Surgery and health-related quality of life – A prospective follow up study on breast cancer patients in Finland

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ABSTRACT

Introduction: The influence of different surgical approaches on breast cancer patients’ Health-related Quality of life (HRQoL) is an important determinant when making decisions on the choice of treatment. Knowledge on how patients actually perceive different surgical treatments regarding long-term HRQoL is still scarce.

Materials & methods: 1065 patients with primary breast cancer operated on from 2008 to 2015 at Helsinki University Hospital, Finland were prospectively followed-up for two years. They filled in two HRQoL questionnaires, the EORTC QLQ C30 – BR 23 and the 15D, at baseline and at 3, 6, 12 and 24 months after surgery. Clinical data on treatments given and the course of recovery were collected from patient records. Patients were divided into four mutually exclusive groups according to surgical method: breast resection (n = 415), oncoplastic resection (n = 248), mastectomy (n = 351) and immediate reconstruction (n = 51). Clinical data were combined with HRQoL scores and analysed as multivariate modelling.

Results: All groups experienced initially worsening overall HRQoL after baseline. Oncoplastic resection patients had the best body image and their HRQoL reached the highest level at treatments at 12 months whereas the reconstruction patients reached the highest HRQoL level first at 24 months. Mastectomy patients had the lowest scores throughout the 24-month follow-up.

Conclusion: Extensive surgery, in terms of immediate reconstruction, led to slower HRQoL recovery than oncoplastic techniques. Mastectomy patients are at risk of having the lowest HRQoL scores throughout their recovery after surgery.

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Introduction

The method and timing of surgical treatment of breast cancer is determined by the stage of the disease, general health of the patient and patient’s and surgeon’s preferences. Breast cancer operations differ in anatomical extent to treat the disease. Studies have indicated that the oncological safety is independent of the surgical method [3–5]. Less is known about the effect of the surgical method on Health-related quality of life (HRQoL) which is considered an important aspect of high-quality healthcare [6]. There are a number of different options for evaluating breast cancer patients perceived well-being, ranging from historical self-assessment with questionnaires to modern validated tools with specific and/or targeted questionnaires [7–9]. Studies on surgical methods reflecting HRQoL are still scarce, often not prospective, and limited in their comparison of surgical methods [3,6]. A recent systematic review addressed breast cancer patients HRQOL and surgical methods based on studies in which breast reconstruction was compared to mastectomy and breast-conserving surgery. The systematic review included 16 eligible studies in its meta-analysis the main findings of which were: breast reconstruction and breast-conserving surgery both produce better HRQOL outcomes in comparison to mastectomy. In addition, the review concluded that it would be beneficial to incorporate both breast/surgery specific and generic HRQOL instruments into breast cancer studies to cover the heterogeneity of study groups [10].

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surgery to reconstruction using a breast specific HRQoL instrument, the BREATHE-Q. The study reported that breast-conserving surgery was associated with less complications and need for revisional surgery in comparison to both alloogenous and autogenous reconstruction methods. Furthermore, breast conserving surgery led to better sexual well-being and satisfaction with the breast [11]. Our study complements the above mentioned studies by investigating breast cancer patients HRQOL in a prospective manner with both breast cancer specific (EORTC QLQ-C30- BR23) and generic (15D) HRQoL instruments. Furthermore, to find out whether different surgical methods lead to different HRQoL results or complications, our study includes all different surgical method groups: breast-conserving surgery, mastectomy and breast reconstruction methods. HRQOL is an important aspect when choosing surgical modalities for breast cancer patients.

**Material and methods**

**Patients**

1065 patients diagnosed with primary breast cancer at Helsinki and Uusimaa Hospital District (HUH) Finland between September 2008 and September 2015 participated in the study. Participation did not affect the treatment plan or offer financial compensation for the patients. The study was approved by the University of Helsinki Ethics committee (Permission 68 [June 11, 2008, 207/13/02/08]). Part of the patients (n = 130) received also peer support in the context of a concomitant randomized substudy in addition to usual care.

**Questionnaires**

Patients filled in an informed consent form and two quality of life questionnaires: the generic 15D and the cancer specific EORTC QLQ30-C30 with its QLQ-BR23 breast cancer specific module [8,9]. The questionnaires were collected at the time of diagnosis and later at 3, 6, 12 and 24 months after primary surgery. The generic and the cancer-specific HRQoL instrument complement each other and provide a wider perspective than a disease-specific instrument alone. Both instruments are well established and have been used widely to study breast cancer patients [12–16].

The 15D is a generic HRQoL instrument, which produces an overall quality of life score and a health profile. The questionnaire consists of 15 dimensions (Mobility, Vision, Hearing, Breathing, Sleeping, Eating, Speech, Excretion, Usual Activities, Mental Function, Discomfort and Symptoms, Depression, Distress, Vitality, Sexual Activity). Each dimension is rated by the patient from 1 (best situation) to 5 (worst situation). In comparing the 15D scores, the minimum clinically important difference (change) (MID) is 0.015 [17].

The EORTC QLQ-C30 is a cancer-specific HRQoL instrument developed by the European Organisation for Research and Treatment of Cancer. It is validated in more than 100 countries and in wide use around the globe. The EORTC QLQ-C30 produces functional status and symptom scores, which patients rate from 1 to 4 and 1 to 7 accordingly. It also provides an overall Quality of life score. The BR23 is a set of 23 breast cancer specific questions which produce 4 functional scores (Body Image, Sexual functioning, Sexual enjoyment and Future perspective) and 4 symptom scores (Systemic therapy side effects, Breast symptoms, Arm symptoms and Upset by hair loss). Scores range from 0 to 100. For functional scores a high score indicates good health whereas for symptom scores a high score indicates problems in that area [9]. The significance of the changes in the EORTC score can be interpreted as minimal for a score change between 5 and 10, intermediate for a change between 10 and 20, and large for a change >20 [18]. A MID for the EORTC has not been firmly established and there is some variation in the interpretation of the absolute values within different studies [16,19].

**Clinical data**

Hospital records were viewed for medical data on patients' health status, treatments given, and the course of surgical care. Patients were divided into groups depending on the type of primary surgery: resection of the breast (n = 415), oncoplastic resection (n = 248), mastectomy (n = 351), and immediate reconstruction (n = 51).

Resection and oncoplastic resection were identified as being either a simple resection of the breast cancer site with/without skin and underlying fascia removed with moderate reshaping of breast tissue if needed, or oncoplastic resection, which included removal of the tumour and more excessive remodeling, reshaping and/or replacing breast tissue with/without repositioning of the nipple in order to achieve better cosmesis. Unlike the oncoplastic group, the reconstruction group included also use of pedicled flaps. Thus the classification we use for oncoplastic resection differs slightly from some other classifications of oncoplastic methods (level 2 techniques) [4,20]. The codes and techniques of the surgical methods used were recorded from patient records. Based on the Nordic Classification of Surgical Procedures (NCSP), oncoplastic resection is defined by code HAB50 and thus differentiated from resection of the breast HAB40 or lumpectomy HAB99.

The Reconstruction group consisted of patients who underwent immediate breast reconstruction by either implants or autologous tissue reconstruction (or both combined). Autologous tissue reconstruction included both pedicled and microsurgical flaps.

Data on comorbidities were collected from hospital records using the ICD-10 for identifying medical conditions. The Charlson comorbidity index was used with the latest suggested rating for the comorbidities (where certain comorbidities get higher and some lower points compared to the initial introduction of the index) [21–23]. In addition we recorded patients' body-mass index (BMI), smoking status and diabetes status if available, as those are considered important influencers of HRQoL and factors that might correlate with complications [24,25].

Complications were identified as a recorded abnormality in the normal recovery process after surgery. They included wound healing, bleeding and thromboembolic complications leading to need of medication and/or extra procedures. Excessive seroma formation needing aspiration more than 10 times was noted as a potential independent factor influencing HRQoL even though having seroma is considered to be part of the healing process and not an actual complication.

**Statistical analysis**

The distribution of results for both HRQoL instruments was slightly skewed. Therefore, non-parametric tests (Kruskal-Wallis) were used in the analyses. For regression analysis we performed a Box-Cox transformation to ensure normality of the data. Statistical analysis was performed using SPSS 25.0 software and partly NCSS software. We performed a stepwise linear regression analysis (One-way ANOVA) to find possible explanatory factors affecting HRQoL. Variables chosen for analysis were: tumour specifics (T-, N-, M-classification, Grade of the disease), BMI, oncological treatments (radiation therapy, chemotherapy and hormonal treatment), whether or not having complications, excessive seroma formation (seroma aspirated more than 10 times), multiple surgery and recurrence of the disease.
Results

Patient characteristics

The age of the 1065 patients varied from 24 to 89 (mean 59.7 years, SD 10.4) reconstruction patients being approximately 10 years younger than patients in the other groups. Part of our study population (n = 130) received peer support via telephone. In that randomized intervention study there was no statistically significant difference in participants’ overall HRQoL compared to the controls [26]. We also compared those patients overall HRQoL at all time points to that of the whole cohort but found no statistically significant difference in the change of HRQoL.

Two breast cancer patients were male, 48 had had an earlier breast cancer and 39 some other cancer at baseline. 107 patients were active smokers.

The Charlson comorbidity points varied from 0 (no significant comorbidities) to 1–7 (Mean 0.327, SD 0.733). Most of the recruited patients (n = 844) had no comorbidities. 119 patients had 1 point, 85 had 2 points and 14 had 3 points. Patients with Charlson index ≥4 (n = 3) were excluded because of small group size. 72 patients were diabetics.

Treatment

351 patients had mastectomy, 415 breast resection, 248 oncoplastic resection and 51 immediate breast reconstruction (of which 76% were autologous). 402 patients had axillary clearance, the rest sentinel node biopsy or no biopsy at all (DCIS with no immediate reconstruction).

Radiation therapy was given to 840 patients (79% of all), 523 (49%) received chemotherapy, and 766 (72%) endocrine treatment. 351 patients had mastectomy, 415 breast resection, 248 oncological resection and 51 immediate breast reconstruction (of which 76% were autologous). 402 patients had axillary clearance, the rest sentinel node biopsy or no biopsy at all (DCIS with no immediate reconstruction).

Follow up

105 (10%) patients had post-surgery wound infection and 32 (3%) some other complication. 18 (13%) of those having a complication were diabetic. 102 (10%) patients needed more than one surgical procedure, irrespective of the reason, did not seem to affect HRQoL with either measuring tool. Axillary clearance other than one surgical procedure, irrespective of the reason, did not seem to affect HRQoL with either measuring tool. Axillary clearance after positive sentinel node biopsy. 309 (29%) patients had post-surgery seroma. Of them 43 (4%) had to have the seroma aspirated more than 10 times. 16 patients (1.5%) died, 32 (3%) patients had a recurrence and 22 (2%) another malignancy during follow-up. 50 patients (14% of mastectomy group) underwent delayed breast reconstruction during the two-year follow-up.

Response rate and missing data

During our study period of two years, patients who were willing to participate and fill in the questionnaires, did so quite conscientiously. Response rates are listed in Table 1. The number of missing answers was similar in all groups at all timepoints thus not affecting the analysis. Questions concerning sexual wellbeing were most often left unanswered. Some data were missing at baseline from around 5% of all respondents and the amount of missing data increased a bit with time: at 12 months some data were missing from 7.3% to 14.2% and at 24 months from 14.3 to 19.5% of respondents, depending on the question.

HRQoL results

Age had a statistically significant effect on HRQoL measured with the 15D (tested with Spearman correlation, p = 0.008) whereas it did not affect the EORTC results in a statistically significant manner (p = 0.396).

Comorbidities affected HRQoL negatively when measured with the 15D (p < 0.001) but not when measured with EORTC (p = 0.071). BMI correlated negatively with HRQoL with both instruments and at all measuring points (p < 0.05).

Active smoking (p = 0.023) and higher BMI (p = 0.006) correlated statistically significantly with the occurrence of complications, whereas diabetes (p = 0.561) did not.

Patients who had to go through more than 10 times of seroma aspiration, experienced some negative effect on HRQoL at 6 months measured with the 15D (p = 0.040). Having to go through more than one surgical procedure, irrespective of the reason, did not seem to affect HRQoL with either measuring tool. Axillary clearance correlated negatively with HRQoL based on both instruments from 3 months to 12 months (p < 0.01) but only EORTC showed negative correlation on HRQoL in axillary clearance patients still at 24 months (p = 0.002).

The higher the tumour grade, the poorer the HRQoL measured

Table 1

| Table 1 | Patient characteristics. DCIS – ductal carcinoma in situ. |
|---------|----------------------------------------------------------|
|         | Resection n = 415 | Oncoplastic Resection n = 248 | Mastectomy n = 351 | Reconstruction n = 51 |
| Age mean (SD) | 61.7 years (8.6) | 59.4 years (8.6) | 59.1 years (12.1) | 48.5 years (11) |
| Axillary clearance n (%) | 86 (21) | 87 (35) | 210 (60) | 19 (37) |
| Oncological treatment | | | | |
| Radiation therapy n (%) | 413 (100) | 239 (96) | 171 (49) | 17 (33) |
| Chemotherapy n (%) | 131 (32) | 129 (52) | 231 (66) | 32 (63) |
| Endocrine treatment n (%) | 279 (67) | 187 (75) | 266 (76) | 34 (67) |
| Tumour characteristics | | | | |
| Ductal carcinoma n (%) | 296 (71) | 167 (67) | 218 (62) | 27 (53) |
| Lobular carcinoma n (%) | 58 (14) | 41 (17) | 96 (27) | 13 (26) |
| DCIS n (%) | 18 (4) | 7 (2.8) | 11 (3) | 5 (10) |
| T1/T2/T3/T4 n (%) | 348(84%)/60(15%)/10(2%) | 170(69%)/75(30%)/2(1%) | 152(43%)/159(45%)/8(2%) | 31(6)/163(31)/3(6)% |
| N0/N1/N2/N3 n (%) | 317(76%)/83(20%)/12(3%)/3(1%) | 159(61%)/72(29%)/20(8%)/5(2%) | 154(44%)/122(35%)/54(15%)/20(6%) | 32(63)/163(31)/3(6)/0 |
| Grade 1/2/3 n (%) | 170(41%)/151(36%)/82(22%) | 69(28%)/105(42%)/74(30%) | 62(18%)/131(37%)/157(45%) | 5(10)/20(39)/25(49) |
| 15D/EORTC | | | | |
| Response % | | | | |
| 3 Months | 96.1/95.7 | 93.9/92.3 | 93.9/92.5 | 94.1/92.2 |
| 6 Months | 96.9/95.4 | 95.1/92.7 | 97.1/94.8 | 98/96.1 |
| 12 Months | 95.2/95.2 | 94.7/93.1 | 96/93.9 | 98/96.1 |
| 24 Months | 90.6/89.6 | 88.6/86.5 | 91.5/90 | 92.2/90.2 |
with both instruments at 3 months. By contrast, larger tumour size (T-classification) affected only HRQoL measured with the EORTC at 12 months. Nodal status (N-classification) was significantly negatively associated with HRQoL at all measuring points with the 15D but with the EORTC only at 3 months. Distant metastasis (M-classification) influenced HRQoL measured with the EORTC at 24 months. Detecting a recurrence did not impair HRQoL. Of the oncological treatments, radiation therapy or hormonal treatment did not affect HRQoL, but chemotherapy led to deteriorated HRQoL especially at 6 months. Table 2 represents regression analyses results.

**Appendix 1** shows the mean 15D scores at different timepoints for different groups. In all groups the mean score deteriorated in a clinically important manner from baseline to 3 months. Of the treatment groups, the oncoplastic resection group showed clinically important improvement from the initially worst situation (at 3 months) at 12 and 24 months, and the reconstruction group at 24 months. In the resection and mastectomy groups the 15D score did not improve in a clinically significant manner from the 3-month lowest level during the entire 24-month follow-up.

Based on both instruments, the mastectomy group had the lowest HRQoL score at baseline and at 24 months compared to the other groups. According to the EORTC, the reconstruction group had the most marked improvement of HRQoL at 24 months. Fig. 1 and Fig. 2 show mean HRQoL scores within groups by time.

The EORTC symptom scales showed constantly that fatigue, pain and sleeping were impaired in all groups at all measuring points.

The mastectomy group reported pain more than the other groups throughout the study, but the differences were statistically significant only at baseline.

To study the difference of EORTC patient-reported symptoms between our study groups we did a variance analysis for all the studied time points with all reported symptom scales. Tables 3 and 4 demonstrate those EORTC results that were different between study groups at timepoints baseline and 24 months.

Based on EORTC Functional scales, reconstruction patients had the best Physical and Sexual functioning throughout the study compared to the other groups. Their social functioning scale was the best at baseline and at 24 months, but their Body image score was the worst of all groups at 24 months. When comparing changes in mean EORTC scores at 24 months, there were statistically significant differences between groups in Financial difficulties, Physical functioning, Body image, Sexual functioning and Arm symptoms. Body image also decreased in a clinically significant manner (intermediate 10-20-point change) from baseline to 24 months in the mastectomy and reconstruction groups. In arm symptoms, the oncoplastic and mastectomy groups reported a minimally clinically important decrease (5–10 points) in EORTC points [18]. At 12 months, patients who had delayed reconstruction did not differ from the rest of the mastectomy patients. At 24 months, there was only a small and insignificant difference in the EORTC global score (74.32 in the mastectomy group compared to 73.84 with delayed reconstruction). However, regarding the 15D, the delayed reconstruction patients reported a borderline clinically importantly better total 15D score at 24 months compared to the rest of the mastectomy patients (0.915 vs 0.890).

**Discussion**

Our prospective study describes the healing process of breast cancer patients in Finland’s biggest breast cancer and plastic surgery units. We used well established and accepted HRQoL questionnaires available at the time of onset of this study. Unfortunately, data on baseline response rate is missing as the recruitment process was long and interrupted at some time points to allow collection of data for some other breast cancer projects of the hospital. As a consequence of that, we are not absolutely certain about the baseline response rate and do not report it here. However, once the patients had agreed to participate, they responded to the follow-up questionnaires very well as evidenced by the high response rates over 90%.

The amount of missing data was similar in all groups. Questions about sexual wellbeing seemed to be the most difficult to answer for all patients. Searching for common factors for non-response did not reveal any obvious reasons; some patients did not answer at some timepoints but then answered at the next one whereas some patients suffering from recurrence returned all questionnaires at all timepoints. Neither the mean age nor the number of complications differed between respondents and non-respondents. The only difference we found was in the mastectomy group in which the group of non-respondents comprised a larger percentage of patients having received chemotherapy (76% vs. 66%). However, we have no reason to assume that some groups would be over- or underrepresented in our study.

High research activity and multiple ongoing studies in our clinic affected the quite long recruitment period of our study: at times we were forced to halt our recruitment process so that the burden caused by studies for the same patients didn't get too high.

At the onset of our study, in year 2008, the proportion of oncoplastic techniques of all breast conserving techniques was 13.8%. That proportion had risen to 44.3% in year 2011, and thereafter varied yearly from 31.9% to 48.3%. All study patients received similar oncological treatment regardless of when they were recruited to the study. In Finland, reconstruction methods have

Table 2.

| Variable     | 3 Months          | 6 Months          | 12 Months         | 24 Months         |
|--------------|-------------------|-------------------|-------------------|-------------------|
|              | p-value | Std Co | p-value | Std Co | p-value | Std Co | p-value | Std Co |
| Grade        |         |        |         |        |         |        |         |        |
| EORTC 15D   | 0.015*  | -0.094 | ns      | ns     | ns      | ns     | ns      | ns     |
| T-class      | 0.000*** | -0.150 | ns      | ns     | 0.014*  | -0.086 | ns      | ns     |
| N-class      |         |        |         |        |         |        |         |        |
| EORTC 15D   | 0.000*** | -0.174 | ns      | ns     | 0.001*** | -0.106 | 0.002** | -0.103 |
| M-class      |         |        |         |        |         |        |         |        |
| EORTC 15D   | 0.012*  | -0.094 | -        | ns     | 0.032*  | -0.079 | 0.032*  | -        |
| BMI          |         |        |         |        |         |        |         |        |
| EORTC 15D   | 0.002** | -0.113 | -        | ns     | 0.000*** | -0.245 | 0.013*  | -0.082 |
| Chemotherapy|         |        |         |        |         |        |         |        |
| EORTC 15D   | -       |        | 0.000*** | -0.158 | 0.000*** | -        | 0.013*  | -        |

*p < 0.05, **p < 0.01, ***p < 0.001.
traditionally been more autologous than implant-based and this has not changed radically over time. This may be a cultural difference as our clinic has a strong tradition of microsurgical reconstruction — or a result of our easily accessible and virtually free health care for the patient. Patients pay for their hospital stay, but the extent of the surgical procedure is not a financial issue for the patient — the amount of personal cost being the same whether they have a resection procedure or a microsurgical operation.

Both EORTC and 15D describe the healing process of breast cancer patients well. The ceiling effect (patients reporting prefect health) was relatively low at baseline for both instruments: 8% for 15D and 15.3% for EORTC. At later measurement points the ceiling effect was even lower. Mastectomy patients had the lowest reported HRQoL at baseline and at 24 months, which might be because of a heavier disease burden. According to generally approved guidelines regarding which patients can be offered immediate reconstruction, the reconstruction group is probably healthier in many aspects. Still, all breast cancer patients deserve careful planning on what would be the best surgical approach for each individual [25].

Methods of breast reconstruction cannot be randomized because surgical treatment is always tailored for each patient. Following the AMAROS-study, the international guidelines for breast cancer treatment have changed and nowadays axillary clearance is performed less frequently [27,28]. Our results are in line with those of past studies: pain, fatigue and sleeping disorders are important factors that need to be addressed throughout the breast cancer patients’ care. Large studies, such as ours, are needed to investigate HRQoL in the pursuit to provide best possible treatment for each individual.

Conclusions

Our study showed that reconstruction patients had good physical functioning and their sexual wellbeing was the least impaired of all study groups. Patients treated with oncoplastic resection had the best body image and their overall HRQoL reached a higher level already at 12 months after surgery whereas reconstruction patients needed a longer time to recover. Mastectomy patients had the lowest scores which needs to be taken into account when planning
surgery for future patients. Wider use of oncoplastic techniques is associated with less mastectomies and probably higher HRQoL. Reconstructive surgery appears to, according to our results, provide good quality of life. In practice, for the planning of surgical options, these results could be useful: patients should be offered oncoplastic surgical treatment when applicable. Those, who require mastectomy, should be offered reconstructive options and they should be warned about the possibility that regaining good HRQoL may take a longer time.

Author contributions

All authors participated in the designing and performing of this study and contributed to the writing of this article.

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CRediT authorship contribution statement

Mervi Rautalin: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. Tiina Jahkola: Conceptualization, Methodology, Writing - review & editing. Risto P. Roine: Conceptualization, Methodology, Data curation, Resources, Writing - review & editing, Supervision.

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Appendix. 115D Mean score by groups. * MID ≥0.015 change from baseline ** MID ≥ 0.015 change from lowest measured timepoint within groups

| 15D mean score | Resection | Oncoplastic resection | Mastectomy | Reconstruction |
|----------------|-----------|-----------------------|------------|----------------|
| Baseline       | 0.921     | 0.930                 | 0.910      | 0.932          |
| 3 Months       | 0.895*    | 0.888*                | 0.881*     | 0.88*          |
| 6 Months       | 0.896     | 0.896                 | 0.886      | 0.888          |
| 12 Months      | 0.891      | 0.905**               | 0.891      | 0.887          |
| 24 Months      | 0.897     | 0.904**               | 0.890      | 0.903**        |

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