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RETURNING TO WORK AFTER BREAST CANCER SURGERY: A RANDOMISED CONTROLLED TRIAL ON THE EFFECT OF PAIN NEUROSCIENCE EDUCATION

An De Groef, Phd[1,2,3*], Elien Van der Gucht, Phd[1,2,3*], Nele Devoogdt, PhD[2,4], Ann Smeets, PhD[5], Koen Bernar, Msc[6], Bart Morlion, PhD[6,7], Lode Godderis, PhD[8,9], Tessa De Vrieze, PhD[1,2], Steffen Fieuws, PhD[10], Mira Meeus, PhD[1,3,11], Lore Dams, PhD[1,2,3]

*shared first authors

[1]University of Antwerp, Faculty of Medicine and Health Sciences, Department of Rehabilitation Sciences and Physiotherapy, MOVANT, Antwerp, Belgium
[2]KU Leuven - University of Leuven, Department of Rehabilitation Sciences, Leuven, Belgium
[3]Pain In Motion International research group, www.paininmotion.be
[4]Department of Vascular Surgery and Department of Physical Medicine and Rehabilitation, Center for Lymphedema, UZ Leuven - University Hospitals Leuven, Leuven, Belgium.
[5]Department of Surgical Oncology, University Hospitals Leuven, Leuven, Belgium
[6]The Leuven Centre for Algology and Pain Management, University Hospitals Leuven, Leuven, Belgium
[7]Department of Cardiovascular Sciences, Section Anaesthesiology and Algology, KU Leuven - University of Leuven, Leuven, Belgium
[8]Centre for Environment and Health, University of Leuven, Leuven, Belgium
[9]IDEWE, External Service for Prevention and Protection at Work, Leuven, Belgium
[10]Interuniversity Center for Biostatistics and Statistical Bioinformatics, University of Leuven and University of Hasselt, Leuven, Belgium.
[11]Ghent University, Faculty of Medicine and Health Sciences, Department of Rehabilitation Sciences and Physiotherapy, Ghent, Belgium

Corresponding author
An De Groef
Department of Rehabilitation Sciences and Physiotherapy
KU Leuven
ON4 – Herestraat 49 – box 1510
3000 Leuven
an.degroef@uantwerpen.be

ABSTRACT

Purpose: The aim of this study was to investigate the effect of pain neuroscience education compared to biomedical pain education after breast cancer surgery on (1) work status, (2) time until work resumption and (3) change in return-to-work expectations up to 18 months post-surgery.

Methods: Participants were randomly assigned to either pain neuroscience education (intervention group) or biomedical pain education (control group) in addition to a standard physical therapy program after surgery for breast cancer. The first four months following surgery, one to two physiotherapy sessions and three educational sessions were scheduled. After, two educational sessions and two physiotherapy sessions were held at six and eight months postoperatively. All outcomes were assessed at four, six, eight, 12 and 18 months postoperatively.

Results: At 12 months, in the intervention group, 71% of the women returned to work compared to 53% in the control group (18 percentage points difference, 95%CI:-0.1 to 35;p=0.07). At 18 months, the differences decreased to 9 percentage points, 95%CI:-26 to 7;p=0.35). Neither time until work resumption (p=0.46) nor change in estimation of own ability to return to work up to 18 months postoperatively (p=0.21) significantly differed between both groups.

Conclusion: No significant differences were found regarding return to work outcomes between women receiving pain neuroscience education versus biomedical pain education after breast cancer surgery. Further research is warranted to explore the potential role of pain neuroscience education in return-to-work interventions following breast cancer surgery.

Key Words: rehabilitation, breast neoplasms, pain, return to work

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women worldwide and its incidence is increasing [1]. Although improved treatment options have resulted in an increase in survival, 90% of survivors experience persistent physical, mental and social sequelae [2-5], which in turn can negatively impact resumption of functional activities and life roles [2, 6-9].

Breast cancer survivors have indeed higher unemployment and diminished work ability compared to healthy controls [8, 10]. This puts an economic burden on both patients and society, since almost half of the survivors are younger than 65 years old [10]. At the individual level, long-term work disability is related to financial difficulties, future unemployment, psychological problems and social exclusion.[11] Therefore, it is important to prevent long-term absenteeism and encourage work resumption.

Various factors influencing work resumption have been identified, both modifiable and non-modifiable.[12] The former group is of primary interest, as these can potentially guide interventions aimed at facilitating return to work. One of these modifiable factors is *pain*, a common and long-lasting reported side effect of breast cancer treatment.[13] Today, up to 72% of breast cancer survivors still report pain persisting at one year after surgery.[14] Pain is a complex biopsychosocial experience, not only influenced by structural damage, but also by various psychosocial factors.[15] In addition, pain is a strong predictor for long-term absenteeism.[16] An important way in which pain influences return to work is through pain-related beliefs/perceptions, including kinesiophobia (i.e. fear of movement) and pain catastrophizing.[17] In addition, return to work expectations have been shown to predict return to work outcomes and successful work functioning.[17, 18] For the above reasons, it might be an interesting approach to explore the effect of biopsychosocial pain interventions on work resumption after breast cancer.

Pain neuroscience education (PNE) is one of those applications of the **biopsychosocial** model of pain, which considers an array of many psychosocial contributing factors in addition to explaining pain from a strict biomedical or structural perspective.[19-23] The **biomedical** vision on pain may indirectly hamper functioning, viewing pain as a sign of tissue damage.[24] This view might be true in the acute phase, as pain then serves a protective role, but the contributing role of psychosocial factors increases with pain persistence. PNE explains the neurobiology and neurophysiological concepts of pain within the nervous system, so patients understand how their pain is produced. They learn that pain is not always a true representation of the actual state of the tissues, but that it is the nervous system's interpretation of the threat of their injury, which in turn is subject to various psychological factors (e.g. fear avoidance, pain catastrophizing, expectations, cognitions and beliefs).[25] Once people correct their erroneous pain-related beliefs/perceptions and perceive pain as less threatening, they may be more likely to engage in activities previously avoided because of pain, including work-related activities.

Several systematic reviews indicate that PNE is effective in populations with persistent non-cancer pain at, among others, improving pain ratings, pain knowledge, disability, pain catastrophizing, kinesiophobia, attitudes regarding pain, physical movement and work status.[25-28] However, the positive results should be viewed in light of the heterogeneous nature of the studies (e.g. education-only approaches versus PNE combined with movement-based therapy, type of control intervention, follow-up period, different outcome measures and diagnosis). To our knowledge, only two studies have looked at the effect of PNE compared to biomedical pain education (BPE) in a breast cancer only

population.[29, 30] Both found inconclusive results regarding pain and did not report on the effect on work resumption.

Consequently, the key research question of this study was whether PNE would result in improved return to work compared with BPE, both in addition to a standard physiotherapy program. More specifically, we evaluated (1) *work status at 12 and 18 months postoperatively,* (2) *time until work resumption* and (3) *return to work expectations*.

METHODS

Study design

The present manuscript reports on secondary analyses of the EduCan Trial.[31] The EduCan trial was a parallel, two-arm randomized controlled trial, approved by the Ethical Committee of the University Hospitals Leuven (s60702) and registered at ClinicalTrials.gov (NCT03351075). A detailed description of the protocol has been published elsewhere.[31] Findings were reported in accordance with the CONsolidated Standards of Reporting Trials (CONSORT) guidelines.[32, 33]

Participants

Recruitment took place at the Multidisciplinary Breast Center of the University Hospitals Leuven campus Gasthuisberg (Belgium) between November 2017 and March 2020. Potential participants signed informed consent prior to inclusion. Inclusion criteria were: diagnosed with histologically confirmed invasive or non-invasive primary breast cancer, scheduled for one of the following surgeries: mastectomy including either a sentinel node biopsy or axillary lymph node dissection (with or without breast reconstruction) or breast conserving surgery including axillary lymph node dissection, no active metastasis, female, aged 18 years or older, could comply with the study protocol, comprehended the Dutch language (reading, listening, writing and speaking).

Randomization and masking

After enrollment (by L.D. and E.V.d.G.), participants were randomly assigned (1:1) to the intervention (PNE) or control group (BPE). This computer-generated randomization was performed by an independent coworker (T.D.V.) using permuted blocks (size=4). Participants, assessors, physical therapists and those who interpreted the data were blind to group allocation. An independent statistician (S.F.) of the Center for Biostatistics of KU Leuven analyzed the data to ensure additional blinding of the research team.

Interventions

All interventions took place at the Department of Physical Medicine and Rehabilitation of the University Hospitals Leuven campus Gasthuisberg (Belgium). The interventions are described in detail in the study protocol. [31]

In summary, all participants attended a **standard physical therapy program** (1-2 times per week, one-on-one 30', 12 weeks) that included manual techniques, specific exercises and general exercise advice to increase physical activity level (intensive phase). At 6, 8 and 12 months after surgery, a single follow-up session was organized for everyone (maintenance phase). In addition, all participants received 6 **educational sessions**; 3 sessions in the intensive phase (starting 1-3 weeks after surgery) and two sessions in the maintenance phase at 6, 8 and 12 months after surgery. In the control group, the learning goal consisted of gaining biomedically oriented knowledge about pain after breast cancer treatment. Participants received information about the side effects of these different treatment modalities, the role of different structures and injured versus healthy tissue in acute and persistent pain. In the intervention group, the learning goal consisted of gaining biopsychosocial oriented knowledge about pain after breast cancer treatment. The physiological and psychological processes involved in the pain experience were explained to help participants reconceptualize pain. Participants received information about the differences between acute and persistent pain, pain as a product of

the brain, how pain becomes persistent, and potential pain sustaining factors (e.g. emotions, stress, pain cognitions and behavior).

Outcomes and measurements

The outcomes of interest for this secondary analysis were threefold:

1. *Work status at 12 and 18 months postoperatively, i.e. the* proportion of women working at 12 and 18 months after surgery, respectively

2. *Time until work resumption* (time between surgery and return to work)

The information for the first two outcomes was obtained by a questionnaire developed by the research team. This included questions regarding the moment when participants had stopped working because of breast cancer diagnosis, whether or not they had returned to work (yes/no, independent of whether this was full- or part-time) and in case of the latter the date of work resumption. In addition, they had to indicate whether they were working according to a part-time or full-time work schedule. The participants filled out this questionnaire at four (A4), six (A6), eight (A8), 12 (A12) and 18 (A18) months after surgery.

3. *Return to work expectations* (estimation of own ability to return to work)

The third outcome was evaluated with one item on the Quickscan questionnaire (a questionnaire assessing return to work needs and predicts risks of long-term sick leave).[34] The item on return to work expectations was used for this outcome and covered the following question: “Do you think you can restart your normal work within a period of four weeks, without limitations due to your illness?” which was rated on a 6-point Likert-scale (0=’certainly not’ to 5=’most certainly’). At four (A4), six (A6), eight (A8), 12 (A12) and 18 (A18) months after surgery, participants completed the questions at home, either written or electronically.

As baseline patient characteristics, patient-related outcomes (age, body mass index, employment status, educational level) and cancer-related outcomes (type of breast surgery, tumor size, lymph node stage, cancer treatments) are given. In addition, pain intensity (with Visual Analogue Scale, 0 no pain to 100 worst pain) and pain-related disability (with Pain Disability Index, 0 no disability to 70 highest disability). [35]

Statistical analysis

Sample size calculation was based on the primary outcome of the EduCan trial (i.e. pain-related disability measured with the Pain Disability Index).[31] Results of the primary analysis are reported elsewhere [36].

Statistical analyses were according to the intention-to-treat principle. *Work status at 12 and 18 months postoperatively* was compared using a Fisher exact test. Note that the work status could not be derived from the Kaplan-Meier curve since work status is reversible. In addition, the complement of Kaplan-Meier estimates were used to visualize the univariate relationship between the educational interventions and *time until work resumption*. Differences were tested using the log-rank test. Only the time between surgery and the first moment of return to work was evaluated. Whether or not a subject kept working after work resumption was irrelevant for this particular analysis (i.e. time until work resumption) and subjects who never stopped working were not included in this analysis. For subjects who never stopped working, the interval between the date of stop working and the surgery

was not defined and they were not included in the analysis of this outcome. A linear model for longitudinal measures with an unstructured covariance matrix was used to compare the *mean return to work expectation* (based on the Quickscan) between both groups, at each time point separately, as well as average over the four time points. All analyses were performed using SAS software, version 9.4 of the SAS System for Windows.

RESULTS

Between November 16, 2017 and February 28, 2020, 184 participants were included in the EduCan trial. One hundred fifteen participants (62.5%) were working at time of diagnosis (IG=58; CG=57), among which four planned to retire in the near future. From the resulting 111 participants (IG=56; CG=55) included in this study, five never stopped working throughout the entire treatment period (IG=2; CG=3). A participant flowchart is shown in Figure 1**.** Patient characteristics are portrayed in Table 1.

[insert Figure 1 here]

Table 1 Patient characteristics (according to treatment allocation) (N=111).

	Intervention group n=56	**Control group** n=55
Age (years)	49.6 (7.6) / 50.5 (10.5)	48.8 (7.3) / 50.2 (9.0)
Body mass index (kg/m²)	24.8 (4.2) / 24.0 (5.0)	25.5 (5.6) / 24.7 (6.0)
Employment status		
Student	0 (0.0)	1 (1.8)
Employee	47 (83.9)	44 (80.0)
Self-employed	6 (10.7)	12 (21.8)
Unemployed	2 (3.6)	0 (0.0)
Looking for a job	0 (0.0)	0 (0.0)
Educational level		
Primary education or no diploma	1 (1.8)	3 (5.6)
Lower secondary education	1 (1.8)	0 (0.0)
Upper secondary education	14 (25.0)	12 (22.2)
Higher education: professional bachelor	20 (35.7)	23 (42.6)
Higher education: academic bachelor or master	20 (35.7)	16 (29.6)
Pain (Visual Analogue Scale) 0-100		
Preoperatively	12.7 (15.8) / 9.5 (19.0)	15.9 (21.8) / 8 (24.0)
One week postoperatively	32.4 (21.8) / 28.5 (29.0)	34.8 (21.0) / 33.0 (27.0)
Four months postoperatively	23.2 (22.2) / 16.0 (32.0)	24.7 (20.9) / 24.0 (43.5)
12 months postoperatively	20.5 (19.4) / 15.0 (24.0)	27.2 (23.6) / 25.5 (36.8)
18 months postoperatively	17.8 (20.1) / 15 (22)	25.2 (25.4)/ 16.0 (45)
Pain-related disability (Pain Disability Index) 0-70		
Preoperatively	4.4 (9.3) / 0 (3)	4.4 (7.1) / 0 (7.5)
One week postoperatively	23.3 (15.9) / 23 (27)	24.7 (15.1) / 25 (24)
Four months postoperatively	8.8 (12.1) / 3 (16)	9.7 (11.5) / 5.5 (12.5)
12 months postoperatively	6.5 (11.3) / 2 (7.5)	12.4 (15.1) / 6 (19)
18 months postoperatively	7.4 (10.7) / 3 (10)	9.6 (11.1) / 5 (16)
Type of breast surgery		
Mastectomy		
Sentinel node biopsy	21 (37.5)	24 (43.6)
Axillary lymph node dissection	27 (48.2)	22 (40.0)
Tissue expander	1 (1.8)	1 (1.8)
Immediate reconstruction	5 (8.9)	3 (5.5)
Breast conserving		
Axillary lymph node dissection	2 (3.6)	5 (9.1)
Tumor size		
pT0	6 (10.7)	6 (10.9)
pTis	5 (8.9)	5 (9.1)
pT1	19 (33.9)	16 (29.1)
pT2	18 (32.1)	21 (38.2)
pT3	6 (10.7)	7 (12.7)
pT4	2 (3.6)	0 (0.0)
Lymph node stage		
pNX	0 (0.0)	0 (0.0)
pN0	29 (51.8)	31 (56.4)

pN1	21 (37.5)	16 (29.1)
pN2	5 (8.9)	5 (9.1)
pN3	1 (1.8)	3 (5.5)
Treatments		
Neo-adjuvant chemotherapy	3 (5.4)	0 (0.0)
Radiotherapy	43 (76.8)	40 (72.7)
Chemotherapy	37 (66.1)	36 (65.5)
Hormone therapy	39 (69.6)	38 (69.1)
Target therapy/immunotherapy	17 (30.4)	13 (23.6)

n=sample size
Data are mean (standard deviation) / median (interquartile range), or numbers (percentages)

The percentage of women working at 12 months postoperatively was 71% (95% CI 0.57 to 0.82) in the group receiving PNE and 53% (95% CI 0.39 to 0.67) in the BPE group. Difference in proportion was 18 percentage points (95% CI -0.36 to 0.01) (p=0.07). At 18 months postoperatively, the difference in proportion decreased to 9 percentage points (95% CI -0.26 to 0.078) (p=0.352) with 81% (95% CI 0.68 to 0.91) of women working in the group receiving PNE and 72% (95%CI 0.56 to 0.84) in the group receiving BPE.

Time until work resumption is portrayed in Figure 2. Among those that had returned to work within 18 months after surgery, median time between surgery and return to work did not differ significantly between the two groups (IG=9.9 months; CG=10.1 months) (p=0.46).

[Insert Figure 2 here]

Estimation of own ability to return to work (return to work expectations) did neither differ significantly between the two groups at the separate time points, nor after comparing the overall difference (irrespective of time point) (p=0.21). Mean scores (averaged over the timepoints) for IG and CG were 2.33 (95% CI 1.92-2.74) and 1.95 (95% CI 1.53-2.37), respectively.

DISCUSSION

Because pain is a frequently reported side effect of breast cancer treatments and is known to impact return to work, it was hypothesized that work resumption would be more successful among breast cancer patients who received PNE versus those assigned to BPE. Despite the outcomes being in favor of the PNE group, none of the results were statistically significant.

To our knowledge, no data have shown the effectiveness of PNE on work resumption after breast cancer surgery. A study in chronic low back pain patients showed that the PNE group was twice as likely as the control group to have a greater improvement in work status 12 months post intervention (OR=2.4; 95%CI 0.9-6.6).[37] Apart from the population, a difference with our study was that they had only included patients with persistent pain, whereas our sample was a mix of people with and without (persistent) pain. In addition, pain levels in our study sample receiving PNE post-surgery were lower (mean of 31.8/100) compared to baseline pain levels in the sample with chronic low back pain receiving PNE (mean of 66/100).

Despite the lack of statistically significant differences between the PNE and BPE group, one notable observation was that when both groups were combined, the proportion of women working at one year after surgery exceeded the reported prevalence one year after breast cancer diagnosis reported in a large-scale study by a Belgian health insurance fund.[38] They reported that 35% of female breast cancer patients had resumed their work one year and 67% two years after diagnosis.[38] An important side note however, is that time until work resumption in the study by the Belgian health insurance fund was calculated using the time between *diagnosis* and work resumption, whereas we had used the time between *surgery* and work resumption for this calculation. As a result, their one-year window does not exactly correspond to ours, as neo-adjuvant chemotherapy (after diagnosis and before surgery) may have led to an underestimation on our part. However, even after this correction, more women in our study were found to be working at that time. Additionally, our numbers may be an overestimation because of the research setting. All participants engaged in an intensive physiotherapy program at a specialized center with dedicated physical therapists. This attention given to the participants may have influenced our results. This finding could provide an argument for further investigation of the effectiveness of combining physical therapy with PNE after surgery for breast cancer.

A *first* possible explanation of the lack of statistically significant findings is that our sample consisted of people with and without pain. It is questionable whether extensively educating people without pain on pain is meaningful. Possibly, people who were in pain may have returned to work despite being in pain, and other who were not in pain may have decided not to for other reasons. Unfortunately, data on the reason not returning to work is not available in our study. Apart from pain (and arm morbidity, which was dealt with during the physiotherapy sessions), one's decision to return to work can depend on various other modifiable and non-modifiable factors. For example, life satisfaction, better role-functioning, self- and environment-motivation and social support positively influence return to work.[39, 40] Other comorbidities and symptoms (such as fatigue and depression) and barriers at the workplace (including manual work, stressful job and lack of support from colleagues) can hinder work ability and resumption.[12, 39, 41, 42] The importance of these factors (including pain) in work resumption may vary from one individual to another, as no two persons, nor two jobs, are identical. Therefore, a more extensive, individually tailored intervention may be needed, focusing on both personal factors and those related to the work environment.

A *second* reason for the overall lack of difference in results between both groups could be the fact that the PNE intervention was not powerful enough to create lasting changes. Living in a biomedically focused world, the group receiving PNE might have needed a more intensive approach in order to shift their vision on pain and result in measurable changes, while the BPE group was being taught on widely accepted concepts. We do not know to which extent people had implemented the educational knowledge, which makes it difficult to make assumptions about the actual effect of PNE. It could have been possible that PNE had induced a progress through the stages of behavior change, but not yet to the extent that this progression had influenced return to work outcomes.

This research was **limited** in several ways. *First*, our study may have been underpowered to address the research questions due to a lack of sample size calculation for this secondary aim. A *second* limitation was the study design. Randomized controlled trials may not be the optimal way to evaluate complicated interventions like PNE, since they tend to interact with individual factors for which cannot be controlled. *Furthermore*, sampling bias may have comprised external validity, since patients' willingness to participate may have been related to characteristics affecting the study, resulting in a non-representative sample.

A *first* key **strength** of the present study was that the study participants, physiotherapists and people interpreting the results were blinded to group allocation, which minimized detection and performance bias. *Secondly*, an intention-to-treat analysis was carried out, which lowered the risk of bias induced by comparing groups that differed in prognostic variables caused by dropouts. *Thirdly*, the study design, being both a limitation and a strength, allowed for establishment of causal relationships and ensured excellent internal validity.

As stated in the introduction, we hypothesized that once people correct their pain-related beliefs and perceive pain as less threatening, they will be more likely to engage in activities they had previously avoided because of pain, including work-related activities. However, we did not include an outcome measure to evaluate the patient's pain-related perceptions, so we were unable to determine the interaction between these perceptions and the overt behavioral response (return to work parameters). Therefore, future research on the effect of PNE on work resumption after breast cancer should include outcome measures to assess possible change in factors preceding behavior change. Moreover, further studies could be undertaken to compare the characteristics (including their level of pain-related disability) of the patients in the PNE group that had returned to work to the ones who had not. By investigating the factors correlated with work resumption, responders and non-responders to PNE can be defined. At last, in the present study, all participants were given education on pain in the post-surgical phase, regardless of whether they had pain or not. The idea behind this was that pain can fluctuate over the cancer treatment course and although not in pain at the moment of the education, the understanding of pain may help them in a later stage when pain does occur. It should be further studied whether this approach effectively leads to changes in how a person thinks about pain.

This study was the first to compare the effects of two approaches to pain (PNE versus BPE) on return to work after surgery for breast cancer. While none of differences between the groups were statistically significant, the proportion of women working one year and 18 months postoperatively was 18% and 9% higher, respectively, for those who had received PNE. Although further research is warranted to confirm this finding as being clinically relevant, this study could be a first step toward the potential application of pain neuroscience education in return-to-work interventions following breast cancer surgery.

STATEMENTS & DECLARATIONS

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Competing Interests

All authors have completed the ICMJE uniform disclosure form (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. Bart Morlio has served as a consultant for Reckitt-Benekiser, Grunenthal, Pfizer, GSK, and as a speaker for Grunenthal, Krka, GSK Belgium.

Author Contributions

An De Groef, Nele Devoogdt, Ann Smeets, Bart Morlion, Lode Godderis and Mira Meeus conceived and designed the study and analyses;

Elien Van der Gucht, Lore Dams and Koen Bernar collected the data;

An De Groef, Elien Van der Gucht, Steffen Fieuws and Lore Dams performed the analyses;

An De Groef, Elien Van der Gucht and Lore Dams wrote the first version of the paper.

All co-authors reviewed and approved the final manuscript.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the Ethical Committee of the University Hospitals Leuven (s60702)

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Consent to Publish

n/a

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FIGURE LEGENDS

Figure 1. Flowchart of the participants in the intervention and control group. A1=postoperative assessment; A4/12/18=assessment at four, 12 and 18 months after surgery.

Figure 2. Complement of Kaplan-Meier curve describing time between surgery and work resumption.