 81 patients were invited for participation. Sixty patients accepted the invitation and 57 were randomized.Twenty-seven patients were randomized to the active group and 30 to the control group. The reasons for the eight dropouts are shown in the consort flow chart (Fig. 2). This study was terminated prematurely because of slow accrual as a result of the institution of video-assisted thoracoscopic surgery (VATS) by the end of 2008.

Baseline characteristics (n = 49) are depicted in Table 1. Ten of 23 patients in the active group, and six out of 26 patients in the control group received ACT, but differences between both groups were not statistically significant.

Quality of Life

The primary endpoint of this study was the difference in SGRQ total score from baseline to 12 months and this was 2.71(±6.90 SD) on a scale from 0 to 100 points (p = 0.69). (Fig. 3*A*). The SGRQ scores for the domains of symptoms, activity, and impact on daily life were not different between both groups.

The scores of the SF-36 domains of physical functioning, mental health, social functioning, role limitations because of emotional problems, and vitality were also not different in both groups after 3 months. The control group reported less role limitations because of physical problems at 3 months when compared with the active group (p = 0.03) (Fig. 3*B*). However, at 12 months, this difference disappeared. The scores of the general health in the active group seemed to be worse than in the control group at 3 and 6 months (p = 0.065 and p = 0.29, respectively [Fig. 3*C*]).



WC, withdrew consent; VATS, video-assisted thoracoscopic surgery; PFT, pulmonary function test; 6MWD, 6 minute walk distance; SGRQ, St. George's Respiratory Questionnaire; MPQ, McGill Pain Questionnaire; SF-36, short form 36; ACT, adjuvant chemotherapy

FIGURE 2. Consort flow chart. 6MWD, 6-minute walking distance; QOL, quality of life.

TABLE 1. Baseline Characteristics

	Active Group ($n = 23$)	Control Group ($n = 26$)	p
Age (yr)	63.6 ± 10.2	63.2 ± 10.3	0.89
Sex male/female (%male)	21/2 (91%)	19/7 (73%)	0.15
Current smoker yes/no (%yes)	3/19 (13%)	6/19 (23%)	0.47
BMI (kg/m^2)	26.1 ± 4.0	25.9 ± 3.5	
FEV1 (L)	2.7 ± 0.6	2.5 ± 0.9	0.35
FEV1%predicted	84.7 ± 18.9	84.2 ± 23.3	0.94
IVC (L)	3.8 ± 1.0	3.7 ± 1.1	0.76
IVC %predicted	89.7 ± 21.9	94.8 ± 21.4	0.42
FEV1 %Vcmax	64.6 ± 10.0	63.4 ± 10.8	0.73
PEF (L/s)	8.1 ± 1.9	7.1 ± 2.3	0.13
6MWD (meter)	521 ± 95	510 ± 121	0.75
Adjuvant chemotherapy yes/no (%yes)	10/13 (44%)	6/20 (23%)	0.13
Surgery:			0.55
Lobectomy/bilobectomy	13 (57%)	16 (61%)	
Pneumonectomy	9 (39%)	9 (35%)	
VATS with minithoracotomy	1 (4%)	0	
Wedge resection	0	1 (4%)	

BMI, body mass index; FEV1, forced expiratory volume in 1 second; IVC, inspiratory vital capacity; PEF, peak flow; 6MWD, 6-minute walking distance. Data are mean and SD for the upper 11 variables.

Finally, the quality of life index of the MPQ-DLV showed higher scores postoperatively, and as expected, improving in both groups over the observation period of 12 months. There were no significant differences between both groups at the evaluation points as illustrated in Figure 3*D*.

Exercise Tolerance

The rehabilitation program improved the 6MWD after 3 months in the active group compared with the control group (mean difference between the groups adjusted for baseline characteristics was 94 ± 38 m [$p = 0.024$], Fig. 4). In the active group, only eight out of 23 patients performed a 6MWD at 3 months of rehabilitation. The mean baseline 6MWD of these eight patients was comparable to the mean 6MWD measured at baseline in patients with baseline measurement only (524 versus 519; $p = 0.90$). The 6MWD (mean SD) in the active group improved from 524 m (± 81) to 567 m (±78) ($p = 0.037$) (Table 2 and 3). In the active patients, 15 out of 23 did not perform a repeated 6MWD test because they dropped out or felt unable to perform the test. After 3 months of follow-up, the 6MWD in the control group decreased from 555 m (±113) to 491 m (±109) but this difference was not significant ($p = 0.079$, Fig. 4). In the control group, 11 patients out of 25 performed repeated 6MWD tests.

Only two out of 10 patients that were randomized to rehabilitation and received concurrent ACT performed a repeated 6MWD after 3 months. In the control group, a similar low rate of two out of six was observed in patients treated with ACT. Repeated 6MWD tests were available in six out of 13 and nine out of 20 patients that did not have ACT, in the active and the control group, respectively.

Patients of both groups were asked during follow-up whether they had performed any physical training activities. The active group showed a gradual decline during 1st year of follow-up from 19 out of 21 (90%) after 1 month to 17 out of 21 (81%) after 3 months, and further down to nine out of 16 (56%) after 1 year. However, the control group showed an initial low rate of physical training, one out of 27 (4%), which increased to a persistent one-third after 3 months.

Pulmonary Function Tests

The changes in PFT after thoracotomy were not significantly different between the two groups (Table 1 and 2).

Pain

Patients in the active group reported significantly more pain (measured by the Visual Analogue Scale of the MPQ-DLV) than the control group after 3 months ($p = 0.042$) and after 6 months (measured by the total pain rating index of the MPQ-DLV [$p = 0.010$]) as shown in Figure 5*A* and *B*.

In the pain-specific domain of the SF-36, active patients also reported more pain ($p = 0.028$) compared with controls after 3 months (Fig. 5*C*). The use of analgesics over time decreased significantly within subjects of both groups ($p < 0.001$, not shown). The use of analgesics at 3 months was higher in the active group compared with controls ($p = 0.048$) as shown in Figure 5*D*.

Medical Social Work

Inpatient counselling (1 to 5 sessions per patient) by medical social work was provided for eight out of 23 patients (35%). Outpatient counselling (1 to 6 sessions per patient) was provided for four out of 23 patients (17%).

Compliance to Training Sessions

Only three out of 10 patients who were treated with ACT participated in the training program until week 12, as opposed to eight out of 13 of patients who did not receive ACT (Table 3). Attendance rates of patients treated with ACT and those without chemotherapy are given in Table 3.

DISCUSSION

This study is among the first to evaluate the effects of pulmonary rehabilitation for patients with resectable lung cancer after thoracotomy. To our knowledge, it was the first time that patients receiving ACT were also included. Although the primary end point of improvement of QOL was not observed, we observed significant improvements in exercise tolerance in patients receiving rehabilitation but also more perception of pain compared with the control group despite optimal pain control by a specialized team. In both groups study drop out rates were quite high indicating burdensome participation for many patients that was even more pronounced when ACTwas used. This was illustrated by the limited attendance to the training sessions in this subgroup. Therefore, rehabilitation should not be started before 3 or 4 months after a thoracotomy.

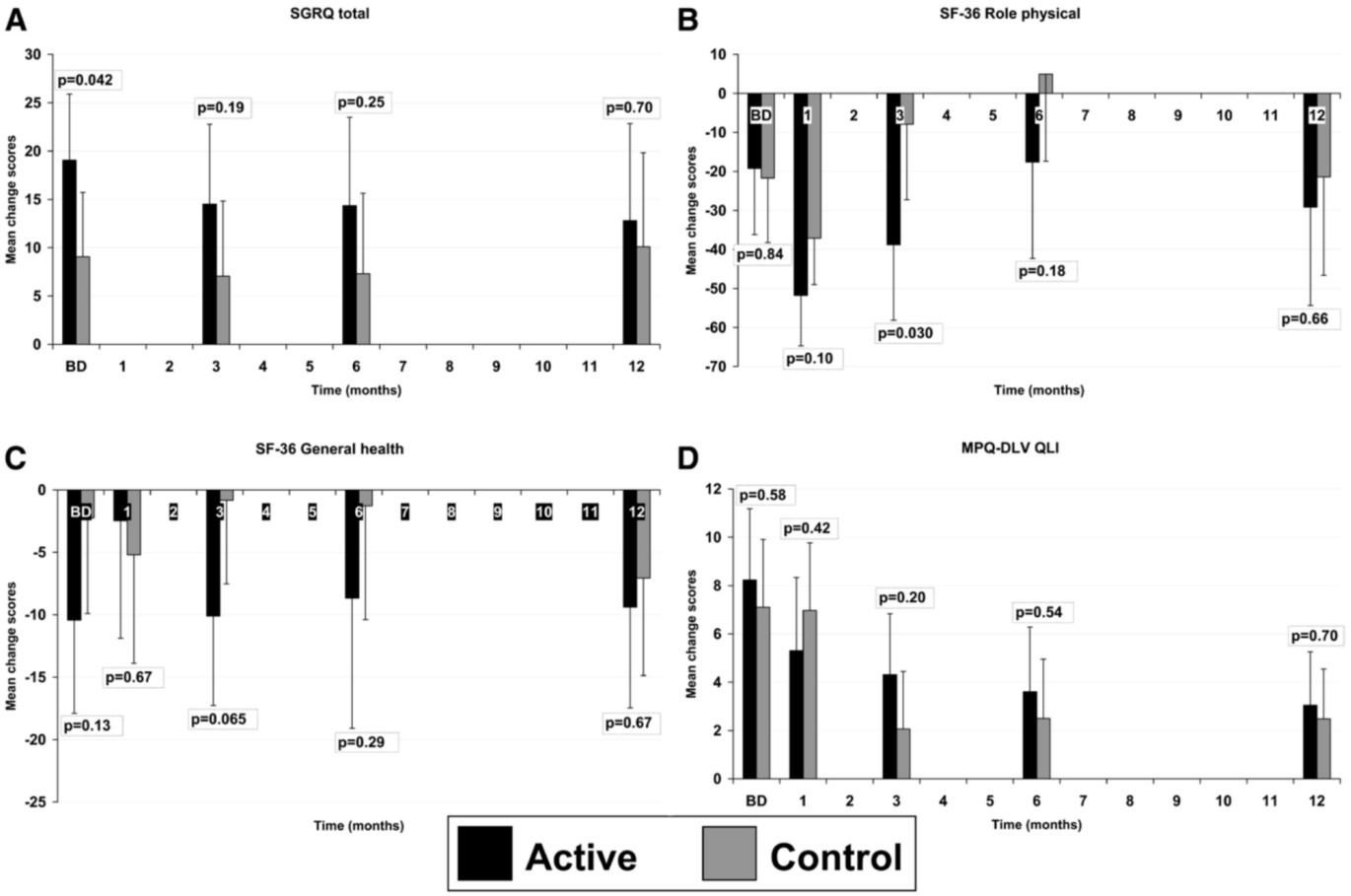


FIGURE 3. Quality of life and impact of pain on quality of life in resectable lung cancer patients treated in a postthoracotomy rehabilitation program (actives) or receiving usual care (controls). *A*, SGRQ. *B,* SF-36 role physical. *C*, SF-36 general health. *D*, MPQ-DLV QLI. SGRG, St. George's Respiratory Questionnaire; SF-36, Short Form health survey; MPQ-DLV QLI, Dutch Version of the McGill Pain Questionnaire quality of life index; BD, before discharge. Error bars represent 95% confidence intervals.

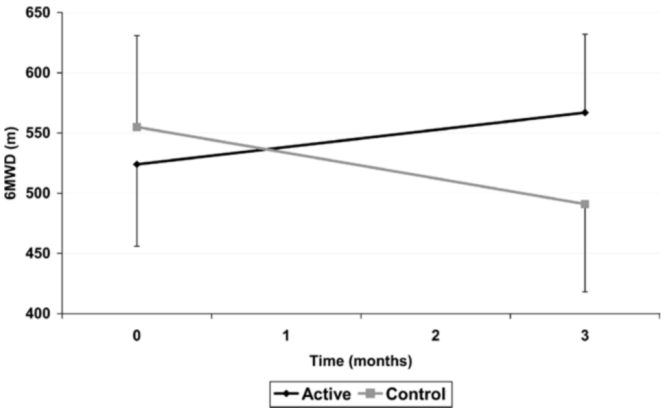


FIGURE 4. Exercise tolerance in patients treated in a pulmonary rehabilitation program (actives) compared with usual care (controls) measured with the 6-minute walking distance, before and 3 months after discharge from hospital. Only the results of patients with a paired (preoperative/postoperative) 6MWD test were used. 6-MWD, 6-minute walking distance. Error bars represent 95% confidence intervals.

For cardiac rehabilitation, recommendations for starting such programs is generally 2 to 4 weeks after uncomplicated coronary and valvular procedures.[20] Thoracotomy with spreading ribs and reduction of functional pulmonary tissue leads to more local morbidity than is usually expected after a sternotomy.

Quality of Life

Both groups in this study showed a slight but significant improvement in respiratory symptoms during the observation period but this did not result in improved QOL with rehabilitation. Changes in generic QOL scores in both groups assessed by another test, SF-36, were similar for almost all domains. Both groups distinguished role limitations because of physical problems that were experienced more severely in patients in the active group at 3 months after discharge. Unfortunately, this part of the SF-36 questionnaire was completed by only a minority of patients because the questions were not applicable to patients who were permanently disabled or retired. Our study failed to confirm the influence of rehabilitation on QOL and confirms the results of one previous study.[12]

TABLE 2. Changes in Lung Function and 6MWD from Baseline and at 3 Months Adjusted for Baseline Value

	Active Group (n = 9)	Control Group (n = 14)	Mean Difference (A–C)	p
FEV1 (L)	−0.44 ± 0.14	−0.58 ± 0.11	0.15 ± 0.8	0.42
FEV1 %predicted	−15.0 ± 4.7	−17.8 ± 3.8	2.8 ± 6.1	0.65
IVC (L)	−0.21 ± 0.25 (n = 8)	−0.77 ± 0.19	0.56 ± 0.32	0.093
IVC %predicted	−7.3 ± 6.3 (n = 8)	−18.8 ± 4.7	11.5 ± 8.1	0.17
6MWD (m)	35 ± 29 (n = 8)	−59 ± 24 (n=11)	94 ± 38	0.024

Mean ± SE.
FEV1, forced expiratory volume in 1 second; IVC, inspiratory vital capacity; PEF, peak flow; 6MWD, 6-minute walking distance.

TABLE 3. Dropout Numbers and Attendance Rates in Relation to the Use of Adjuvant Chemotherapy in the Active Group (n = 21)

	Adjuvant Chemotherapy		
	Yes No. of Patients	No No. of Patients	p
Randomized to training[a]	9	12	
Completed training	3	8	0.20
Attendance rate (mean)	43% ±31	62% ±37	0.15[b]
Attendance rate (median)	33%	83%	0.39

[a]One patient with ACT and one patient without ACT did not attend at all. Of the two patients, one treated with ACT and one not treated with ACT. No data regarding attendance was available.
[b]Mann–Whitney U test.

We observed an initial postoperative decline in general health, and physical and social functioning, and also observed an increased role of physical and emotional problems in both groups. All these domains did not restore the preoperative levels after 12 months of follow-up. This is in contrast to reports in previous studies that showed recovering QOL (without rehabilitation) within 6 to 9 months.[6–8]

Exercise Tolerance

Patients did perform physically better with the rehabilitation program. After 2 months of exercise training there was an 8% improvement (94 m) in the 6MWD test. This improvement seems modest, but it is an improvement compared with the preoperative level. Improvements of 6MWD tests after a rehabilitation program of 43% and 32%, reported in two small nonrandomized studies, were compared with baseline postoperative values.[10,11] There is one previous randomized trial studying the effect of rehabilitation after thoracotomy. The training program in that study (5-day postoperative inpatient training followed by nonsupervised training at home with home support) did not result in improved exercise tolerance as measured with the 6MWD.[12]

Compared with the training sessions in our rehabilitation program, the training intensity in both the nonrandomized studies was higher. Patients in the larger study followed an inpatient program of 3-hour sessions daily starting immediately after surgery and continuing for 1 month.[11] The smaller nonrandomized study started later (between 2.5 and 9.3 months, postoperatively), and the training sessions were also on a daily base.[10] The exercise training in the randomized study was intensive in the immediate postoperative phase, but thereafter supervised training stopped, and exercise training proceeded to a home-based nonsupervised program.[12] These patients were not trained on cycle ergometers and treadmills at predefined moderate to high levels (based on peak performance on incremental cycle ergometry) as was the case in our study. Supervision and training up to submaximal levels is probably necessary to improve exercise tolerance in these patients as we demonstrated in our study.

Pain

Patients in both groups experienced a decrease in pain over time, in the observation period, but the active patients reported significantly more pain after 3 and 6 months, despite the intensified pain treatment reflected by higher use of analgesics. All patients were treated similarly with epidural analgesics immediately postoperation and therefore, acute pain scores showed no differences before hospital discharge. The similar pain scores of both groups, 1 month after discharge, was not surprising because it coincided with the first outpatient contact of the active group with the specialized pain team. Until that moment patients had a comparable treatment provided by pulmonologists and general practitioners. From that visit on, patients in the active group started exercise training under optimized pain treatment and monitoring. Perhaps, the intensive physical training program had detrimental effects on pain by constantly stretching the painful thoracic cage and fresh scars.

Prescheduled visits to a specialized pain-treating anesthesiologist as an elementary component of the study protocol was absent in all former studies. Information on the course and intensity of pain during postthoracotomy rehabilitation is minimal in those studies.[10,11] One randomized study measured pain as part of a QOL questionnaire but did not find a difference in perception of pain between the active and control group.[12] However, in those studies, as opposed to our study, exercise training was nonsupervised and the level of exercise was not defined; therefore, patients might have performed their exercise training at lower levels than our patients.

Remarkably, the impact of pain on QOL did not differ in both groups in our study. It is likely that rehabilitating patients accept some amount of pain as part of their recovery.

Adjuvant Chemotherapy

We demonstrated that ACTand exercise sessions were hard to combine. Patients treated with ACT had higher rates

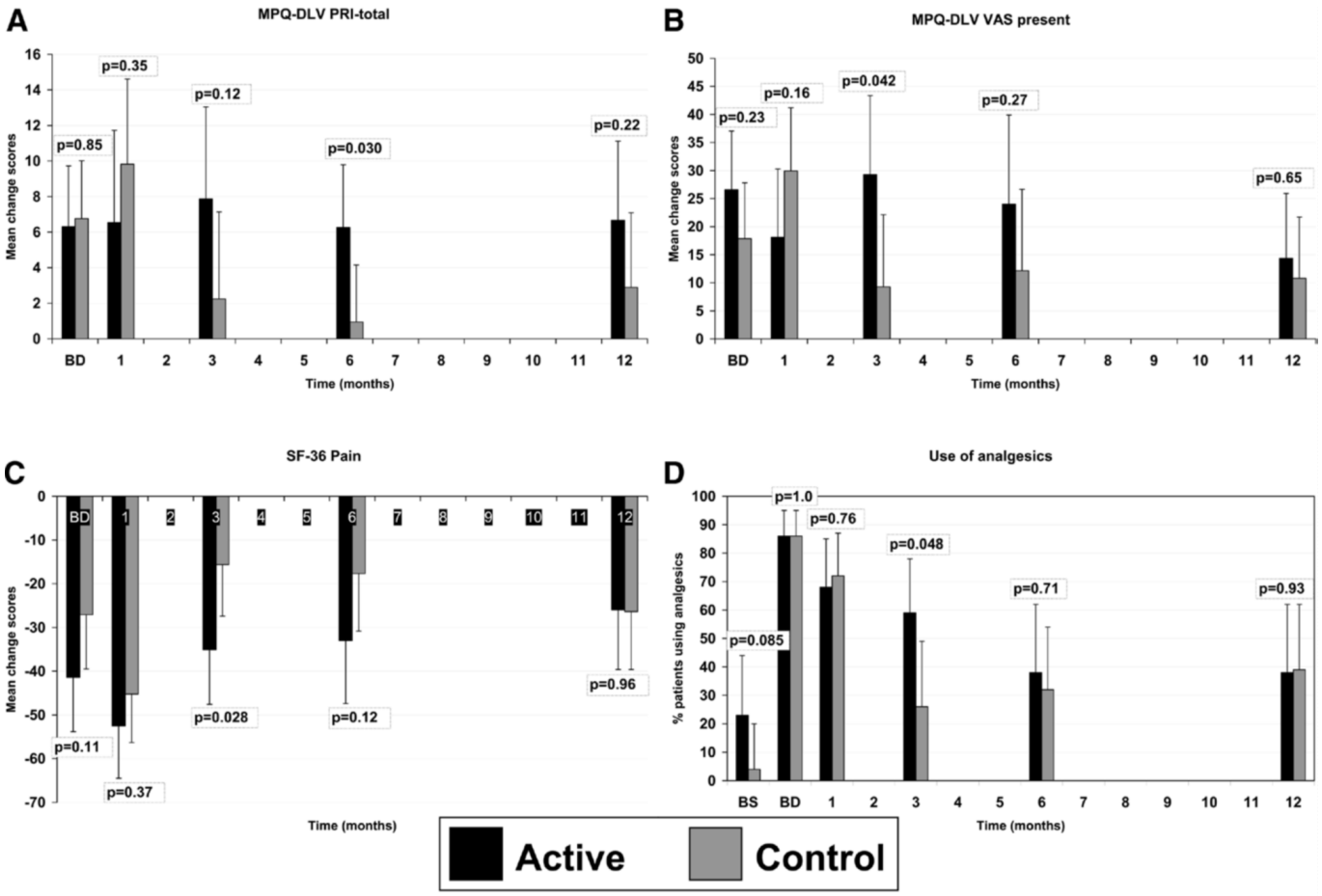


FIGURE 5. Sensation of pain and use of analgesics in resectable lung cancer patients treated in a postthoracotomy rehabilitation program (actives) or receiving usual care (controls). *A*, MPQ-DLV PRI total. *B*, MPQ-DLV VAS present. *C*, SF-36 pain. *D*, use of analgesics. MPQ-DLV PRI total, total pain rating index of the Dutch version of the McGill Pain Questionnaire; MPQ-DLV VAS, Dutch version of the McGill Pain Questionnaire Visual Analogue Scale; SF-36, Short Form health survey; BS, before surgery; BD, before discharge. Error bars represent 95% confidence intervals.

of nonattendance at training sessions and resigned more often from further training than the controls did. The very low number of repeated 6MWD tests in the active group also reflected the high dropout rate in the subgroup of patients receiving ACT.

Video-Assisted Thoracoscopic Surgery

Inclusion of patients in this study was terminated prematurely before the planned number was reached. This was caused by the introduction of VATS by the end of 2008. The majority of patients from then on were operated by this approach and accrual decreased. For patients suffering less acute pain after VATS, rehabilitation and particularly physical exercise training was more likely to be feasible. Furthermore, VATS is relatively more often applied in smaller tumors requiring no ACT. Further studies on immediate postoperative rehabilitation should be performed in a more homogenous group suffering less pain and not treated with ACT, for instance in patients with lower stages of lung cancer treated with VATS.

Limitations

We expected to find an improvement of respiratory symptoms and QOL with rehabilitation analogous to the results of rehabilitation for patients with chronic obstructive lung diseases. The tool we used to measure improvements in QOL (SGRQ) was developed for patients with chronic obstructive pulmonary diseases. Premature closure of the study resulted in a lower number of patients than originally calculated, thereby decreasing the power of the study. Furthermore, there were many dropouts caused by premature termination of participation particularly because of pain, and the burden of ACT, and its toxicity. Nevertheless, we do consider our study population as representative of the majority of patients receiving lung cancer surgery in community hospitals, and patient selection was diminished by preoperative

randomization. Despite serious limitations, significant differences were observed between study groups regarding exercise tolerance, pain sensation, and QOL.

CONCLUSION

The multidisciplinary rehabilitation program assessed in this study did not result in improved disease-specific QOL after thoracotomy. Rehabilitating patients experienced more physical limitations compared with controls at 3 months because of early start of rehabilitation after thoracotomy, especially in ACT patients. However, we observed a significant improvement of exercise tolerance in the active group 3 months after discharge. This benefit was at the expense of significant more pain despite programmed pain management by experienced specialists. An accelerated return to higher exercise levels without improving QOL does not outweigh increased and prolonged pain sensation. We suggest starting rehabilitation programs for patients with lung cancer not before 3 to 4 months after thoracotomy.

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