

Treatment Related Morbidity in Breast Cancer Patients

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Summary

In a prospective study, long term upper-limb morbidity, perceived disabilities in activities of daily life (ADL) and quality of life (QOL) were assessed before, at one year and two years after sentinel lymph node biopsy (SLNB) or axillary lymph node dissections (ALND) for breast cancer.

Considerable treatment related upper-limb morbidity was observed. Significant ($p < 0.05$) changes between before and up till two years after surgery were found in almost all assessments of shoulder function, ADL and several QOL subscales. Patients in the ALND group showed significant more changes in range of motion (ROM), grip strength, arm volume, ADL and QOL physical- and role functioning, pain and sleeplessness and arm symptoms compared to the SLNB group. Multivariate linear regression analysis showed that radiation therapy on the axilla is besides ALND an important factor in the prediction of impaired shoulder ROM and arm edema.

Introduction

The aim of modern breast cancer treatment is to obtain local tumor control, optimal lymph node staging with minimal treatment related morbidity, good functional result and when possible preservation of the breast. Axillary lymph node status based on the amount of positive axillary lymph nodes in relation to the total amount of resected lymph nodes is an important prognostic factor in patients with breast cancer.¹ Axillary lymph node dissection (ALND) still is associated with upper limb morbidity such as pain, numbness, lymphedema,

weakness and impaired shoulder range of motion.² Persisting upper limb morbidity can affect the ability to perform ADL and QOL.^{2,3,4}

Sentinel lymph node biopsy (SLNB) was introduced for staging of the axilla to reduce the number of unnecessary ALND's.⁵ SLNB is an accurate and safe procedure to predict metastatic disease in clinically negative axillary lymph nodes and is more and more accepted in breast cancer treatment.^{5,6}

The aim of the current prospective study was to analyze upper limb morbidity, perceived disability in ADL and QOL till two years after SLNB or ALND. The second aim was to analyze to which extent ALND and other treatment variables could predict upper limb morbidity, perceived disability and decreased QOL. At third, correlations between upper-limb morbidity and disability in ADL and reduction in QOL were analyzed.

Materials and Methods

From June 1999 to June 2001, patients with breast carcinoma stage I or stage II entered the study.⁷ Two groups of breast cancer patients participated in the prospective study, patients who underwent conventional breast cancer treatment with an ALND and patients who were treated according the SLNB concept.

Sentinel lymph nodes were identified by pre-operative lymphoscintigraphy followed by intra-operative tracing using a gamma probe and Patent blue dye® (Blue Patenté; Labatoire Guerbet, Aulnay-sous-Bois, France). The procedure has been previously described in detail.⁸ Surgical and adjuvant treatments were applied according to the protocol of the Comprehensive Cancer Centre North-Netherlands (CCCN) in both groups (Table 1).

Upper limb function and ADL were assessed one day before surgery (t0) and two years after surgery (t1). Pain was assessed with the Visual Analogue Scale (VAS).⁹ Upper limb function was assessed by means of a protocollized physical examination. Active shoulder range of motion was measured, using a goniometer (Isomed Inclinator; Portland, Oregon, USA) according to a standardized protocol in forward flexion, abduction and external rotation.¹⁰ Muscle strength of shoulder abductors and elbow flexors were measured using a handheld dynamometer (Citec®; Groningen, The Netherlands).¹¹ For assessment of the grip strength, a Yamar® hand-dynamometer (Bollingbrook, Illinois, USA) was used.¹²

Arm volume was assessed by means of surface circumference measurements (at 4 cm intervals) and a mathematical formula (Sitzia's formula) derived from a formula for a frustum.^{13,14}

ADL was assessed with the Shoulder Disability Questionnaire (SDQ) and the Groningen Activity Restriction Scale (GARS). The SDQ is a functional status measure that covers 16 items. It was designed to evaluate the ability to perform daily activities in patients with shoulder disorders (shoulder related ADLs).¹⁵ The GARS assesses the perceived restrictions (disability) in performing 18 ADLs.¹⁶

Quality of Life was assessed with help of the EORTC QLQ-C30 questionnaire supplemented with the EORTC Breast Module (EORTC QLQ-BR23).¹⁷

The core questionnaire is intended to measure general aspects of health related QOL specific to cancer patients. It incorporates five functional scales on physical, role, cognitive, emotional and social functioning. The supplementary EORTC Breast module is a site specific module which includes four functional scales on body image, sexual functioning, sexual enjoyment (satisfaction), future perspective and four symptom scales/items including arm symptoms, breast symptoms, systemic-therapy side effects and upsetness by hair loss. A linear transformation to a '0-100' scale of the EORTC QLQ-C30 and the QLQ-BR23 was carried out according to the EORTC Scoring Manual.¹⁸ A higher mean score for functional scales and global QOL reflects a better level of functioning, but a higher mean score for the symptom scales/items reflects more symptoms/problems.

Statistical analyses included descriptive statistics and *t*-tests for independent samples for between-group comparisons and *t*-tests for dependent samples for within-group comparisons. Pearson's χ^2 test was used for dichotomous variables. To answer the question in which extent treatment variables could predict upper limb morbidity, perceived disability and poorer QOL, multivariate linear regression analyses were performed. Differences were accepted as significant if *p* values were <0.05. SPSS® Base 11.5 software for Windows®, SPSS Inc., was used for statistical analysis.

Results

In the period 1999-2001, 204 consecutive patients with invasive breast carcinoma were included in the study. After two years 181 patients could be evaluated; 57 patients (32%) in the SLNB group and 124 patients (68%) in the ALND group. TNM classification, receptor status and treatment characteristics of these patients are presented in Table 1.

After two years substantial long-term treatment-related upper-limb morbidity was observed for the whole study group. Significant changes between before surgery and two years after surgery were found in all assessments except strength of the elbow flexors (Table 2). ADL increased as assessed with the SDQ (10.5; SD 29.9) and the GARS (1.8; SD 5.7) and also significant changes were found for QOL assessed with the EORTC QLQ-C30 and QLQ-BR23. Physical and role functions decreased. Emotional function and symptom scales/items such as fatigue, pain, dyspnoea, constipation and financial problems increased. From the functional scales of the breast cancer module, body image decreased (-3.2 SD 17.1) while future perspective increased (12.7 SD 28.2). Also here was an increase of side effects (4.8 SD 13.2) and arm symptoms (8.8 SD 19.4) (Table 2)

Several changes in upper-limb function (upper-limb morbidity), ADL (perceived disability) and QOL between before surgery and two years after treatment were significantly different between the SLNB group and the ALND group in favor of the first.

Multivariate linear regression analysis to predict the mean change in upper-limb function, ADL and QOL was performed and ALND was a significant factor in the prediction in the majority of mean changes in the performed

Table 1. Tumor-node-metastasis classification, receptor status and treatment characteristics of the patients who completed the assessments before surgery and two years after initial treatment

Variable	SLNB (n=57)	ALND (n=124)	Total (n=181)
Patient age, years, mean (SD)	57 (11.9)	55 (11.0)	56 (11.3)
Tumor-Node-Metastasis classification			
Stage I	44 (77%)	39 (32%)	83 (45%)
Stage IIA	11 (19%)	66 (53%)	77 (43%)
Stage IIB	2 (4%)	19 (15%)	21 (12%)
Estrogen-receptor status			
Positive	35 (61%)	89 (72%)	124 (68%)
Negative	22 (39%)	35 (28%)	57 (32%)
Surgical treatment of breast			
Mastectomy	17 (30%)	57 (46%)	74 (40%)
Lumpectomy	40 (70%)	67 (54%)	107 (60%)
Adjuvant therapies*			
Radiotherapy of breast	37 (65%)	79 (64%)	116 (64%)
Radiotherapy of axilla	0 (0%)	14 (11%)	14 (8%)
Chemotherapy	9 (16%)	51 (41%)	60 (33%)
Hormonal therapy	10 (18%)	64 (52%)	74 (41%)

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assessments of upper-limb function, ADL and QOL. Radiation of the axilla was significant in forward flexion, abduction, abduction/external rotation and arm volume. Mastectomy was a predictor for the SDQ, QOL scales/items social functioning, appetite loss and body image and breast symptoms.

Conclusions

This study showed significant long-term upper limb morbidity, associated ADL disability and also decreased QOL in breast cancer patients undergoing SLNB and/or ALND two years after treatment. Patients undergoing SLNB had significantly less long-term upper limb morbidity, ADL disabilities and declination of some items of QOL two years after treatment compared to patients undergoing ALND. In the assessment of changes in upper limb function, ADL and QOL, ALND is the most frequent found predictor of deterioration. Additional radiation on the axilla predicts a further decrease in shoulder ROM and arm edema.

Significant differences between the groups concerned numbness, shoulder ROM in abduction, abduction/external rotation, grip strength and arm volume. Decrease in upper limb function in the SLNB group was only significant for ROM in abduction/external rotation, strength shoulder-abductors and grip strength. The perceived disabilities in ADL assessed in this study with the SDQ and GARS are significant but relatively mild. The difference in mean change of ADL between pre surgery and two years after surgery comparing SLNB and ALND is significant using the GARS but not for the SDQ. Concerning QOL for the entire study group a significant decrease was found over the two years for physical and role functioning and body image whereas emotional functioning and future perspective showed significant increase over this period (Table 2). The improvement of emotional functioning and future perspective can be explained by the fact that the first assessment took place one day before surgery. Obviously at this time patients were nervous and stressed and also uncertain about their future perspective.²¹ Two years later these aspects were highly improved.

All significant changes over the two years after treatment in the SLNB group are for the better and the significant changes over the two years after treatment in the ALND group are for the worse except emotional functioning and future perspective. Nevertheless the interpretation of the scores on the EORTC QLQ-C30 and QLQ-BR23 in relation to clinical relevance needs some discussion. All the statistically significant differences found in our study within and between the groups could be interpreted as relatively small clinically important differences except the improvement of emotional functioning which could be interpreted as a very large clinically important difference.

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