Background: Recently, evaluation of quality of life (QOL) has been recognized as a significant outcome measure in the treatment of several cancers. In this study, the Anti-Cancer Drugs–Breast (ACD-B) QOL scale was used to assess disease-specific survival in women with breast cancer undergoing preoperative chemotherapy (POC).

Methods: QOL-ACD-B scores were evaluated before and after POC. The cut-off value of QOL-ACD-B contributing to events such as relapse or death was calculated by receiver operating characteristic (ROC) curve analysis.

Results: In 300 women with breast cancer treated with POC, QOL was significantly reduced ($P < 0.001$). A high QOL-ACD-B score before POC was an independent factor in the multivariable analysis of overall survival (hazard ratio 0.26, 95 per cent c.i. 0.04 to 0.96).

Conclusion: Evaluation by QOL-ACD-B before POC may be useful to predict the prognosis of patients with breast cancer undergoing POC.

Introduction

Evaluation of quality of life (QOL) has been recognized as an important outcome measure in the treatment of cancer\(^1\). QOL contributes to ‘health’, defined by the WHO in 1946 as ‘a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity\(^2\). Health-related QOL is often set as a secondary endpoint in clinical trials. Reporting on health-related QOL is increasing, with several studies of multiple cancer types indicating that it could affect prognosis\(^3\)–\(^6\).

The QOL scale, Quality of Life Questionnaire for Cancer Patients Treated with Anti-Cancer Drugs (QOL-ACD), is a disease-specific measure supported by the Japanese Ministry of Health and Welfare\(^7\). QOL-ACD-B is an instrument that focuses on patients with breast cancer and the evaluation of treatment\(^8\).

This study was designed to see whether QOL-ACD-B could be used as a prognostic marker in women with locally advanced breast cancer scheduled to receive preoperative chemotherapy (POC). QOL-ACD-B scores were measured before and after POC.

Methods

This study was conducted at the Osaka City University, Graduate School of Medicine, according to the REporting Recommendations for Tumour MARKer Prognostic Studies guidelines (REMARK)\(^9\). This research was performed in accordance with the provisions of the Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013). The protocol was approved by the ethics committee of Osaka City University (approval number 926). Written informed consent was obtained from all patients.

Patients

Women with locally advanced breast cancer, diagnosed as stage IIA (T1 N1 M0 or T2 N0 M0), IIB (T2 N1 M0 or T3 N0 M0), IIIA (T1–2 N2 M0 or T3 N1–2 M0), IIIB (T4 N0–2 M0) or IIIC (any T N3 M0), and treated
Table 1. Quality-of-Life Questionnaire for Cancer Patients Treated with Anti-Cancer Drugs–Breast (QOL-ACD-B)

| No. | Question                                                                                           |
|-----|----------------------------------------------------------------------------------------------------|
| 1   | Did you have pain or numbness in the chest, armpits or arms on the diseased side?                  |
| 2   | Did you have swollen arms on the diseased side?                                                    |
| 3   | Were you able to raise your arm completely on the diseased side?                                   |
| 4   | Were you concerned about the skin symptoms (redness, swelling, hotness, itching, etc.) around the chest on the diseased side? |
| 5   | Did you have any pain related to disease or treatment?                                              |
| 6   | (Please answer this question only if you had surgery) Were you satisfied with the appearance of your breasts and surgical scar? |

Satisfaction with treatment and coping with disease

| No. | Question                                                                                           |
|-----|----------------------------------------------------------------------------------------------------|
| 7   | Were you satisfied with the explanation from your doctor about your medical condition and treatment? |
| 8   | Were you satisfied with the hospital facilities and staff other than doctors?                      |
| 9   | Do you feel that you have adequately accepted your disease?                                       |
| 10  | Have you tried to face up to the disease positively?                                                |

Side-effects of treatment

| No. | Question                                                                                           |
|-----|----------------------------------------------------------------------------------------------------|
| 11  | Did you have hair loss?                                                                           |
| 12  | Did you feel tired?                                                                               |
| 13  | Did you suffer from hot flushes and sweating of your body and forehead?                           |
| 14  | Did you suffer from changes in taste (abnormalities)?                                              |

Dress, sexual aspect, other

| No. | Question                                                                                           |
|-----|----------------------------------------------------------------------------------------------------|
| 15  | Do you find it difficult to wear the clothes you want to wear?                                    |
| 16  | Do you feel hesitant about undressing in public, such as at a hot spring?                         |
| 17  | Are you satisfied with your sex life?                                                              |
| 18  | Are you worried that your family will get the same disease?                                        |

with POC between February 2007 and December 2016 at Osaka City University Hospital were included. Patients who started treatment with POC but who could not subsequently undergo surgery were excluded. Initial clinical investigation and restaging after POC included ultrasonography, CT and bone scintigraphy. Breast cancers were classified as subtypes according to the immunohistochemistry expression of oestrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor (HER) 2 and Ki67, and then categorized as luminal A (ER+ and/or PgR+, HER2−, Ki67-low), luminal B (ER+ and/or PgR+, HER2−, Ki67-high), HER2-enriched breast cancers (HER2BC) (ER−, PgR− and HER2+), and triple-negative breast cancers (TNBC) (ER−, PgR− and HER2−). Luminal A and luminal B types were considered hormone receptor-positive breast cancer (HRBC).

Table 2. Clinicopathological features of patients treated with preoperative chemotherapy

|                        | No. of patients* |
|------------------------|------------------|
| Age (years)†           | 55 (27–90)       |
| Tumour size (cm)†      | 2.9 (1.0–9.8)    |
| Skin infiltration      |                  |
| No                     | 262 (87.3)       |
| Yes                    | 38 (12.7)        |
| Lymph node metastasis  |                  |
| N0                     | 90 (30.0)        |
| N1                     | 116 (38.7)       |
| N2                     | 65 (21.7)        |
| N3                     | 29 (9.7)         |
| Oestrogen receptor status |                |
| Negative               | 155 (51.7)       |
| Positive               | 145 (48.3)       |
| Progestrone receptor status |            |
| Negative               | 200 (66.7)       |
| Positive               | 100 (33.3)       |
| HER2 status            |                  |
| Negative               | 212 (70.7)       |
| Positive               | 88 (29.3)        |
| Ki67 status            |                  |
| Negative               | 96 (32.0)        |
| Positive               | 204 (68.0)       |
| Intrinsic subtype      |                  |
| HRBC                   | 149 (49.7)       |
| HER2BC                 | 57 (19.0)        |
| TNBC                   | 94 (31.3)        |
| ORR                    |                  |
| Non-responder          | 32 (10.7)        |
| Responder              | 268 (89.3)       |
| pCR                    |                  |
| No                     | 201 (67.0)       |
| Yes                    | 99 (33.0)        |
| Recurrence             |                  |
| No                     | 238 (79.3)       |
| Yes                    | 62 (20.7)        |
| Died from breast cancer|                  |
| No                     | 270 (90.0)       |
| Yes                    | 30 (10.0)        |
| QOL-ACD-B score before POC |              |
| Low                    | 220 (73.3)       |
| High                   | 80 (26.7)        |
| QOL-ACD-B score after POC |              |
| Low                    | 248 (82.7)       |
| High                   | 52 (17.3)        |

*With percentages in parentheses unless indicated otherwise; †values are median (range). HER, human epidermal growth factor receptor; HRBC, hormone receptor-positive breast cancer (oestrogen receptor (ER)+ and/or progesterone receptor (PgR)+); HER2BC, human epidermal growth factor receptor 2-enriched breast cancer (ER−, PgR− and HER2+); TNBC, triple-negative breast cancer (ER−, PgR− and HER2−); ORR, objective response rate; pCR, pathological complete response.
Table 3  Comparison of clinicopathological features and QOL-ACD-B score before and after preoperative chemotherapy

|                      | QOL-ACD-B score before POC | P*            | QOL-ACD-B score after POC | P*            |
|----------------------|-----------------------------|---------------|---------------------------|---------------|
|                      | High (n = 80) | Low (n = 220) |               | High (n = 52) | Low (n = 248) |
| Age at operation (years) |              |               |               |              |               |
| ≤ 55                 | 48 (60)       | 106 (49:1)    | 0.095         | 24 (46)      | 132 (53:2)    | 0.355         |
| > 55                 | 32 (40)       | 112 (50:9)    |               | 28 (54)      | 116 (46:8)    |               |
| Tumour size (cm)     |               |               | 0.005         |               |               | 0.509         |
| ≤ 2.9                | 51 (64)       | 100 (45:5)    |               | 24 (46)      | 127 (51:2)    |               |
| > 2.9                | 29 (36)       | 120 (54:5)    |               | 28 (54)      | 121 (48:8)    |               |
| Skin infiltration    |               |               | < 0.001       |               |               | 0.850         |
| No                   | 79 (99)       | 183 (83:2)    |               | 45 (87)      | 217 (87:5)    |               |
| Yes                  | 1 (1)         | 37 (16:8)     |               | 7 (13)       | 31 (12:5)     |               |
| Lymph node status    |               |               | < 0.001       |               |               | 0.144         |
| Negative             | 36 (45)       | 54 (24:5)     |               | 20 (38)      | 70 (28:2)     |               |
| Positive             | 44 (55)       | 166 (75:5)    |               | 32 (62)      | 178 (71:8)    |               |
| Oestrogen receptor status |            |               | 0.862         |               |               | 0.239         |
| Negative             | 42 (53)       | 113 (51:4)    |               | 23 (44)      | 132 (53:2)    |               |
| Positive             | 38 (47)       | 107 (48:6)    |               | 29 (56)      | 116 (46:8)    |               |
| Progesterone receptor status |     |               | 0.646         |               |               | 0.390         |
| Negative             | 55 (69)       | 145 (65:9)    |               | 32 (62)      | 168 (67:7)    |               |
| Positive             | 25 (31)       | 75 (34:1)     |               | 20 (38)      | 80 (32:3)     |               |
| HER2 status          |               |               | 0.481         |               |               | 0.733         |
| Negative             | 59 (74)       | 153 (69:5)    |               | 41 (79)      | 171 (69:0)    |               |
| Positive             | 21 (28)       | 67 (30:5)     |               | 11 (21)      | 77 (31:0)     |               |
| Ki67 status          |               |               | 0.469         |               |               | 0.274         |
| Negative             | 23 (29)       | 73 (33:2)     |               | 20 (38)      | 76 (30:6)     |               |
| Positive             | 57 (71)       | 147 (66:8)    |               | 32 (62)      | 172 (69:4)    |               |
| Intrinsic subtype HRBC |            |               | 0.945         |               |               | 0.204         |
| No                   | 40 (50)       | 111 (50:5)    |               | 22 (42)      | 129 (52:0)    |               |
| Yes                  | 40 (50)       | 109 (49:5)    |               | 30 (58)      | 119 (48:0)    |               |
| Intrinsic subtype HER2BC |          |               | 0.466         |               |               | 0.733         |
| No                   | 67 (84)       | 176 (80:0)    |               | 43 (83)      | 200 (80:6)    |               |
| Yes                  | 13 (16)       | 44 (20:0)     |               | 9 (17)       | 48 (19:4)     |               |
| Intrinsic subtype TNBC |            |               | 0.588         |               |               | 0.280         |
| No                   | 53 (66)       | 153 (69:5)    |               | 39 (75)      | 167 (67:3)    |               |
| Yes                  | 27 (34)       | 67 (30:5)     |               | 13 (25)      | 81 (32:7)     |               |
| ORR                  |               |               | 0.822         |               |               | 0.025         |
| Non-responder        | 8 (10)        | 24 (10:9)     |               | 1 (2)        | 31 (12:5)     |               |
| Responder            | 72 (90)       | 196 (89:1)    |               | 51 (88)      | 217 (87:5)    |               |
| Pathological response |           |               | 0.658         |               |               | 0.708         |
| Not pCR              | 52 (65)       | 149 (67:7)    |               | 36 (69)      | 165 (66:5)    |               |
| pCR                  | 28 (35)       | 71 (32:3)     |               | 16 (31)      | 83 (33:5)     |               |
| QOL-ACD-B score after POC |          |               | 0.766         |               |               |               |
| Low                  | 67 (84)       | 181 (82:3)    |               | –           | –              |               |
| High                 | 13 (16)       | 39 (17:7)     |               | –           | –              |               |

Values in parentheses are percentages. POC, preoperative chemotherapy; HER, human epidermal growth factor receptor; HRBC, hormone receptor-positive breast cancer (oestrogen receptor (ER)+ and/or progesterone receptor (PgR)+); HER2BC, human epidermal growth factor receptor 2-enriched breast cancer (ER−, PgR− and HER2+); TNBC, triple-negative breast cancer (ER−, PgR− and HER2−); ORR, objective response rate; pCR, pathological complete response. *χ² test.

Preoperative chemotherapy

POC consisted of four courses of FEC 100 (500 mg/m²) fluorouracil injection (TOWA, Kyoto, Japan), 100 mg/m² epirubicin (Nippon Kayaku, Tokyo, Japan) and 500 mg/m² cyclophosphamide (Endoxan®; Shionogi, Tokyo, Japan) every 3 weeks, followed by 12 courses of 80 mg/m² paclitaxel (TAXOL® injection; Bristol-Myers Squibb, New York, USA) administered weekly. In addition, patients with HER2-positive breast cancer were given trastuzumab (Herceptin®; Chugai, Tokyo, Japan) weekly (2 mg/kg) or every 3 weeks (6 mg/kg) during paclitaxel treatment. The antitumour effect of POC was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) within 1 week after completion of POC. Patients with a clinical partial response (cPR) or clinical complete response (cCR) were considered as responders for the objective response rate (ORR). Patients with clinically stable or clinical progressive disease were defined as non-responders for the ORR.
Quality-of-life scores in breast cancer chemotherapy

Women underwent mastectomy or breast-conserving surgery after POC. The effect of POC was evaluated in resected specimens. A pathological complete response (pCR) was defined as the complete disappearance of invasive components of the lesion, with or without intraductal components, including that in the lymph nodes, according to the National Surgical Adjuvant Breast and Bowel Project B-18 protocol. All patients who had breast-conserving surgery received postoperative radiotherapy to the remnant breast tissue. The standard postoperative adjuvant therapy was chosen based on the intrinsic disease subtype.

QOL-ACD-B

QOL-ACD-B includes 18 items with four subscales: Physical symptoms and pain (6 items); Satisfaction with treatment and coping with disease (4 items); Side-effects of treatment (4 items); and Dress, sexual aspect, other (4 items) (Table 1). Patients answer questions by checking the number on the scale that best describes their state. Each item is evaluated by scores of 1–5, with 1 being the worst and 5 the best. Scores for the whole QOL questionnaire and each subscale were calculated by subtracting 1 from the mean of the items checked and multiplying by 25, so that the minimum value was 0 and the maximum 100.

In this study, QOL-ACD-B was used to evaluate QOL retrospectively. Initially, nurses and pharmacists who were in charge of patients undergoing chemotherapy gave questionnaires to all patients with cancer who were receiving chemotherapy, not just women with breast cancer. Thus, although some items did not apply to breast cancer treatment, those that corresponded to the QOL-ACD-B were used as they were. Items with detailed descriptions in the medical record were inferred from sentences and scoring. Subjects that were difficult to evaluate were treated as ‘no answer’. Changes were calculated by evaluating QOL scores before and after POC for each patient, and evaluated in relation to clinical factors and survival.

Survival

Disease-free survival (DFS) was defined as the time interval from the date of primary surgery to the date of disease progression and/or recurrence. Overall survival (OS) was defined, in days, as the date of the primary surgery to the date of death. All women were followed up with a physical examination every 3 months, ultrasonography every 6 months, and CT and bone scintigraphy annually.

Statistical analysis

Statistical analysis was performed using the JMP® 13 software package (SAS Institute, Cary, North Carolina, USA). The relationship between each factor was examined with the $\chi^2$ test. Distributions of the QOL score before and after POC were expressed in box–whisker plots, with comparisons using Student’s $t$ test. The Kaplan–Meier method and log rank test were used to compare DFS and OS, and QOL-ACD-B scores. Hazard ratios (HRs) and 95 per cent confidence intervals were calculated with the Cox proportional hazards model. Univariable and multivariable analyses were performed using the Cox regression model, with a backward stepwise method used for variable selection in the multivariable analyses. $P<0.050$ was considered statistically significant, even in univariable and multivariable analysis of prognosis. The cut-off value for QOL before and after POC was determined by receiver operating characteristic (ROC) curve analysis of events (recurrence or death before recurrence).

Results

Clinicopathological features of patients included in the study are shown in Table 2. Median age at operation was 55 (range 27–90) years and median tumour diameter was 2.9 (1.0–9.8) cm. Thirty-eight patients (12.7 per cent) had skin infiltration and 210 (70.0 per cent) were diagnosed with lymph node metastasis at the time of breast cancer diagnosis. One hundred and forty-nine women (49.7 per cent)
were diagnosed with HRBC, 57 (19.0 per cent) with HER2BC and 94 (31.3 per cent) with TNBC. The response rate in the study cohort was 89.3 per cent, with 99 women (33.0 per cent) achieving a pCR. The median duration of follow-up after surgery was 1477 (range 63–3524) days.

Comparison of clinicopathological features and QOL-ACD-B score

Median QOL before POC was 92.188 (range 64.063–98.438), and the cut-off value was the same as the median (Fig. S1A, supporting information). In addition, median QOL after POC was 82.813 (42.188–96.875), but the cut-off value was 89.025 (Fig. S1B, supporting information).

Changes in quality-of-life scores before and after preoperative chemotherapy

Clinicopathological features and QOL-ACD-B scores before and after POC are compared in Table 3. Before POC, tumour size was significantly greater, and skin infiltration and lymph node metastasis were observed more frequently in patients with low QOL scores than in those with high scores ($P = 0.005$, $P < 0.001$ and $P < 0.001$).
Table 4  Univariable and multivariable analysis of disease-free survival in 300 patients treated with preoperative chemotherapy

|                      | Univariable analysis |                      | Multivariable analysis |                      |
|----------------------|----------------------|----------------------|------------------------|----------------------|
|                      | Hazard ratio         | P                     | Hazard ratio           | P                     |
| Age at operation (years) |                      |                      |                        |                      |
| ≤ 55                 | 0.69 (0.41, 1.14)    | 0.151                | 0.64 (0.37, 1.08)      | 0.094                |
| > 55                 | 1.00 (reference)     |                      | 1.00 (reference)       |                      |
| Tumour size (cm)     |                      |                      |                        |                      |
| ≤ 2.9                | 1.30 (0.79, 2.15)    | 0.306                | 0.78 (0.45, 1.36)      | 0.375                |
| > 2.9                | 1.00 (reference)     |                      | 1.00 (reference)       |                      |
| Skin infiltration    |                      |                      |                        |                      |
| No                   | 2.03 (1.06, 3.65)    | 0.035                | 2.43 (1.17, 4.78)      | 0.018                |
| Yes                  | 1.00 (reference)     |                      | 1.00 (reference)       |                      |
| Lymph node status    |                      |                      |                        |                      |
| Negative             | 2.43 (1.26, 5.27)    | 0.007                | 2.19 (1.08, 4.97)      | 0.030                |
| Positive             | 1.00 (reference)     |                      | 1.00 (reference)       |                      |
| Oestrogen receptor status | 0.75 (0.45, 1.24)    | 0.262                | 0.17 (0.05, 0.59)      | 0.005                |
| Positive             | 1.00 (reference)     |                      | 1.00 (reference)       |                      |
| Progesterone receptor status | 0.93 (0.54, 1.55)    | 0.781                | 1.20 (0.56, 2.69)      | 0.645                |
| Positive             | 1.00 (reference)     |                      | 1.00 (reference)       |                      |
| HER2 status          |                      |                      |                        |                      |
| Negative             | 0.59 (0.30, 1.06)    | 0.080                | 0.26 (0.07, 0.78)      | 0.014                |
| Positive             | 1.00 (reference)     |                      | 1.00 (reference)       |                      |
| Ki67 status          |                      |                      |                        |                      |
| Negative             | 0.94 (0.56, 1.63)    | 0.830                | 1.10 (0.62, 1.99)      | 0.755                |
| Positive             | 1.00 (reference)     |                      | 1.00 (reference)       |                      |
| Intrinsic subtype TNBC| 1.53 (0.91, 2.54)    | 0.109                | 0.32 (0.08, 1.18)      | 0.087                |
| No                   | 1.00 (reference)     |                      | 1.00 (reference)       |                      |
| Yes                  |                      |                      |                        |                      |
| ORR                  |                      |                      |                        |                      |
| Non-responder        | 0.27 (0.15, 0.49)    | < 0.001              | 0.20 (0.10, 0.39)      | < 0.001              |
| Responder            | 1.00 (reference)     |                      | 1.00 (reference)       |                      |
| Pathological response|                      |                      |                        |                      |
| Not pCR              | 0.44 (0.22, 0.80)    | 0.006                | 0.44 (0.21, 0.88)      | 0.020                |
| pCR                  | 1.00 (reference)     |                      | 1.00 (reference)       |                      |
| QOL-ACD-B score before POC |                  |                      |                        |                      |
| Low                  | 0.45 (0.21, 0.87)    | 0.017                | 0.52 (0.23, 1.05)      | 0.070                |
| High                 | 1.00 (reference)     |                      | 1.00 (reference)       |                      |
| QOL-ACD-B score after POC |                  |                      |                        |                      |
| Low                  | 0.46 (0.18, 0.99)    | 0.047                | 0.54 (0.20, 1.20)      | 0.135                |
| High                 | 1.00 (reference)     |                      | 1.00 (reference)       |                      |

Values in parentheses are 95% per cent confidence intervals. HER, human epidermal growth factor receptor; TNBC, triple-negative breast cancer; ORR, objective response rate; pCR, pathological complete response; POC, preoperative chemotherapy.

respectively). After POC, the ORR was greater in patients with high QOL scores than in those with low scores ($P = 0.025$). There was no significant difference in QOL scores before and after POC ($P = 0.766$). Before POC, when comparing high and low QOL groups on subscales, the low QOL group had a significantly lower score for Physical symptoms and pain ($P < 0.001$) and Dress, sexual aspect, other categories ($P < 0.001$), whereas Satisfaction with treatment and coping with disease ($P = 0.443$), and Side-effects of treatment categories showed no change ($P = 0.253$) (Fig. S2, supporting information). After POC, there was no significant difference between Physical symptoms and pain, and Dress, sexual aspect, other categories ($P = 0.114$ and $P = 0.369$ respectively) (Fig. S3, supporting information).

Although there was no significant difference between each QOL group before and after POC, comparison of all QOL groups showed a significant decrease in QOL after POC ($P < 0.001$) (Fig. I). When subscale score changes before and after POC were examined, there was a significant decrease in Physical symptoms and pain, and Side-effects of treatment (both $P < 0.001$) (Fig. S4A,C, supporting information). Satisfaction
Table 5  Univariable and multivariable analysis of overall survival in 300 patients treated with preoperative chemotherapy

|                      | Univariable analysis | Multiavariable analysis |
|----------------------|----------------------|-------------------------|
|                      | Hazard ratio | P  | Hazard ratio | P  |
| Age at operation (years) |             |    |              |    |
| ≤ 55                 | 0.66 (0.31, 1.37) | 0.268 | 0.79 (0.36, 1.69) | 0.546 |
| > 55                 | 1.00 (reference) |    | 1.00 (reference) |    |
| Tumour size (cm)     |             |    |              |    |
| ≤ 2.9                | 1.00 (reference) |    | 1.00 (reference) |    |
| > 2.9                | 0.591 |    | 0.88 (0.37, 2.03) | 0.762 |
| Skin infiltration    |             |    |              |    |
| No                   | 1.00 (reference) |    | 1.00 (reference) |    |
| Yes                  | 2.23 (0.88, 4.97) | 0.086 | 2.66 (0.92, 7.29) | 0.071 |
| Lymph node status    |             |    |              |    |
| Negative             | 3.30 (1.16, 13.82) | 0.022 | 2.17 (0.69, 9.87) | 0.203 |
| Positive             | 1.00 (reference) |    | 1.00 (reference) |    |
| Oestrogen receptor status |       |    |              |    |
| Negative             | 0.48 (0.21, 1.00) | 0.505 | 0.06 (0.01, 0.38) | 0.004 |
| Positive             | 1.00 (reference) |    | 1.00 (reference) |    |
| Progesterone receptor status |    |    |              |    |
| Negative             | 0.88 (0.39, 1.84) | 0.742 | 2.52 (0.63, 12.49) | 0.201 |
| Positive             | 1.00 (reference) |    | 1.00 (reference) |    |
| HER2 status          |             |    |              |    |
| Negative             | 0.29 (0.07, 0.82) | 0.017 | 0.09 (0.01, 0.64) | 0.013 |
| Positive             | 1.00 (reference) |    | 1.00 (reference) |    |
| Ki67 status          |             |    |              |    |
| Negative             | 1.43 (0.66, 3.43) | 0.374 | 1.26 (0.52, 3.27) | 0.620 |
| Positive             | 1.00 (reference) |    | 1.00 (reference) |    |
| Intrinsic subtype TNBC |             |    |              |    |
| No                   | 2.85 (1.37, 6.03) | 0.005 | 0.26 (0.03, 2.40) | 0.239 |
| Yes                  | 1.00 (reference) |    | 1.00 (reference) |    |
| ORR                  |             |    |              |    |
| Non-responder        | 0.23 (0.10, 0.55) | 0.002 | 0.20 (0.08, 0.53) | 0.002 |
| Responder            | 1.00 (reference) |    | 1.00 (reference) |    |
| Pathological response |             |    |              |    |
| Not pCR              | 0.38 (0.13, 0.91) | 0.028 | 0.38 (0.11, 1.06) | 0.066 |
| pCR                  | 1.00 (reference) |    | 1.00 (reference) |    |
| QOL-ACD-B score before POC |       |    |              |    |
| Low                  | 0.21 (0.03, 0.69) | 0.007 | 0.26 (0.04, 0.96) | 0.042 |
| High                 | 1.00 (reference) |    | 1.00 (reference) |    |
| QOL-ACD-B score after POC |       |    |              |    |
| Low                  | 0.30 (0.05, 0.99) | 0.048 | 0.34 (0.05, 1.26) | 0.116 |
| High                 | 1.00 (reference) |    | 1.00 (reference) |    |

Values in parentheses are 95 per cent confidence intervals. HER, human epidermal growth factor receptor; TNBC, triple-negative breast cancer; ORR, objective response rate; pCR, pathological complete response; POC, preoperative chemotherapy.

with treatment and coping with disease showed no change ($P=0.725$) (Fig. S4B, supporting information), whereas Dress, sexual aspect, other showed a significant increase ($P<0.001$) (Fig. S4D, supporting information).

Comparison of QOL-ACD-B scores with disease-free and overall survival

The cut-off value for the QOL-ACD-B score contributing to DFS was calculated from ROC analysis, yielding a distribution of 80 patients (26.7 per cent) in the high QOL group and 220 (73.3 per cent) in the low QOL group before POC (area under the receiver operating characteristic (ROC) curve (AUC 0.674, 95 per cent c.i. 0.599 to 0.748, $P<0.001$; sensitivity 72.7 per cent, specificity 46.9 per cent) (Fig. S1A, supporting information). After POC, there were 52 patients (17.3 per cent) in the high QOL group and 248 (82.7 per cent) in the low QOL group (AUC 0.607, 0.529 to 0.684, $P=0.010$; sensitivity 37.5 per cent, specificity 15.6 per cent) (Fig. S1B, supporting information).

Before POC, high QOL score was significantly associated with better survival, in terms of both DFS ($P=0.025$) and OS ($P=0.018$) (Fig. 2a,b). After POC, there was no
Discussion

Reports that patients’ QOL has an influence on cancer treatment are increasing. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30), Functional Assessment of Cancer Therapy (FACT) and Cancer Rehabilitation Evaluation System (CARES) are used to assess QOL for various cancers. This study used the Japanese QOL-ACD-B questionnaire, which is a specific QOL scale for breast cancer.

In the present study, patients with a low QOL-ACD-B score before POC had worse DFS and OS than those with high scores. In subscale analysis, scores were influenced mainly the categories by Physical symptoms and pain, and Dress, sexual aspect, other. When examining the relationship with clinical features, in patients with a low QOL score before POC, tumour size was significantly greater, and both skin infiltration and lymph node metastasis were observed with a higher frequency.

QOL-ACD-B scores fell significantly after administration of POC. Side-effects such as hair loss, fatigue, numbness and taste disorder resulting from POC treatment may all have affected QOL-ACD-B scores. Chee Chean and colleagues examined QOL after the treatment of breast cancer with anticancer drugs and reported that age, stage and co-morbidity showed no clear association with global health status. In the present study, there was no significant difference between QOL scores before and after POC, and the difference in Physical symptoms and pain, and Dress, sexual aspect, other subscale category scores seen before POC was not apparent after POC, probably reflecting tumour shrinkage in patients who initially experienced pain and skin ulceration, with improved QOL due to the disappearance of breast cancer symptoms. One study found no significant difference in physical symptoms or functional aspects between older and young women, although younger patients experienced a significant decrease in QOL; however, the present study found no influence related to age.

In terms of the relationship between QOL and prognosis, some studies found both QOL score and QOL score change after treatment to be significant predictors of subsequent patient survival. Furthermore, several studies have reported that appetite loss and pain are independent prognostic factors of QOL measures. The present study also analysed the change in QOL before and after POC, but this was not a significant predictor of prognosis (data not shown). Although the QOL-ACD-B does include many items of physical QOL, there are few mental or social QOL items. Previous reports have shown improvement in both QOL and prognosis with the early use of psychological care and palliative treatment. By changing the items of QOL evaluation, such as increasing the number of mental or social QOL items, it may be possible to show that the change in QOL affects prognosis.

The main limitation of this study is its retrospective design, where QOL was evaluated from information obtained from retrieved medical records. There are, however, relatively few interventional studies that have evaluated QOL as in previous studies. To evaluate QOL with greater precision, a prospective study is warranted. The present study might also be considered a reference for setting new evaluation items, in addition to those in the existing questionnaire.

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**Supporting information**

Additional supporting information can be found online in the Supporting Information section at the end of the article.