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Second operation is not related to psychological outcome in breast cancer patients

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Abstract

To examine the effect of multiple surgical treatments on psychological outcomes in women with early stage breast cancer (BC) in a prospective follow-up study. Questionnaires for depressive symptoms (CES-D), fatigue (FAS), anxiety (STAI-State), physical health (WHOQOL-100), psychological health (WHOQOL-100), and overall quality of life and general health (WHOQOL-100) were completed before diagnosis (Time-1) and 1 (Time-2), 3 (Time-3), 6 (Time-4), and 12 (Time-5) months after the last surgical treatment. From the 217 participating women with early stage BC, 78 (35.9%) needed an additional surgical treatment. Using general linear model (repeated measures) psychosocial outcomes over time were investigated for the breast conserving therapy and mastectomy group, accounting for type of surgery, disease stage, and hormonal therapy. Psychological outcomes did not significantly change over time, with the exception of anxiety \[\text{Wilks’ Lambda} = .72, F(4,86) = 8.55, p<.0001, \text{partial eta squared} = .29\]. On average, women with one and women with two surgical treatments did not differ on any outcome measure. No interaction effects were found, indicating that changes in outcomes over time were the same for both groups. Women who had a repeat surgical treatment did not score differently on psychological outcome measures compared with women who were treated ‘efficiently’.

Key terms: breast neoplasm, mastectomy, breast-conserving therapy, reexcisions, second surgery
Introduction

Breast cancer (BC) is the most common malignancy in women \(^1\) and the most frequent cause of death in women aged 35 to 60 years in Europe \(^2\). In the Netherlands, one in every nine women will develop breast cancer before the age of 85 \(^3\). The prevalence of BC increases with age from 3.4\% at age 50-69 to 6\% of women older than 70 \(^4\).

Surgical treatment is usually the initial treatment for invasive early stage BC. Surgical options include breast conserving therapy (i.e., lumpectomy and a sentinel node procedure or axillary lymph node dissection followed by radiotherapy; BCT) or mastectomy (i.e., removal of the breast and sentinel node procedure or axillary lymph node dissection; MTC). Although physicians strive to treat women as effectively as possible, i.e. with a minimum of surgical treatments, in practice this is not always possible. For instance, some of the women with early stage BC who initially received BCT appear to need additional surgery when the margin of tissue around the tumor is not cancer-free. It is estimated that of patients undergoing BCT 30 to 60\% will require a re-excision for residual tissue \(^5\). The majority of studies examining the effects of surgical treatment in oncology have focused on the effects of type of surgery or adjuvant therapy on clinical \(^6, 7\) or psychosocial outcomes \(^8-14\). In general, no differences are found when comparing the long-term survival rate in women with BCT and MTC \(^6, 7\). However, the incidence of local recurrences is higher in BCT \(^7\). Regarding, for instance, general quality of life, studies do not report differences between surgical options \(^15\). However, women with BCT report fewer difficulties with body image than women with MTC \(^8, 16\). Recently, several studies have focused on determining those clinical factors which may be associated with re-excision after BCT \(^5, 17-20\). Tumor size \(^17, 18, 20\), tumor type \(^18\), multifocality \(^17\), and the presence of an in situ component \(^17, 20\), for instance, have been proposed as risk factors for at least one repeat surgical treatment. However, results are rather inconsistent and definite conclusions cannot yet be drawn. To the best of our knowledge, it remains unclear
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whether there is a relationship between the number of surgical treatments women receive after BC diagnosis and psychological outcomes. Therefore, the aim of this prospective follow-up study was to examine the relationship between second surgery and psychological outcomes (i.e., state anxiety, fatigue, depressive symptoms, and aspects of quality of life). We hypothesize that both groups will improve over time with regard to the selected psychological outcomes, but that women with re-excisions will temporarily have more negative scores. We also expect that differences between the groups will not be significant at 12-months after surgical treatment.

Methods

Women with a palpable lump in the breast or an abnormality on a screening mammography were referred by their general practitioner to the Department of Surgery of the outpatient clinics of the St. Elisabeth Hospital (Tilburg), the Maasland Hospital (Sittard), or the Jeroen Bosch Hospital (Den Bosch) in The Netherlands. The present study is part of a larger study that focuses on the role of personality on the quality of life in women with early stage BC who could choose between breast conserving and ablative surgical treatment. The inclusion of patients took place from September 2002 until September 2006. From the 799 eligible women, 609 (76.2%) completed the first set of questionnaires before they visited the surgeon or radiologist, i.e. before the diagnosis, benign or malignant, was known (Time-1). In this group (N = 609), 225 appeared to have early stage BC; the others had a benign breast problem (BBP).

The main reasons for not participating were the length of questionnaires and the amount of stress at the first visit to the hospital. Women with a history of abnormalities in the breast, benign or malignant, or a breast tumor that was too large (>5 centimeter) for BCT, were excluded from the study. Participants had to be able to read and write in Dutch.
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After the baseline measurement before diagnosis (Time-1), the participants were divided in two groups: women with early stage breast cancer (BC group) and women with benign breast problems (BBP group). Thereafter, women completed questionnaires at 1, (Time-2), 3 (Time-3), 6 (Time-4), and 12 (Time-5) months after the last surgical treatment (BC). Only the women with a BC diagnosis participated in the present study. The time points were chosen in such a way that the follow-up measures would not interfere with the time of the treatment modalities. Questionnaires were filled in at home and returned in a stamped addressed envelope. Participation in the study was not known to the surgeon in attendance and, therefore, could not affect treatment and clinical follow-up. The local ethics committee approved the study. All the participants gave written informed consent.

Measures

Questionnaires assessing socio-demographic factors (marital status, children, paid work, and education level) and psychological factors (depressive symptoms, fatigue, state anxiety, quality of life) were completed at Time-1. At the other time points women again completed questionnaires on psychological factors.

The Center for Epidemiological Studies- Depression Scale (CES-D) \(^{21}\) is a 20-item self-report scale measuring the presence and degree of depressive symptoms over the past week. The rating scale ranges from 0 (seldom or never) to 3 (almost always). Scores can range from 0 to 60. A score of 16 or higher is indicative of experiencing depressive symptoms. The CES-D has been established as a valid and reliable measure of depressive symptoms in BC patients \(^{22}\). Reliability and criterion validity are good \(^{23,24}\).

The Fatigue Assessment Scale (FAS) \(^{25}\) is a 10-item questionnaire assessing perceived fatigue and exhaustion. The response scale is a 5-point rating scale ranging from 1 (never) to 5 (always). Scores on the FAS range from 10 to 50. A score of 22 or higher represents being...
tired, indicating that patients feel substantially fatigued and that this affects daily life. The psychometric properties are good.

The STAI consists of two 20-item scales for measuring state anxiety and trait anxiety. In the present study, only the State Anxiety scale was used. This scale assesses how persons feel at a particular moment in time. The STAI State scale has a 4-point rating scale ranging from 1 (almost never) to 4 (almost always). A score of 38 or higher represents being anxious. The Dutch version of the STAI-State scale has good reliability and validity.

The World Health Organization Quality of Life assessment instrument (WHOQOL-100) Dutch version, is a cross-culturally developed generic multi-dimensional quality of life (QOL) measure. This instrument covers 24 specific facets of QOL, assessed by 96 questions, and one General Health and Overall Quality of Life facet. In the present study, only the Overall Quality of Life and General Health facet, the Physical Health domain, and the Psychological Health domain were used. In the general population, the mean values of these facets are 13.3 (SD = 0.8), 13.3 (SD = 0.9), 13.9 (SD = 0.5), respectively. A high facet score indicates good QOL. Reliability and validity are adequate and sensitivity is high.

**Statistical procedure**

Student t-tests and Chi-square tests were used to examine the potential differences between participants and non-participants. To examine the influence across time of the number of surgical treatments on depressive symptoms, state anxiety, overall quality of life and general health, physical health, and psychological health, multivariate analysis of variance (MANOVA) with repeated measures were used. Partial eta squared (effect size) was derived from the general linear model. An effect size between 0.01 and 0.06 is considered as a small effect, while effect sizes between 0.06 and 0.13 and greater than 0.14 are considered as
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moderate and strong effect sizes, respectively\textsuperscript{35}. Multiple post hoc comparisons were corrected with the Bonferroni method. Subsequently, multivariate analysis of covariance (MANCOVA) with repeated measures was used, in which type of surgery (BCT/MTC), disease stage, and hormone therapy (yes/no) were used as covariates as women with one and two surgical treatments differed on these patient characteristics (see Table 1). A p-value < .05 was considered to be statistically significant. In the text mean scores and standard deviations are provided as follows (M ± SD). All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Chicago, IL, USA; version 14.0).

Results

At baseline, 225 women completed psychological outcome questionnaires. Figure 1 presents a flow chart of this study. Participants did not differ from non-participants with regard to sociodemographic (i.e., age, partner status, job status, educational level) and clinical (i.e., chemotherapy, radiotherapy, hormone therapy) variables. Eight persons were removed from the analyses, because they did not have surgery (n = 4) or had more than two surgical treatments (n = 4). From the 217 participating women, 77 (35.5%) needed one repeat surgical treatment. Eight persons (10.4%) received a second operation due to complications. Twenty-two women (28.6%) were converted from BCT to MTC in a second surgery. No differences were found between the women who received one or two surgical treatments with regard to sociodemographic variables. However, women differed on the clinical characteristics: hormone therapy (yes/no), type of surgery (BCT/MTC), and disease stage (stage 0 / I / IIa / IIb) (see Table 1).

* Insert Figure 1 and Table 1 about here *
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Concerning fatigue, women with one or two surgical treatments did not score differently on symptoms of fatigue \([F(1,105)=.01, p = .92]\). However, an effect for time was found (See Table 2). Mean scores of fatigue scores at Time-1 (20.03 ± 7.36) were statistically lower than scores at Time-2 (22.95 ± 7.52, \(p<.0001\)) and Time-3 (22.94 ± 8.09, \(p<.0001\)). In addition, mean fatigue scores at Time-5 (20.57 ± 7.11) were significantly lower than mean scores at Time-2 (\(p=.001\)) and Time-3 (\(p<.0001\)). No relationship was found between time and number of surgical treatments. After controlling for clinical factors, the effect for time did not remain significant [Wilks’ Lambda = .97, \(F(4,99) = .89, p=.474\), partial eta squared = .04].

Women with one or two surgical treatments did not differ on symptoms of anxiety \([F(1,92) = .013, p = .91]\). However, an effect for time was found, indicating a decrease in symptoms of anxiety over time (see Figure 2). Mean scores of state anxiety scores at Time-1 were statistically different from scores at subsequent time points (\(p<.0001\)). In addition, scores on Time-2 (37.00 ± 11.26) were different from scores on Time-5 (34.38 ± 10.63, \(p = .047\)). No relationship was found between time and number of surgical treatment. After controlling for possible confounders, the effect for time remained significant [Wilks’ Lambda = .72, \(F(4,86) = 8.55, p<.0001\), partial eta squared = .29].

* Insert figure 2 about here *

Women with one and women with two surgical treatments did not differ on symptoms of depressive symptoms \([F(1,109)=.14, p=.71\), partial eta squared = .001, observed power = .07\). Concerning depressive symptoms, an effect for time was found, indicating that depressive symptoms decrease over time. Mean scores of depressive symptoms at Time-1 (14.54 ± 9.61) were statistically different from Time-4 (11.68 ± 10.25, \(p=.02\)) and Time-5
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(10.31 ± 8.50, \(p<.0001\)). Mean scores at Time-5 were also different from Time-2 (13.08 ± 9.78, \(p=.001\)) and Time-3 (12.63 ± 9.95, \(p=.003\)). No interaction effect was found. After controlling for possible confounders, the effect for time did not remain significant [Wilks’ Lambda = .93, \(F(4,103) = 1.94, p=.11\), partial eta squared = .07].

Concerning Overall QOL and General Health, no effect for time was found. No interaction effect (time by number of surgical treatments) was found, showing that the number of surgical treatments exerted a stable effect on Overall QOL and General Health scores. Women with one or two surgical treatments did not differ on symptoms of Overall QOL and General Health [\(F(1,113)=.59, p = .45\), partial eta squared = .01, observed power = .12]. However, the univariate approach produced different results. Using the Greenhouse-Geiser estimates of sphericity (\(\varepsilon = .90\)), an effect for time was found [\(F(3.59, 405.18) = 3.23, p<.05\)].

With regard to Physical Health, women with one or two surgical treatments did not differ on Physical Health [\(F(1,113)=.36, p = .55\), partial eta squared = .03, observed power = .09]. An effect for time was found, indicating that Physical Health increases over time. Mean scores of Physical Health scores at Time-5 (14.60 ± 2.51) were statistically different from scores at Time-2 (14.04 ± 2.46; \(p=.006\)) and Time-4 (14.08 ± 2.42; \(p=.016\)). No interaction effect (time by number of surgical treatments) was found, showing that the number of surgical treatments exerted a stable effect on Physical Health scores. After controlling for possible confounders, the effect for time did not remain significant [Wilks’ Lambda = .97, \(F(4, 107) = .72, p=.58\), partial eta squared = .03].

Women with one or two surgical treatments did not differ on Psychological Health [\(F(1,114)=.98, p = .33\), partial eta squared = .01, observed power = .17]. Again an effect for time was found, this time indicating that Psychological Health improved over time. Mean scores of Psychological Health scores at Time-5 (15.35 ± 2.02) were statistically different
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from scores at Time-1 (14.81 ± 1.93; p<.05), Time-2 (14.89 ± 2.03; p<.01), and Time-3 (15.02 ± 2.04; p<.05). No interaction effect (time by number of surgical treatments) was found, showing that the number of surgical treatments exerted a stable effect on Psychological Health scores. After controlling for possible confounders, the effect for time did not remain significant [Wilks’ Lambda = .96, F(4, 108) = .1.21, p = .31, partial eta squared = .04].

Discussion

In the Netherlands, there is a fierce debate about the number of re-excisions in women with BC. The Inspection for Health Care suggested that, as a rule of thumb, 1 out of 9 women may get a second surgical treatment. Besides the costs associated with additional surgery, it is also speculated that women who get additional surgery will have, at least initially, more stress 18. However, no study has documented the effect of the number of surgical treatments on psychological outcomes. Does the group of women with more than one surgical treatment have more psychological problems than women who received just one operation? Therefore, the aim of this prospective follow-up study was to examine potential differences between women who received one surgical treatment and women who received two surgical treatments. This study showed that, in general, both groups did not differ on psychological outcomes, such as depressive symptoms and anxiety, over time. In addition, scores on depressive symptoms, anxiety, and fatigue initially decreased over time when we did not control for clinical factors. Sukegawa et al. 36 have examined anxiety (STAI) in women awaiting surgery for suspected ovarian cancer. Before surgery, women scored high on state anxiety (50.1 ± 10.7), while these anxiety levels dropped considerably within the two weeks after surgical treatment (43.2 ± 11.4). In our study, we also found high anxiety scores before diagnosis and the anxiety levels also dropped significantly post-surgery. With regard to Overall QOL and General Health, the opposite trend was found. However, when adjuvant
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therapy and type of surgery were taken into account, these time effects disappeared. The
effect for time remained present with regard to Physical Health. These findings may seem
counter-intuitive at first glance. However, several explanations are suggested here. The fact
that some women in our study needed an additional surgical treatment may not be easy for
women initially. However, women may also realize that an extra surgery is for their own
benefit. Irrespective of the number of surgical treatment, the aim is to remove malignant
tissue from the body. Another explanation may be that the data set is somewhat biased. For
instance, women with more than an additional surgical treatment tend to drop out more often
from the study compared with women with one surgery. However, this suggestion was not
supported by our findings. Both groups did not differ on whether they drop out or the moment
they dropped out from our study ($p > .24$).

Major strength of this study is its longitudinal design. However, this study has several
limitations. First, women who receive multiple surgical treatments may vary in the type of
treatment performed. However, as we used a rather small sample, it was not possible to divide
the sample and examine whether women who received, for instance, BCT twice or women
who were converted from BCT to MTC differ in psychological functioning. Thus, our
analyses were performed on a rather heterogeneous group. It would be interesting for future
studies to further address this issue. Second, this study focused on psychological outcomes
after surgical treatment. Therefore, no information is present on whether women with a
repeated surgical treatment score differently on clinical physical outcomes compared with
women who were operated only once or whether women with a second operation experience
more often psychiatric disorders (e.g., clinical depression). In order to partly overcome this
limitation, we have assessed women on the WHOQOL-100-domain Physical health. Based on
this self-evaluation, no differences were found between women operated once and women
operated twice. Third, the time points were chosen in such a way that the follow-up measures
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would not interfere with the time of the treatment modalities. As a consequence, the timing of the second measurement point is dependent of the last surgical treatment, which is different in both surgical groups. Thus, information on psychological outcomes after the first surgical treatment is lacking. However, since, both groups do not differ at one month after surgical treatment, we may conclude that potential differences at that point were not long-lasting, since no differences were found at all measurement points. Fourth, studies like the current one often show relatively high attrition 37. Also our study had 71% of the women with early stage BC still in the study at one-year after surgical treatment. This might have influenced our results. In addition, 191 patients refused to participate. The majority of patients who refused to participate had benign breast problems (n = 117; 67% ), while 64 patients (23%) had early stage breast cancer. Of these 64 patients, 24 women had a second operation.

This study shows that before diagnosis, women in both groups are stressed, however, one-year after surgery most women seem to be recovered psychologically. Clinically, it is important to assist those women who have on average more psychological problems than others and to monitor those with ongoing problems.

In conclusion, women with early stage BC receiving multiple surgical treatments do not have worse psychological outcomes compared with women with one surgical treatment.
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References


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37. Arving C, Glimelius B, Brandberg Y. Four weeks of daily assessments of anxiety, depression and activity compared to a point assessment with the Hospital Anxiety and Depression Scale. Qual Life Res 2008;17:95-104.
Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Number of operations</th>
<th>One</th>
<th>Two</th>
<th>p-value</th>
</tr>
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<tr>
<td>(N = 141)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N = 78)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**Sociodemographic**

| Age, years (mean ± SD) | 59.3 ± 9.1 | 57.8 ± 9.5 | ns       |
| Living with a partner (yes/no/missing) | 114 / 24 / 3 | 63 / 12 / 3 | ns       |
| Having children (yes/no/missing) | 121 / 18 / 2 | 65 / 10 / 3 | ns       |
| Educational level | 54 / 60 / 25 / 3 | 26 / 33 / 13 / 6 | ns       |
| (0-9 yrs/10-14 yrs/ >14 years/missing) |     |     |         |
| Paid work (yes/no/missing) | 50 / 90 / 1 | 36 / 40 / 2 | ns       |

**Clinical**

| Type of surgery (BCT/MTC) | 76 / 64 | 30 / 46 | .003     |
| Conversion from BCT to MTC |     | 22     |         |
| Second operation due to complication |     | 8      |         |
| Chemotherapy (yes/no) | 33 / 108 | 29 / 49 | ns       |
| Hormone therapy (yes/no) | 45 / 96 | 40 / 38 | .003     |
| Radiotherapy (yes/no) | 82 / 59 | 37 / 41 | ns       |
| Disease stage: 0 / I / IIa / IIb | 15 / 71 / 37 / 18 | 9 / 20 / 30 / 17 | .021     |

**Psychological**

| Overall QOL and General Health (mean ± SD) | 15.5 ± 2.6 | 16.0 ± 2.3 | ns       |
| Depressive symptoms (mean ± SD) | 15.2 ± 9.5 | 14.1 ± 9.5 | ns       |
| Fatigue (mean ± SD) | 20.2 ± 6.9 | 18.7 ± 6.5 | ns       |
| Anxiety (mean ± SD) | 47.8 ± 13.7 | 47.8 ± 14.2 | ns       |

Abbreviations: BCT = breast conserving therapy, MTC = mastectomy, SD = standard deviation, ns = not significant (p > .05)
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Table 2. Effects of time for psychological outcomes

<table>
<thead>
<tr>
<th></th>
<th>Wilks’ Lambda</th>
<th>F-value</th>
<th>p-value</th>
<th>Partial eta squared</th>
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</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>.73</td>
<td>F(4,102) = 9.51</td>
<td>&lt;.0001</td>
<td>.27</td>
</tr>
<tr>
<td>Anxiety</td>
<td>.38</td>
<td>F (4, 89) = 36.05</td>
<td>&lt;.0001</td>
<td>.62</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>.78</td>
<td>F(4,106) = 7.51</td>
<td>&lt;.0001</td>
<td>.22</td>
</tr>
<tr>
<td>Overall QOL and General Health</td>
<td>.93</td>
<td>F(4,110) =  .07</td>
<td>.07</td>
<td>.07</td>
</tr>
<tr>
<td>Physical Health</td>
<td>.87</td>
<td>F(4,110) = 4.09</td>
<td>.004</td>
<td>.13</td>
</tr>
<tr>
<td>Psychological Health</td>
<td>.88</td>
<td>F(4,110) = 3.49</td>
<td>.01</td>
<td>.11</td>
</tr>
</tbody>
</table>

Abbreviations: QOL = Quality of Life
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Figure legends

Figure 1. Flow chart of the participants

Figure 2. Mean scores on state anxiety. Women were divided in two groups, according to the number of surgical treatments received. Higher scores indicate higher levels of anxiety.
Women with an abnormality in the breast (before diagnosis): N = 799

Women with breast cancer:
Time-1
N = 217

Not participating:
* Refused to participate: N = 191
* Benign breast diagnosis: N = 381
* No surgery received: N = 4
* More than two operations: N = 4

Women with one operation Time-1
(N = 141)

Time-2
(N = 113)

Time-3
(N = 107)

Time-4
(N = 101)

Time-5
(N = 99)

Women with two operations Time-1
(N = 76)

Time-2
(N = 62)

Time-3
(N = 60)

Time-4
(N = 60)

Time-5
(N = 59)