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Original Article

Impact of modern-day axillary treatment on patient reported arm morbidity and physical functioning in breast cancer patients

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ABSTRACT

Purpose: To reduce arm morbidity, routine axillary lymph node dissection (ALND) is often omitted or replaced by axillary radiotherapy (AxRT) in patients with limited nodal involvement. We evaluated patient-reported arm morbidity and physical functioning in breast cancer patients undergoing modern-day axillary treatment.

Methods: All patients within the UMBRELLA cohort undergoing local radiotherapy with sentinel lymph node biopsy (SLNB), ALND and/or AxRT were selected. Patient-reported arm morbidity and physical functioning were assessed with EORTC QLQ C30/BR23 questionnaires up to eighteen months after initiation of radiotherapy. Patient-reported outcomes were compared between patients with SLNB only, ALND only, AxRT (level I–II), AxRT (level I–IV) or AxRT plus ALND by means of mixed model analysis.

Results: In total, 949 patients were identified; 641 (68%) SLNB only, 57 (6%) ALND only, 94 (10%) AxRT level I–II, 72 (8%) AxRT level I–IV and 85 (9%) ALND + AxRT. SLNB only resulted in the least arm morbidity scores. ALND + AxRT resulted in most arm morbidity, with clinically relevant differences at 18 months. AxRT (level I–II or level I–IV) resulted in significantly less arm symptoms in the first 3 months compared to ALND. Arm symptom scores between those receiving AxRT on levels I–II and I–IV were similar.

Conclusion: Of all axillary management strategies, ALND plus AxRT is associated with worst patient-reported outcomes. AxRT resulted in less arm morbidity compared to ALND. Selective radiotherapy treatment of the axilla, i.e. radiotherapy of levels I–II only instead of levels I–IV, did not lead to clinically relevant reduced arm morbidity.

Axillary lymph node dissection (ALND) has long been the standard treatment in patients with positive sentinel lymph nodes [1]. ALND is associated with severe arm morbidity and reduced health-related quality of life (QOL) [2–6]. Several randomized controlled trials (i.e. Z0011 [7,8], IBSG [9] and AMAROS trial [10]) have shown that ALND can safely be replaced by axillary radiotherapy (AxRT) or even omitted in patients with limited sentinel lymph node involvement, who undergo breast-conserving therapy, without compromising regional control while decreasing arm morbidity. Omitting ALND was associated with axillary recurrence rates of 1% in the respective trials.

Since AxRT leads to less arm morbidity, ALND is increasingly being replaced by radiotherapy of the axillary region [11,12]. In the AMAROS trial [10] axillary radiotherapy, including the supraclavicular field, resulted in significantly less clinical signs of lymphedema compared to ALND (resp. 11% vs. 23% after 5 years) [10]. Although ALND is increasingly replaced by AxRT nowadays, the optimal axillary target volumes (e.g. level I–II, level I–IV or no AxRT) have not yet been determined, which explains why many different AxRT treatment approaches are currently applied [13].

Currently, 10-year overall survival of T1–T3 breast cancer patients with limited sentinel lymph node metastases or clinically node positive patients is 81–93% [8,10,14]. Against the background of the relatively good prognosis of these patients, evaluating long-term treatment toxicity of different axillary treatment strategies becomes even more important, in order for patients to make well informed treatment decisions [15,16].

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The aim of this study was to compare longitudinal patient-reported outcomes on arm morbidity and physical functioning after modern-day axillary treatment in a large cohort of breast cancer patients undergoing routine care.

Methods

This study was conducted within the prospective 'Utrecht cohort for Multiple BReast cancer intErvention studies and long-term evaLuAtion' (UMBRELLA, ClinicalTrials.gov:NCT02839863) [17]. UMBRELLA includes patients over the age of 18 years who were referred to the Department of Radiation Oncology at the University Medical Center (UMC) Utrecht with invasive breast cancer and ductal carcinoma in situ with an indication for adjuvant radiotherapy. The UMBRELLA cohort was approved by the Medical Ethics Review Committee of the University Medical Center Utrecht, The Netherlands. All participants gave written informed consent for the longitudinal collection of clinical data and patient-reported outcomes (PROs) at regular intervals during and after treatment. Clinical data on tumor and treatment characteristics were obtained from the Netherlands Cancer Registry (NCR), part of the Netherlands Comprehensive Cancer Organization (IKNL) [18].

For the present study, we selected all breast cancer patients enrolled between October 2013 and November 2016. All patients with a minimal follow-up of 6 months and who completed at least one PROs' questionnaire were eligible. Patients who developed a second breast tumor after enrollment were excluded. In line with Dutch guidelines for breast cancer treatment [19], patients were treated with (neo)adjuvant systemic treatment. All participants had undergone mastectomy or breast-conserving surgery combined with axillary staging and/or axillary treatment. Definitive axillary staging was done by sentinel lymph node biopsy (SLNB) or axillary lymph node dissection. Axillary lymph node dissection was performed in clinical node positive patients. In cases with a limited number of tumor positive sentinel lymph node(s), ALND was replaced by axillary radiotherapy. Decisions on whether ALND was replaced by AxRT, were made by the multidisciplinary teams and depending on the year of diagnosis, since indications for axillary treatment changed during the study period. In patients with positive sentinel lymph nodes and the presence of risk factors for locoregional recurrence, ALND could be replaced by AxRT of levels I–II or I–IV. High-risk patients for axillary recurrence were treated with AxRT after ALND was performed (Table 1).

All patients were scheduled for whole breast/chest wall conformal radiotherapy (using external tangential beams), 3–6 weeks after surgery. Computed tomography (CT)-based three-dimensional treatment planning was performed, with the patient in a supine position with both arms abducted. The breast or chest wall, and if indicated, lymph node levels, were delineated on a radiotherapy planning CT-scan according to contouring guidelines of the Radiation Therapy Oncology Group (RTOG) and European SocieTy for Radiotherapy and Oncology [20,21]. In most patients, 3D-conformal radiotherapy was used, and a small minority was treated with Volumetric Modulated Arc Therapy (VMAT) or inverse intensity-modulated radiotherapy (IMRT). Prescribed dose for local ± axillary (locoregional) radiotherapy was 42.56 Gy in 16 fractions of 2.66 Gy. In patients with an indication for a boost on the tumor bed, the prescribed dose was 21 or 23 fractions of 2.17 or 2.03 Gy including a simultaneous integrated boost (0.49 Gy or 0.63 Gy, respectively).

Patient-reported outcomes (PROs) were collected by means of validated questionnaires, at baseline and at regular time intervals (at 3, 6, 12, and 18 months after baseline). Baseline questionnaires were filled out upon inclusion before the start of radiotherapy, after breast cancer surgery and axillary staging had already taken place. If patients were treated with neoadjuvant systemic treatment baseline could be filled out during the course of neoadjuvant treatment. As a result a small minority of patients treated with neoadjuvant chemotherapy ($n = 46$), completed their baseline questionnaire more than one month before the start of radiotherapy. Patient-reported outcomes were collected within the Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES) registry [22]. Physical functioning was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [23]. Arm symptoms were evaluated with the EORTC QLQ breast cancer specific module (QLQ-BR23). The arm symptom scale was composed of three items and calculated by answering three questions; 'Did you have any pain in your arm or shoulder in the past week?', 'Did you have a swollen arm or hand in the past week?' and 'Was it difficult to raise your arm or to move it sideways in the past week?'. Higher scores on the physical functioning scale represent better functioning while lower scores on the arm symptom scale indicate less morbidity. Scores were generated in accordance with the EORTC scoring manual [24].

Statistical analysis

Patients were divided into five groups, according to the extent of definitive axillary surgery and radiotherapy treatment in addition to local whole breast/chest wall radiotherapy (Table 1). These are SLNB only; ALND only; AxRT levels I–II; AxRT levels I–IV; ALND + AxRT.

Patient, tumor and treatment characteristics were presented as means with standard errors or median with inter quartile range,

Table 1
Treatment groups according to different axillary treatment strategies and indications for axillary treatment strategy.

Axillary staging/treatment	Treatment group	Axillary lymph node status
1. SLNB[a] + local breast or chest wall radiotherapy	SLNB only	• No positive lymph nodes • Micrometastases[b] without risk factors[c]
2. SLNB + local breast or chest wall radiotherapy + axillary radiotherapy levels I–II	SLNB + AxRT levels I–II	• Micrometastases with at least one risk factor • ≤2 Macrometastases[e] without risk factors
3. SLNB + local breast or chest wall radiotherapy + axillary radiotherapy levels I–IV	SLNB + AxRT levels I–IV	• ≤2 Macrometastases with at least one risk factor • 3 Macrometastases; 1/2 macro-, and 2/1 micrometastases/without risk factors
4. ALND[f] + local breast or chest wall radiotherapy	ALND only	• Limited sentinel nodal involvement
5. ALND + local breast or chest wall radiotherapy + axillary radiotherapy levels II–IV[g]	ALND + AxRT levels II–IV	• Presence of ≥4 tumor positive lymph nodes after ALND

Note: isolated tumor cells were considered as sentinel node negative. Indications for axillary lymph node dissection only (ALND only) changed during the study period and therefore were dependent on year of diagnosis. [a]SLNB; Sentinel lymph node biopsy, [b]Micrometastases; micrometastatic nodal involvement with a metastatic deposit >0.2 mm–<2.0 mm, [c]Risk factors for axillar recurrence; the Bloom–Richardson (BR) grade 3, lymphangio-invasion, tumor size >3 cm, [d]Local; local radiotherapy of the breast or chest wall, [e]Macrometastases; macrometastatic involvement of the axillary nodes of tumor cell deposits >2.0 mm, [f]ALND; Axillary lymph node dissection, [g]Levels II–IV; Axillary radiotherapy treatment after ALND consisted of levels II–IV, level I and level II have were partly dissected during axillary lymph node dissection.

depending on their distribution, and as frequencies with percentages for categorical data. Quality of life data were linearly transformed according to the EORTC manual [24], into scores ranging from 0 to 100 and handled as continuous outcomes.

Mean scores of arm symptoms and physical functioning of the treatment groups were compared before start of radiotherapy, and 3, 6, 12 and 18 months thereafter using descriptive statistics. To compare PROs between treatment groups over time, to observe changes over time and to adjust for potential confounders (e.g. age, time and (neo)adjuvant systemic treatment) linear mixed effect models for repeated measures were used [25]. Linear mixed effect models for repeated measures take correlations between measurements (i.e. physical functioning and arm symptoms at different time-points) within subjects (i.e. a patient) into account. Different linear mixed models were fitted for arm symptoms and physical functioning as a function of treatment group, a (linear) time effect, a time-treatment interaction and adjusting for potential confounders (i.e. age and (neo)adjuvant systemic treatment). All terms were entered as fixed effects in the models. An autoregressive covariance structure of the first order (AR1) was assumed to account for the correlations among observations, supposing that correlations between measurements decline exponentially with distance between various time-points of measurements. Results were presented as mean differences (MD) with 95% confidence intervals. The level of significance was set at $p < 0.05$. Lastly, Cohen's d value was used to indicate the effect size of axillary management on PROs. Cohen's d was calculated as the difference between the means of the reference and axillary treatment group divided by the pooled standard deviation. An effects size of <0.20, 0.2–0.5, and >0.5 corresponded with small, medium, and large effects, respectively. Statistical analyses were performed with Statistical Package for Social Sciences (SPSS) software version 23 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.).

Results

Between October 2013 and November 2016, 1065 of all patients with breast cancer referred to the Department of Radiotherapy at the UMC Utrecht were enrolled in the UMBRELLA cohort. A total of 949 patients (89%) met the inclusion criteria for the present study and were selected for further analysis (Fig. 1). Patients who had not responded to PROs questionnaires (n = 92, 8.6%), were more often treated with mastectomy, with ALND, with (neo)adjuvant systemic therapy and with axillary RT (Supplement Table 1). Response rates of questionnaires ranged between 89 and 92% at baseline measurement and between 58 and 70% at 18 months' follow-up (Fig. 1).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.radonc.2018.07.006.

Patient, tumor and treatment characteristics according to axillary treatment group are presented in Table 2. Most of the patients

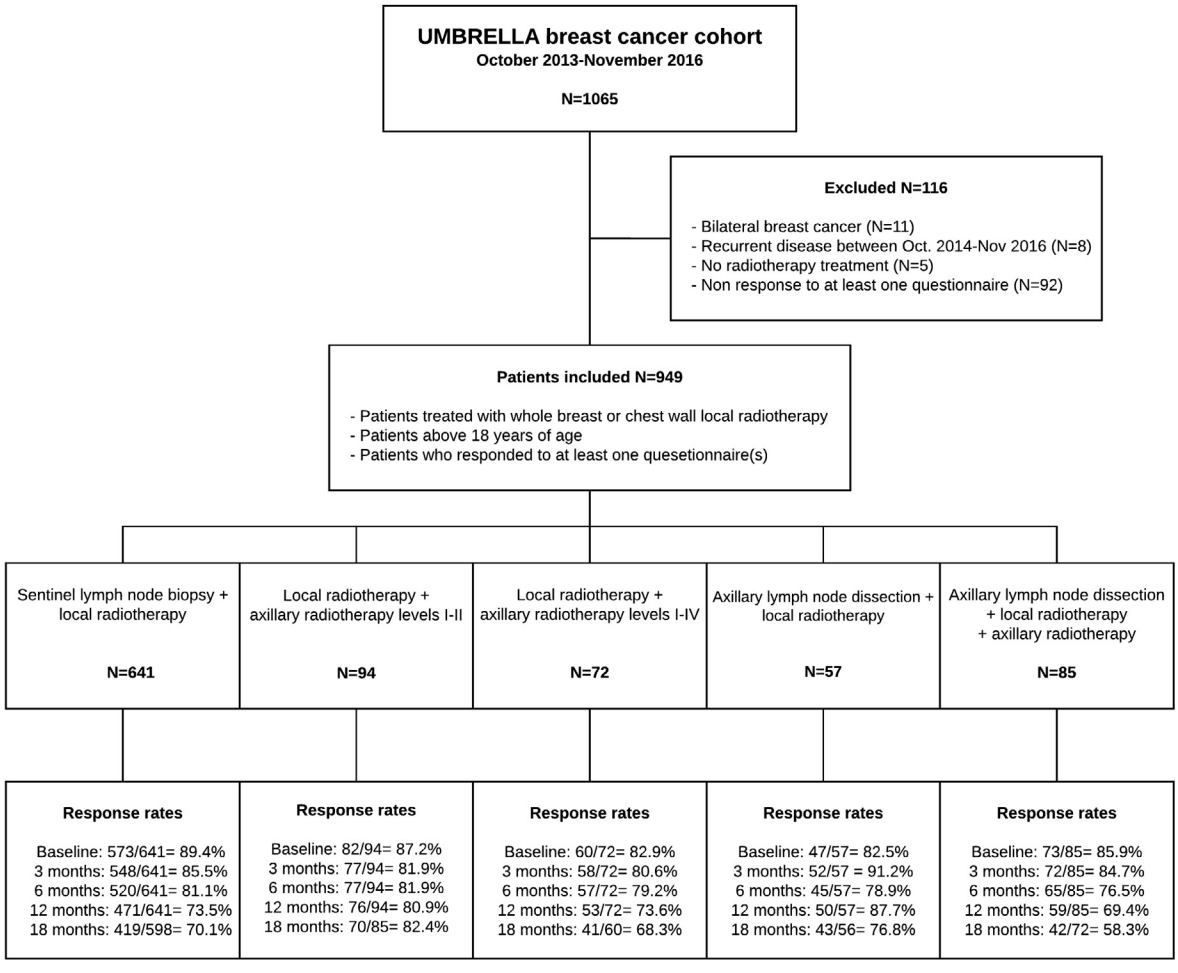

Fig. 1. Flowchart of selected patients and patient-reported outcome questionnaire response rates.

Table 2
Demographics and disease characteristics of respondents participating in the UMBRELLA breast cancer cohort and treated with radiotherapy of breast or chest wall.

	SLNB only	axillary RT levels I–II	axillary RT levels I-IV	ALND only	ALND + axillary RT
Total no. of patients	641 (67.5)	94 (9.9)	72 (7.6)	57 (6.0)	85 (9.0)
Age at inclusion, median (range)	60 (28–82)	55 (30–79)	52 (26–84)	54 (27–82)	54 (32–83)
Pathological tumor stage					
DCIS	97 (15.1)	0 (0.0)	0 (0.0)	0 (0)	0 (0.0)
T0	19 (3.0)	10 (10.6)	7 (9.7)	3 (5.3)	7 (8.2)
T1	416 (64.9)	65 (69.1)	31 (43.1)	25(43.9)	28 (32.9)
T2	83 (12.9)	18 (19.1)	28 (38.9)	20 (35.1)	33 (38.8)
T3-4	4 (0.6)	1 (1.1)	6 (8.3)	6 (10.5)	11 (13.0)
Tx	22 (3.4)	0 (0.0)	0 (0.0)	3 (5.3)	6 (7.1)
Surgical treatment					
Breast conserving surgery	620 (96.7)	73 (77.7)	43 (59.7)	37 (64.9)	31 (36.5)
Mastectomy	20 (3.1)	21 (22.3)	29 (40.3)	20 (35.1)	53 (62.4)
Other*	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Axillary procedure[a]					
No axillary procedure	48 (7.5)	0 (0.0)	0 (0.0)	0 (0.0)	(0.0)
Sentinel lymph node biopsy	593 (92.5)	94 (100.0)	72 (100.0)	N.A.	N.A.
Axillary lymph node dissection	N.A.	N.A	N.A.	31 (54.4)	66 (77.6)
Sentinel lymph node biopsy and axillary lymph node dissection	N.A.	N.A.	N.A.	26 (45.6)	19 (22.4)
Number of lymph nodes removed, median (range)	1 (0–10)	1 (0–7)	2 (0–6)	14 (1–31)	15 (2–32)
Pathological lymph nodes after sentinel lymph node biopsy					
Negative lymph node	525 (81.9)	13 (13.8)	8 (11.1)	4 (7.0)	0 (0.0)
Isolated tumor cells (ICT)	34 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Micrometastases	23 (3.6)	34 (36.2)	5 (6.9)	1 (1.8)	0 (0.0)
Macrometastases	1 (0.2)	39 (41.5)	56 (77.8)	18 (31.6)	14 (16.5)
Lymph node not found	10 (1.6)	3 (3.2)	2 (2.8)	3 (5.3)	5 (5.9)
Missing	48 (7.5)	5 (5.3)	1 (1.4)	31 (54.4)	66 (77.6)
Estrogen receptor status					
Negative	74 (11.5)	12 (12.8)	10 (13.9)	12 (21.1)	21 (24.7)
Positive**	450 (70.2)	82 (87.2)	62 (86.1)	45 (78.9)	64 (75.3)
Unknown	117 (18.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HER2 receptor status					
Negative	459 (71.6)	77 (81.9)	58 (80.6)	48 (84.2)	62 (72.9)
Positive	56 (8.7)	17 (18.1)	14 (19.4)	9 (15.8)	23 (27.1)
Unknown	126 (19.7)	0 (0.0)	(0.0)	0 (0.0)	0 (0.0)
Neo-adjuvant systemic treatment					
None	588 (91.7)	71 (75.5)	43 (59.7)	42 (73.7)	47 (55.3)
Chemotherapy (± immunotherapy)	53 (8.3)	23 (24.5)	29 (40.3)	15 (26.3)	38 (44.7)
Adjuvant systemic treatment					
Yes	267 (41.7)	76 (80.9)	63 (87.5)	48 (84.2)	71 (83.5)
None	374 (58.3)	18 (19.1)	9 (12.5)	9 (15.8)	14 (16.5)
Type of adjuvant systemic treatment					
Chemotherapy (±immunotherapy)	42 (6.6)	7 (7.4)	5 (6.9)	4 (7.0)	13 (15.3)
Chemotherapy (±immunotherapy) + hormonal therapy	75 (11.7)	36 (38.3)	28 (38.9)	28 (49.1)	29 (34.1)
Hormonal therapy	150 (23.4)	33 (35.1)	30 (41.7)	16 (28.1)	29 (34.1)

[a]Regardless of axillary treatment all patients were treated with local radiotherapy of the breast or chest wall.
NOTE: Categories may not sum to total N because of missing values.
Abbreviations: DCIS; ductal carcinoma in situ, Early-IBC; early invasive breast cancer, NA; not applicable, HER2; human epidermal growth factor receptor 2.
*Tumor was removed during breast reduction.
**Estrogen receptor positive >10%.

treated with whole breast/chest wall radiotherapy (n = 641, 67.5%) underwent SLNB only (SLNB only). All other local radiotherapy plus axillary treatment groups (i.e. ALND only, AxRT (levels I–II or levels I–IV), ALND + AxRT) included 57–94 patients, ranging from 5 to 10% of the total study population (Table 2). With a median age of 60 years, patients treated with SLNB only group were older than patients in the other treatment groups with median ages between 52 and 55 years.

At all time points, patients treated with SLNB only and local radiotherapy to the breast or thoracic wall had the least arm symptoms scores, while patients treated in addition to local radiotherapy with ALND and AxRT reported most arm symptoms at all follow-up time points (Fig. 2). At baseline, before the start of radiotherapy, patients treated with AxRT levels I–IV reported more arm morbidity than patients treated with AxRT levels I–II. All patients showed a slight improvement in arm function at three months compared to baseline scores, while symptoms worsened in all groups 6 months after baseline. Arm morbidity stabilized after six months, with a slight improvement after SLNB only and AxRT I–II (Fig. 2).

After adjustment, arm morbidity remained significantly worse up to eighteen months in patients treated with ALND ± AxRT compared to those receiving SLNB only with clinically important changes (MD 11.8–18.4, ES 0.7–1.1 indicating a large effect, Table 3). Arm morbidity was significantly worse after AxRT (levels I–II or levels I–IV) compared to SLNB only at six, twelve and eighteen months after start of radiotherapy with medium effect of treatment (MD 6.1–7.6, ES 0.4–0.5, Table 3).

Direct comparison of arm morbidity scores between patients treated with ALND and patients treated with AxRT (levels I–II or levels I–IV), showed more symptoms in patients treated with ALND. At baseline and three months ALND patients reported significantly more arm symptoms (MD 16.4, 95% CI 8.7–24.0 and MD 8.6, 95% CI 1.5–16.1 respectively) with a large effect at baseline (ES 0.7). No clinically relevant differences in arm morbidity scores between patients treated with levels I–II and levels I–IV AxRT were observed (Supplement Table 2).

Patient-reported lymphedema (arm and hand swelling according to EORTC QLQ-BR23 assessment) was less commonly reported by patients treated with SLNB or AxRT levels I–II/I–IV in addition to

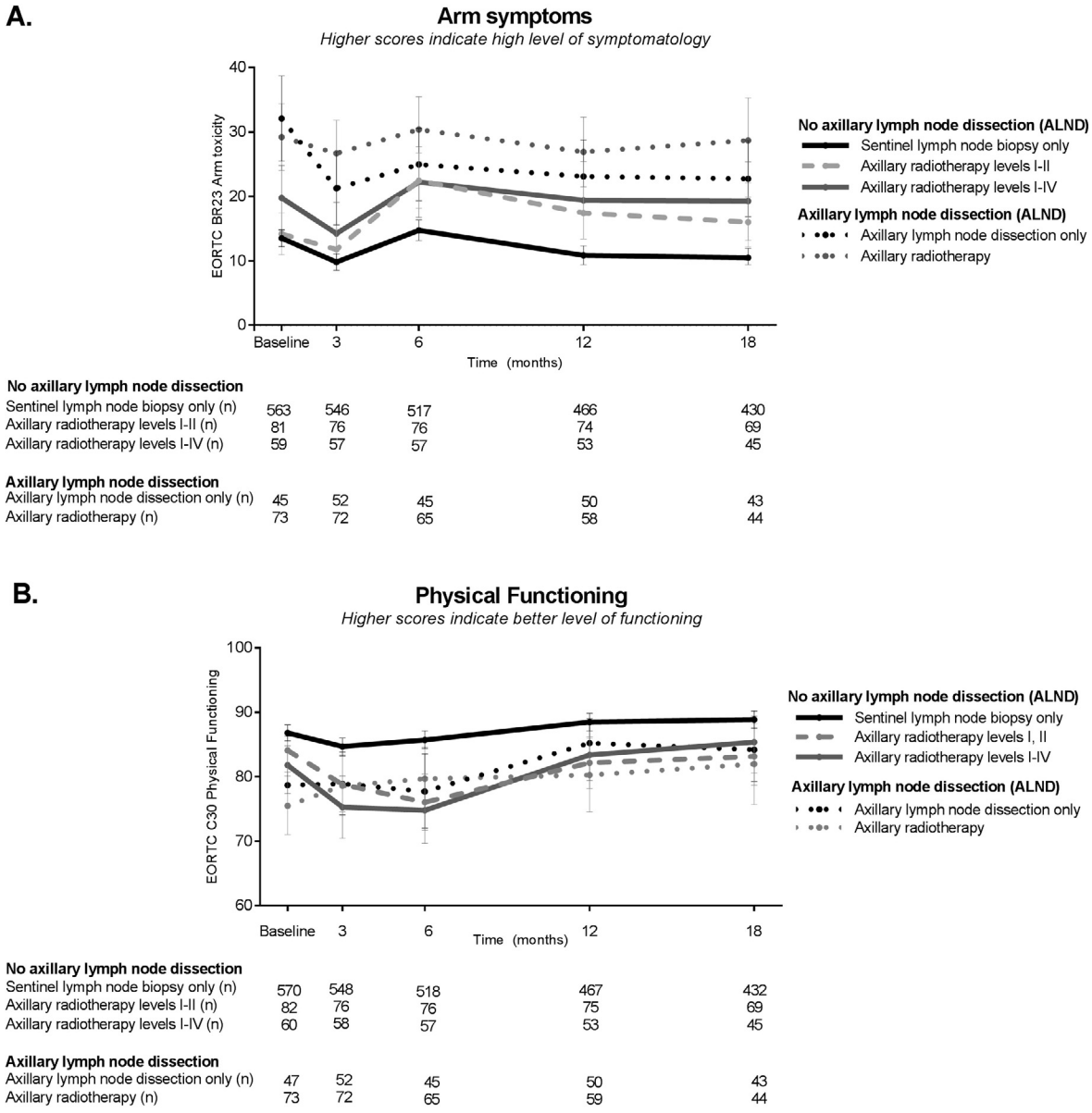

Fig. 2. Patient-reported arm symptoms (A) and physical functioning (B) stratified by different axillary treatment strategies. Assessed with the cancer questionnaire of the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30/BR23). Results are presented in mean scores accompanied with the 95% confidence intervals. Higher scores indicate more arm symptoms and better physical functioning.

local radiotherapy when compared to ALND. In the first six months a higher proportion in all five treatment groups reported mild lymphedema. Although severe arm swelling was rare, it was most predominantly reported by patients treated with axillary lymph node dissection (±AxRT) (Fig. 3).

Compared to patients treated with SLNB only, patients who received any type of axillary treatment reported worse physical functioning (Fig. 2). Physical functioning scores (adjusted for age, time and (neo)adjuvant systemic treatment) were similar among patients treated with AxRT levels I–II, levels I–IV, and ALND only (Supplement Table 2).

Discussion

While axillary treatment strategies for patients with limited metastatic lymph node involvement are changing, evaluating patient-reported treatment toxicity of different axillary treatment strategies becomes of great importance. This large prospective cohort study, including breast cancer patients undergoing routine care, was set up to evaluate patient-reported outcomes after breast cancer treatment. This study showed that axillary surgery and/or axillary radiotherapy impaired patient-reported physical functioning and arm morbidity up to 18 months after surgery. We found more arm morbidity and worse physical functioning scores in patients who received axillary treatment compared to patients treated with SLNB followed by local radiotherapy and no further axillary treatment, with statistically significant and clinically relevant differences in mean scores. Axillary radiotherapy (levels I–II or levels I–IV) resulted in less arm morbidity in the first 3 months compared to axillary lymph node dissection. Surprisingly, no significant differences in patient-reported arm morbidity and physical functioning between irradiated target volumes (i.e. levels I–II vs. levels I–IV) of the axilla were observed.

Table 3
Results from mixed model analysis. Arm symptoms and physical functioning of breast cancer patients after local radiotherapy of the breast or chest wall and different axillary treatment at different time-points.

		Baseline					3 months					6 months					12 months					18 months				
				Between-group difference					Between-group difference					Between-group difference					Between-group difference					Between-group difference		
		N	EMM[a]	MD[b]	95% CI	ES[c]	N	EMM[a]	MD[b]	95% CI	ES[c]	N	EMM[a]	MD[b]	95% CI	ES[c]	N	EMM[a]	MD[b]	95% CI	ES[c]	N	EMM[a]	MD[b]	95% CI	ES[c]
Arm symptoms	SLNB only	563	13.7	Reference group			546	9.6	Reference group			517	14.9	Reference group			466	11.2	Reference group			430	10.8	Reference group		
	Axillary RT levels I–II	81	14.4	0.7	−4.4; 5.9	0.1	76	12.4	2.8	−2.4; 8.1	0.2	76	22.6	**7.7***	2.3; 13.0	0.5	74	17.3	**6.1***	0.6; 11.4	0.4	69	16.2	5.4	−0.1; 10.9	0.3
	Axillary RT levels I–IV	59	19.2	5.5	−0.5; 11.4	0.3	57	14.3	4.7	−1.3; 10.7	0.3	57	22.0	**7.1***	0.9; 13.1	0.4	53	18.2	**7.0***	0.7; 13.2	0.4	45	18.4	**7.6***	.9; 14.2	0.5
	ALND	45	31.1	**17.4***	10.7; 24.1	1.1	52	21.4	**11.8***	5.4; 18.2	0.7	45	26.3	**11.4***	4.6; 18.0	0.7	50	23.7	**12.5 ***	5.9; 19.0	0.8	43	22.1	**11.8***	4.5; 18.3	0.7
	ALND with RT levels II–IV	73	28.4	**14.7***	9.1; 20.3	0.9	72	26.1	**16.5***	10.9; 22.1	1.0	65	30.6	**15.7***	9.8; 21.4	0.9	58	27.6	**16.4***	10.2; 22.4	1.0	44	29.2	**18.4***	11.7; 25.0	1.1
Physical functioning	SLNB only	570	86.4	Reference group			548	84.5	Reference group			518	85.0	Reference group			467	87.6	Reference group			432	87.5	Reference group		
	Axillary RT levels I–II	82	84.0	−2.4	−7.1; 2.5	0.2	76	78.5	**−6.0***	−10.8; −1.1	0.4	76	74.8	**−10.2***	−15.0; −5.2	0.7	75	81.6	**−6.0***	−10.9; −1.0	0.4	69	83.1	−4.3	−9.3; 0.7	0.3
	Axillary RT levels I–IV	60	81.2	−5.2	−10.7; −0.2	0.4	58	72.9	**−11.6***	−17.1; −6.0	0.8	57	73.9	**−11.1***	−16.7; −5.5	0.8	53	80.8	**−6.8***	−12.4; −1.0	0.5	45	82.3	−5.2	−11.1; 0.8	0.4
	ALND	47	80.0	**−6.4***	−12.5; −0.3	0.5	52	79.4	−5.1	−11.0; 0.8	0.4	45	76.3	**−8.7***	−14.8; −2.5	0.6	50	84.3	−3.3	−9.3; 2.7	0.3	43	85.2	−2.3	−8.5; 3.9	0.2
	ALND with RT levels II–IV	73	76.5	**−9.9***	−15.1; −4.7	0.7	72	79.1	**−5.4***	−10.6; −0.2	0.4	65	80.6	−4.4	−9.8; 0.9	0.4	59	79.5	**−8.1***	−13.5; −2.5	0.6	44	80.7	**−6.8***	−12.6; −0.8	0.5

Patient-reported outcomes on arm symptoms according to EORTC QLQ-BR23 and physical functioning according to EORTC QLQ-C30. Scores range from 0 to 100. Higher scores indicate more arm symptoms and better physical functioning. Between-group effects were assessed using mixed models including the measurements obtained at baseline and at 3, 6, 12 and 18 months, adjusted for age and (neo)adjuvant systemic treatment and corrected for multiple testing.

Abbreviations: N; number of patients, EMM; estimated marginal mean, MD; mean difference, CI; 95% confidence interval, ES; effect size, SLNB; sentinel lymph node biopsy, RT; radiotherapy.

[a]Estimated marginal mean scores adjusted for age, (neo)adjuvant systemic treatment. Results based on mixed effect models. [b]Difference in mean score with reference group. [c]Standardized effect size (mean difference divided by the pooled standard deviation) as a measure for minimal clinically important change. Small effect if ES <0.2, medium 0.3–0.5, large effect >0.5. *Significant difference.

Many studies have shown that patients treated with ALND have a high risk of developing upper extremity morbidity, compromised range of motion and muscle strength, chronic pain, lymphedema and decreased degree of activities in daily living [26–28]. The AMAROS trial was conducted to investigate whether AxRT is an appropriate alternative for ALND [10]. AMAROS confirmed that the type of axillary management (AxRT levels I–IV or ALND) in patients with limited nodal involvement significantly affects the clinical signs of lymphedema and arm circumference with comparable regional control 5 years after treatment [10]. In contrast to our findings, the AMAROS trial did not find better arm mobility in the AxRT group, despite lower rates of lymphedema in this patient group. It is possible that arm mobility measured by physicians in the AMAROS study, defined as the range of motion in the four excursions (abduction, adduction, anteversion and retroversion), was normal while the patient nonetheless perceived impaired mobility in the absence of any objective changes. In our study, arm morbidity score was patient-reported and determined by answering questions on pain in the arm, swelling of hand and arm and arm movement. Patient-reported moderate-severe arm swelling (i.e. lymphedema) was higher in patients who underwent ALND, reflecting more arm morbidity. Although patient's perceptions are the most important outcome for individual patients, ideally both objective and subjective symptom assessment is needed to determine the coherence between measured and perceived arm swelling, as there might be discordance between objective and subjective measures [29,30].

Our study showed significantly less patient-reported arm symptoms and less arm swelling in patients treated with SLNB only and local radiotherapy compared to patients treated with local radiotherapy patients and any type of axillary treatment (axillary radiotherapy RT ± ALND or ALND alone). Data from the Z0011 trial [12], in which clinically node negative patients with 1–2 tumor positive sentinel nodes were randomized between ALND and no further axillary treatment after breast conserving surgery, reported that lymphedema in the non-ALND group was significantly less common by subjective report and tended to be less by objective assessment of arm circumference as well [12]. It is noteworthy that the whole-breast 2D radiotherapy technique in the era of the Z0011 trial, naturally included a proportion of the lower levels of the axilla. Moreover, part of the patients were treated with high tangential fields, which makes this group comparable to the axillary radiotherapy level I–II in our study [13].

In line with Shaitelman et al. [31] we found that lymphedema was reported more often after axillary treatment and particularly after the addition of AxRT to ALND. Furthermore, patients treated with ALND and AxRT reported more arm symptoms, less physical functioning compared to SLNB only after only receiving local radiotherapy of the breast/chest wall. This is in concordance with results from the NCIC-CTG MA20 trial [14]. In this trial, lymphedema was significantly more often present in ALND patients treated with regional radiotherapy compared to patients in the local radiotherapy arm. It is most likely that the combined treatment approach of the axilla (i.e. surgery and radiotherapy) causes most morbidity [32,33,34].

This is the first study describing, prospectively collected patient-reported outcomes on the physical adverse effects of modern axillary treatment modalities in routine clinical care. This study emphasizes that if axillary treatment is indicated and ALND can safely be replaced by axillary radiotherapy, patients may benefit from axillary radiotherapy to avoid arm morbidity in the first 3 months after surgery. Furthermore it underscores the importance of modern radiation techniques like IMRT or VMAT that might result in less radiotherapy dose in the shoulder joint and musculature, consequently arm morbidity associated with axillary radiotherapy should be minimized.

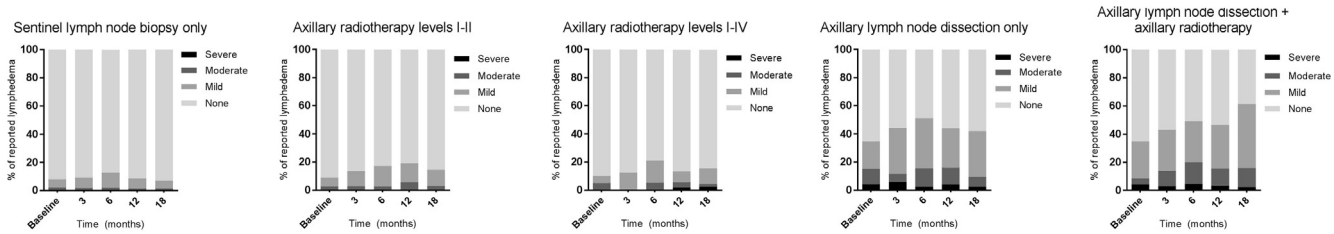

Fig. 3. Percentage of patient-reported lymphedema stratified by different axillary treatment strategies, assessed with the breast cancer questionnaire of the European Organization for Research and Treatment of Cancer (EORTC QLQ-BR23).

An important limitation of our study is that baseline measurement took place several weeks after diagnosis (after surgery, before adjuvant radiotherapy) and therefore, pretreatment arm function was not measured. Axillary surgery like SLNB and ALND was already performed before the baseline measurements. Consequently, baseline symptom score of patients treated with ALND was higher compared to the group without ALND. Also, we only know the prescribed radiotherapy dose on the axilla, and information of the actual dose that was administered to the different axillary levels and on the surrounding organs at risk (e.g. humeral head, shoulder joint and musculature) is lacking. Longer follow-up is needed to evaluate the longer term effect of axillary treatment on arm morbidity in breast cancer patients. Lastly, PRO questionnaire response rates (i.e. patients who returned at least one PRO questionnaire) in the ALND + AxRT group at 18 months are slightly lower. Although the reason for the lower response rates is unclear, it could be that we missed patients who experience more morbidity.

In conclusion, this study showed that patients with no other axillary treatment than SLNB reported low arm morbidity after local breast or chest wall irradiation. In turn, arm morbidity is more often reported by patients treated by ALND compared to patients treated with axillary radiotherapy only and highest when ALND is followed by axillary radiotherapy. Since axillary radiotherapy is more often used to replace axillary dissection in selected patients, these patients can be spared arm morbidity from axillary surgery shortly after surgery. A more selective treatment approach of axillary radiotherapy levels I–II compared to levels I–IV did not result in difference in arm morbidity until 18 months after surgery.

Disclosures

None.

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Meetings

Preliminary results were presented at the European Society for Radiotherapy & Oncology (ESTRO) in 2017 in Vienna and at the European Breast Cancer Conference (EBCC) in 2018 in Spain.

Conflict of interest

None.

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References

[1] Halsted WS. The results of radical operations for the cure of carcinoma of the breast. Ann Surg 1907;46:1–19.
[2] Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 2003;349:546–53.
[3] Land SR, Kopec JA, Julian TB, et al. Patient-reported outcomes in sentinel node-negative adjuvant breast cancer patients receiving sentinel-node biopsy or axillary dissection: National Surgical Adjuvant Breast and Bowel Project phase III protocol B-32. J Clin Oncol 2010;28:3929–36.
[4] Yeoh EK, Denham JW, Davies SA, Spittle MF. Primary breast cancer: complications of axillary management. Acta Radiol Oncol 1986;25:105–8.
[5] Hayes SC, Johansson K, Stout NL, Prosnitz R, Armer JM, Gabram S, et al. Upper-body morbidity after breast cancer: incidence and evidence for evaluation, prevention, and management within a prospective surveillance model of care. Cancer 2012;118:2237–49.
[6] Fleissig A, Fallowfield LJ, Langridge CI, et al. Post-operative arm morbidity and quality of life. Results of the ALMANAC randomized trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. Breast Cancer Res Treat 2006;95:279–93.
[7] Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011;305:569–75.
[8] Giuliano AE, Ballman KV, MCCall L, Beitsch PD, Brennman MB, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial. JAMA 2017;318:918–26.
[9] Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial. Lancet Oncol 2013;14:297–305.
[10] Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981–22023 AMAROS): a randomised, multicenter, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014;15:1303–10.
[11] Poodt IGM, Spronk PER, Vugts G, van Dalen T, Vrancken Peeters MTFD, Rots ML, et al. Trends on axillary surgery in nondistant metastatic breast cancer patients treated between 2011 and 2015. Ann Surg 2017.
[12] Giuliano AE, Morrow M, Duggal S, et al. Should ACOSOG Z0011 change practice with respect to axillary lymph node dissection for a positive sentinel lymph node biopsy in breast cancer? Clin Exp Metastasis 2012;29:687–92.
[13] Jagsi R, Chadha M, Moni J, et al. Radiation field design in the ACOSOG Z0011 (Alliance) trial. J Clin Oncol 2014;32:3600–6.
[14] Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. Regional nodal irradiation in early-stage breast cancer. N Engl J Med 2015;373:307–16.
[15] Hidding JT, Beurskens CH, van der Wees PJ, van Laarhoven HW, Nijhuis-van der Sanden MW. Treatment related impairments in arm and shoulder in patients with breast cancer: a systematic review. PLoS One 2014;9:e96748.
[16] Deutch M, Land S, Begovic M, Sharif S. The incidence of arm edema in women with breast cancer randomized on the National Surgical Adjuvant Breast and Bowel study B-04 to radical mastectomy versus total mastectomy and radiotherapy versus total mastectomy alone. Int J Radiat Oncol Biol Phys 2008;70:1020–4.
[17] Young-Afat DA, van Gils CH, van den Bongard HJGD, Verkooijen HM. The Utrecht cohort for multiple breast cancer intervention studies and long-term evaluation (UMBRELLA). Breast Cancer Res Treat 2017. https://doi.org/10.1007/s10549-017-4242-4.
[18] Netherlands Comprehensive Cancer Organisation (IKNL). [2017,December]. Available from: https://www.iknl.nl/over-iknl/about-iknl or http://www.cijfersoverkanker.nl.
[19] Nationaal Borstkanker Overleg Nederland (NABON). Richtlijn behandeling van het mammacarcinoom. editoî, editors".
[20] White J, Tai A, Arthur D, et al. Breast cancer atlas for radiation therapy planning: consensus definitions. Available at: https://www.rtog.org
[21] Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Biete Sola A, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. Radiother Oncol 2015;114:3–10.

[22] Van de Poll-Franse LV, Horevoorts N, van Eenbergen M, Denollet J, Roukema JA, Aaronson NK, et al. The patient reported outcomes following initial treatment and long term evaluation of survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. Eur J Cancer 2011;47:2188–94.
[23] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.
[24] Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC. Quality of Life Group The EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer; 2001.
[25] Bonnetain F, Fiteni F, Efficace F, Anota A. Statistical challenges in the analysis of health related quality of life in cancer trials. J Clin Oncol 2016;34:1953–6.
[26] Lucci A, McCall LM, Beitsch PD, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. J Clin Oncol 2007;25:3657–63.
[27] Ashikaga T, Krag DN, Land SR, et al. Morbidity results from the NSABP B-32 trial comparing sentinel lymph node dissection versus axillary dissection. J Surg Oncol 2010;102:111–8.
[28] Land SR, Kopec JA, Julisn TB, et al. Patient-reported outcomes in sentinel node-negative adjuvant breast cancer patients receiving sentinel-node biopsy or axillary dissection: National Surgical Adjuvant Breast and Bowel project phase III protocol B-32. J Clin Oncol 2010;28:3929–36.
[29] Armer JM, Radina ME, Porock D, Culbertson SD. Predicting breast cancer related lymphedema using self-reported symptoms. Nurs Res 2003;52:370–9.
[30] McLaughlin SA, Wright MJ, Morris KT, Sampson MR, Brockway JP, et al. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: patient perceptions and precautionary behaviors. J Clin Oncol 2008;10:5220–6.
[31] Shaitelman SF, Chiang Y, Griffin KD, DeSnyder SM, Smith BD, Schaverien MV, et al. Radiation therapy targets and the risk of breast cancer-related lymphedema: a systematic review and network meta-analysis. Breast Cancer Res Treat 2017;162:201–15.
[32] Farace P, Diedda MA, Amichetti M. Radiotherapy or surgery for the axilla in node positive breast cancer? Lancet Oncol 2015;16:e53–4.
[33] Nielsen HM, Blechingberg Friis R, Linnet S, Offerson BV. Loco-regional morbidity after breast conservation and axillary lymph node dissection for early breast cancer with or without regional nodes radiotherapy, perspectives in modern breast cancer treatment: the Skagen Trial 1 is active. Acta Oncolog 2017. https://doi.org/10.1080/0284186X.2016.1277261.
[34] Belmone R, Garin O, Segua M, Pont A, Escalada F, Ferrer M. Quality-of-life of sentinel lymph node bipsy versus axillary lymph node dissection in breast cancer patients. Value Health 2012;15:907–15.