Quality of Life of Croatian Breast Cancer Patients Receiving Adjuvant Treatment – Comparison to Long-Term Breast Cancer Survivors

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ABSTRACT

Quality of life (QoL) is an important outcome in assessment of breast cancer treatment. Data comparing QoL after different adjuvant treatments and QoL data on long-term survivors are modest. The aim of this study was to compare QoL scores of patients receiving adjuvant treatment with long-term breast cancer survivors, and to correlate QoL scores with clinical data. Sixty patients were recruited for the study: 20 during adjuvant radiotherapy, 20 during adjuvant chemotherapy, and 20 long-term breast cancer survivors. QoL was assessed using the self-administered EORTC core questionnaire QLQ-C30 and breast cancer-specific module QLQ-BR23. QoL scores between groups were compared using Kruskal-Wallis test and effects of clinical factors on QoL domains were tested using multiple regression analysis. No differences between three groups were observed in terms of all QoL scores. As measured by QLQ-C30, least affected QoL scales were cognitive functioning, social functioning, and physical functioning in all three patients group, while insomnia and pain scales were the most detrimentally affected. Among the groups, the highest scores of global health status and other functional scales were in adjuvant chemotherapy group. Measured by QLQ-BR23, body image scale was most affected, while sexual functioning scale was minimally affected, in all three groups. Multiple regression analysis has shown that the patient age were the only statistically significant predictor for global health status scale, and constipation scale. Our results demonstrated similar and favorable QoL in all three groups of patients and provided basic information on QoL in Croatian breast cancer patients.

Key words: breast cancer, quality of life, adjuvant chemotherapy, adjuvant radiotherapy, long-term survivors, questionnaires

Introduction

Breast cancer is the most prevalent cancer in women worldwide. There is a constant rising trend in new breast cancer cases in the West Europe and United States, while mortality trends are mostly decreasing. However, in Croatia, both incidence and mortality are still rising, with almost 2500 women diagnosed with breast cancer and more than 950 died in 20081.

The current mainstay of treatment for localised disease is breast conserving surgery (BCS) followed by adjuvant radiotherapy which is equivalent to mastectomy in terms of local control and survival2,3. Mastectomy is reserved for more advanced cases and patient preference, especially when combined with breast reconstruction. Breast cancer patients receive adjuvant chemotherapy and/or radiotherapy based on individual risk assessment of disease recurrence4. Therefore, the multiple modalities of treatment span surgery, chemotherapy, radiation therapy, and endocrine therapy, with use of each modality guided by pathological and clinical disease characteristics.

Quality of life (QoL) can be defined as a complex, multifaceted phenomenon that reflects the physical, mental and social well-being of the individual5. Various treatment interventions and their side effects influence QoL.
Surgery and patient’s awareness of being affected by malignant disease affect QoL extensively, besides the influence of adjuvant treatment. Furthermore, the great majority of breast cancer patients are postmenopausal women with number of comorbidities that impact QoL. A degree of QoL impairment is also present in long term breast cancer survivors.

Improvement of survival rates by earlier detection and improved treatment makes QoL an increasingly relevant endpoint to assess treatment outcomes. Specific domains of QoL scores are influenced by clinical variables, type of treatment, and patient population in different ways and to a different extent. However, data on QoL during and after specific treatment modalities, and associations of QoL with clinical features, are limited, but are considered crucial for using QoL scores in multimodal setting.

In this study we aim to evaluate QoL in three different groups of patients treated for breast cancer at the Oncology Department of University Hospital Center – those receiving adjuvant chemotherapy (AC), those receiving adjuvant radiotherapy (AR), and long term survivors (LTS).

Patients and Methods

Study design

Cross-sectional descriptive study.

Patients and settings

The sample consisted of 60 postmenopausal women with diagnosed, histologically confirmed UICC stage I–IIIa operated breast cancer. Other inclusion criteria were: ability to give consent, to read and speak Croatian, and to understand the purpose of the study. Those who had difficulty in understanding the questionnaire or communicating in Croatian, or had known history of psychiatric disorder or dementia were excluded from study.

Three groups of 20 patients each were enrolled: patients receiving adjuvant chemotherapy following primary surgery (AC), patients receiving adjuvant radiotherapy following primary surgery (AR), and patients who are considered long term survivors who were without local, regional or distant relapse at least 5 years after completion of their surgery and adjuvant treatment (LTS). Eight patients in the AR radiotherapy group received previous adjuvant chemotherapy.

Chemotherapy was given according to our local treatment policy, in concordance with St. Gallen consensus. Majority of patients received FEC (N=17), consisting of fluorouracil 600 mg/m² iv, epirubicin 75 mg/m² iv, and cyclofosfamide 600 mg/m² iv every three weeks for 6 cycles. The remaining patients (N=3) received CMF, consisting of cyclofosfamide 600 mg/m² iv, methotrexate 40 mg/m² iv, 5-fluorouracil 600 mg/m² iv every three weeks for 6 cycles.

Radiotherapy involved whole breast irradiation for all BCS patients (N=12) or chest wall irradiation after mastectomy (N=8) if tumor size was more than 5 cm or if three or more lymph nodes were involved. Regional nodal coverage was added if more than three lymph nodes were involved, irrespective of the type of breast surgery. The prescribed dose for all patients was 2.25 Gy per daily fraction, 5 days per week for 4 weeks, with total dose of 45 Gy, followed by a tumor bed boost of 10 Gy in 4 fractions for BCS patients.

All patients were recruited as outpatients within Oncology Department of University Hospital in period 2007–2008.

Instruments

QoL was assessed using the Croatian version of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 core questionnaire (version 3) with the breast module (EORTC QLQ-BR23) after copyright was obtained. The QLQ-C30 is a validated, self-reported measure of core quality of life items covering physical, personal, role, cognitive, emotional and social domains, as well as global health status. The QLQ-C30 is a 30-item survey with scores ranging from 0 (not at all) to 4 (very much). Patient responses were combined and computed to a 0 to 100 scale according to scoring manual provided by the EORTC. Completion of questionnaire requires an average 11–12 minutes. The C30 questionnaire was found to be reliable and valid in multicultural setting.

The QLQ-BR23 is a tumor specific tool consisting of 23 items pertaining to body image, sexuality, future perspective and side-effects related to different treatment modalities such as surgery, chemotherapy or radiotherapy. Each item is rated on a scale from 0 (not at all) to 4 (very much). With respect to functional scales, higher scores represent higher levels of functioning, while higher symptoms oriented scale score correspond to higher levels of symptoms. The Croatian version of instrument was tested for its validity and reliability. For both the QLQ-C30 and QLQ-BR23, higher functional scale scores represent higher levels of function, while for the symptom oriented scales higher scores represent higher levels of symptoms.

All patients who were offered to enter in study have accepted and successfully fulfilled questionnaires after written informed consent was obtained.

Statistical analysis

χ²-test or Fisher’s exact test were used to compare nominal categorical variables between groups and Kruskal-Wallis test was used to compare ordinal categorical variables and numerical variables between groups. p values <0.05 were considered significant. Effects of clinical and demographic factors on different quality of life scales were tested using multiple regression analysis with a stepwise selection of significant variables. The following variables were included in multiple regression analysis: age (numerical variable), type of surgery (mastectomy vs. breast conserving surgery), tumor diameter (numerical variable), estrogen receptor status (positive vs. negative),...
and axillary involvement (positive vs. negative). For multiple regression analysis p values <0.01 were considered significant to account for multiple comparisons. All statistical analysis was performed using MedCalc (v11.5.1, MedCalc Software, Mariakerke, Belgium).

Procedure
Data were collected from 2007 to 2008. The study was approved by the institutional ethical committee. Relevant clinical data were obtained from review of patients records. Patients receiving adjuvant chemotherapy were assessed during midway through their chemotherapy course, while patients receiving adjuvant radiotherapy were assessed after the third week of radiotherapy (after the middle of radiotherapy course). Breast cancer survivors were assessed on their regular annual outpatient check-up visits. Data were collected by the attending oncologist and study nurse.

Results
Patient’s characteristics are presented in Table 1. The majority of tumors were T2 (2–5 cm), with ductal histology. Most patients in the AR and LTS groups had grade 2 and ER positive cancers. HER2 status was available only in AR and AC groups. No statistically significant difference was found between groups with respect to histology, grade, ER status, HER2 status, or tumor diameter. Regarding axillary involvement, 50% patients in AR group had N0 disease, while in AC and LTS groups 35% and 55% patients had N0 disease, respectively, although this difference was not statistically significant. Women in the LTS group were more likely to have undergone radical surgery (p=0.007, \( \chi^2 \)-test), owing to different practice patterns at the time of their treatment. Patients in AC group were younger than patients in other two groups (p=0.048, Kruskal-Wallis test).

Distribution of scores of QoL scales in QLQ-C30 v 3.0 core questionnaire are presented in Table 2 and Figure 1. There were no statistically significant differences in QoL as measured by the QLQ-C30. According to mean distribution, cognitive functioning, social functioning and physical functioning were the least affected QoL scales in all three patients groups, while insomnia and pain were the most affected. Women in the AC group had the highest global health status QoL score, and also tended to have higher functional scale scores than women in the AR or LTS groups but these differences were not statistically significant.

In QLQ BR23 questionnaire analysis, body image was the most affected scale in all three patients groups, while sexual functioning was minimally affected (Table 3, Figure 2). There was no statistically significant difference between groups (Table 3).

Multiple regression analysis was undertaken to determine associations between QoL scales and clinical factors. Age was the only statistically significant predictor for the global health status scale (adjusted \( R^2=0.18, \beta=-1.11 \), standard error (\( \beta \))=0.3, p=0.0005) and for the constipation scale (adjusted \( R^2=0.11, \beta=0.81 \), standard error (\( \beta \))=0.29, p=0.006). For other QoL scales, no statistically significant predictors were found by multiple regression analysis.

Discussion and Conclusion
This study is first to evaluate impact of adjuvant treatment on QoL in breast cancer patients in Croatia, and to compare it with QoL in breast cancer survivors. This study is a preliminary report to assess patient re-
responses to a quality of life survey, extract initial data regarding patient observed QoL (as most important patient-reported outcome), and evaluate the influence of basic clinical parameters on QoL scales.

Each of aforesaid three dominant breast cancer patient groups has its specific QoL and treatment-related issues that complicate their comparison but from several reports is notable fact that during adjuvant treatment
QoL is decreasing with recovery on pretreatment levels up to six months upon completing treatment. Breast cancer survivors have QoL mainly comparable to the responding women with no history of cancer, but in certain QoL domains there might exist considerable differences in the majority of QoL domains between patients, with no study clearly demonstrating significant difference in overall QoL scores between women who had mastectomy compared to those who had breast conserving surgery.

The three major QoL domains in QLQ-C30 v 3.0 questionnaire, consisting of global health status/QoL, five functional scales and nine symptom scales, do not have the same clinical significance and relevance. In the largest meta-analysis on QoL data within more than ten thousand patients included in EORTC clinical trials, only three out of fifteen scales- physical functioning, pain and fatigue caused by primary treatment were similar among the groups, however. On the other hand, there are reports about worse physical functioning in women undergoing breast conserving surgery compared to those undergoing mastectomy. Many women receiving adjuvant radiotherapy reported problems with body image, particularly those who had undergone mastectomy. We did not find a significant difference in overall QoL scores between women who had mastectomy compared to those who had breast conserving surgery.

The fact that some scales of QoL in the LTS group are affected more than in other two groups (global health status and body image) suggest that some other factors also might influence QoL in breast cancer survivors, such as fear of recurrence and problems associated with aging.

Data on direct comparison of QoL in women undergoing adjuvant chemotherapy or radiotherapy is scarce. One report described how predefined domains of QoL among postmenopausal women change over time, but failed to include scale scores comparisons. The women receiving adjuvant chemotherapy showed a significant decrease in the overall QoL, physical, role, social, and cognitive functioning and body image and anxiety between baseline and the completion of six cycles of chemotherapy, while fatigue, nausea/vomiting, dyspnoea, appetite loss, constipation, pain, systemic therapy side effects, hair loss and depression increased significantly during the same period. On the other hand, among women receiving radiotherapy, a significant decrease was observed for the overall QoL, role and physical functioning, body image and anxiety between baseline and two weeks after completion of the treatment. Significant increases were seen in fatigue and dyspnoea, nausea/vomiting, pain, financial difficulties, constipation, systemic therapy side effects, arm and breast symptoms during the same time frame.

<table>
<thead>
<tr>
<th>Variables</th>
<th>AR (N=20)</th>
<th>AC (N=20)</th>
<th>LTS (N=20)</th>
<th>p (Kruskal-Wallis test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body image /median (IQR)/</td>
<td>AR (20)</td>
<td>AC (20)</td>
<td>LTS (20)</td>
<td>0.863</td>
</tr>
<tr>
<td>Sexual functioning /median (IQR)/</td>
<td>83.4 (37.5)</td>
<td>91.7 (33.3)</td>
<td>87.5 (29.2)</td>
<td>0.825</td>
</tr>
<tr>
<td>Sexual enjoyment /median (IQR)/</td>
<td>0 (8.4)</td>
<td>9 (25)</td>
<td>0 (25)</td>
<td>0.825</td>
</tr>
<tr>
<td>Future perspective /median (IQR)/</td>
<td>33.3 (16.7)</td>
<td>33.3 (50)</td>
<td>66.7 (66.7)</td>
<td>0.460</td>
</tr>
<tr>
<td>Systemic therapy side effects /median (IQR)/</td>
<td>33.3 (50)</td>
<td>33.3 (33.3)</td>
<td>66.7 (50)</td>
<td>0.118</td>
</tr>
<tr>
<td>Breast symptoms /median (IQR)/</td>
<td>16.7 (16.7)</td>
<td>16.7 (12.5)</td>
<td>8.3 (29.15)</td>
<td>0.169</td>
</tr>
<tr>
<td>Arm symptoms /median (IQR)/</td>
<td>16.7 (32.9)</td>
<td>22.2 (16.7)</td>
<td>11.1 (33.3)</td>
<td>0.426</td>
</tr>
<tr>
<td>Upset by hair loss /median (IQR)/</td>
<td>50 (100)</td>
<td>33.3 (66.7)</td>
<td>33.3 (8.3)</td>
<td>0.814</td>
</tr>
</tbody>
</table>

AR – patients receiving adjuvant radiotherapy, AC – patients receiving adjuvant chemotherapy, LTS – patients who are considered as breast cancer survivors, IQR – interquartile range

The relationship between the type of surgery and QoL is controversial. Some studies reported that patients undergoing breast conserving surgery had a better body image while others observed better psychological adjustment in women who had mastectomy despite the similar QoL profile. In work done by Janni et al. was found that women undergoing mastectomy were less satisfied with cosmetic results, reporting higher emotional stress caused by their physical appearance. Regret about...
On multivariate analysis we found significant correlation between age and global health status scale and constipation scale. Age is considered as important predictor of QoL, and global health status likely represent subject’s general QoL. It is expected that with greater number of patients we would yield some other significant correlation between clinical variables and QoL domains.

The purpose of this study is to give insight over QoL domains and influence of clinical variables on QoL in three groups of breast cancer patients most commonly seen in clinical practice. This is the first study conducted in Croatia aiming to evaluate the association between clinical factors and QoL in different groups of women with breast cancer.

We found no statistically significant differences in QoL between patients undergoing adjuvant treatment and the long-term breast cancer survivors in this small pilot exploratory study. This study is hypothesis generating in that some QoL domains may improve and some may not or even worsen during survivorship period. It is worthwhile to alert follow-up care providers of the QoL domains that are impaired in LTBs and particularly of domains impaired to a similar degree as during adjuvant therapy. Future studies to build upon this work are necessary to best guide survivorship care in the growing Croatian breast cancer patient population. In the era of targeted cancer treatment, we should identified subjects with impaired QoL, and to target our attention and care to those affected QoL domains.

The limitations of this study include its cross-sectional design and limited study population, although patient number was sufficient to acquire initial QoL observation. Furthermore, QoL is assessed at one point in time. The trend of QoL and its specific scales, and treatment-related symptoms over time were not evaluated.

In future research, QoL should be assessed with prospective collection of baseline data in order to better delineate associations between QoL and cancer treatment. In addition, larger prospective studies are required to follow the dynamics of QoL scales both in the adjuvant setting and in breast cancer survivors, in order to acquire more detailed information about symptoms and the cancer treatment burden experienced by different groups of patients.

Acknowledgements

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KVALITETA ŽIVOTA U BOLESNICA S RAKOM DOJKE KOJE PRIMAJU ADJUVANTNU TERAPIJU – USPOREDBA S BOLESNICAMA KOJE SU DUGOTRAJNO PREŽIVJELE RAK DOJKE

SAŽETAK

Kvaliteta života (KŽ) je važan detalj u procesu odlučivanju o načinu liječenja raka dojke. Podaci o usporedbi KŽ nakon različitih oblika adjuvantnog liječenja i podataka o KŽ u bolesnica koje su dugotrajno preživjele rak dojke su skromni. Glavni cilj ovog istraživanja bio je usporediti kvantitativne vrijednosti domena KŽ bolesnika koju su primale adjuvantno liječenje s bolesnicima kojih su dugotrajno preživjele rak dojke (u proračunu). Cilj ovog istraživanja bio je usporediti kvantitativne vrijednosti domena KŽ bolesnika koji su primale adjuvantno liječenje s bolesnicima koje su dugotrajno preživjele rak dojke. KŽ je procijenjena primjenom osnovnog EORTC upitnika QLQ-C30 i specifičnog modula za rak dojke QLQ-BR23. Bodovne vrijednosti KŽ uspoređene su između skupina Kruskal-Wallis testom, a utjecaj kliničkih čimbenika na različite domene KŽ testiran je multiplom regresijskom analizom. Nisu nađene razlike između tri skupine niti u jednoj od skala KŽ. Mjerenje KŽ-C30 upitnikom, najmanje pogođene skale su bile kognitivno funkcioniranje, socijalno funkcioniranje i tjelesno funkcioniranje u sve tri skupine bolesnika, dok su skale nesanice i bola bile najizraženije negativno pogođene. Među skupinama, najviše bodovne vrijednosti općeg zdravstvenog statusa i drugih funkcijskih skala bile su u skupini bolesnica koje su primale adjuvantnu kemoterapiju. Mjerenje QLQ-C30 upitnikom, skala predodžbe tijela bila je najviše pogođena dok je skala seksualnog funkcioniranja bila najmanje pogođena u sve tri skupine. Multipla regresijska analiza pokazala je da je dob bolesnika jedini statistički značajan prediktor za skalu općeg zdravstvenog statusa i skalu konstipacije. Naši rezultati su pokazali sličnu i povoljnu KŽ u sve tri skupine bolesnica te su pružili osnovne informacije o KŽ u hrvatskim bolesnicama s raktom dojke.