Original article

Patients' experiences with decisions on timing of chemotherapy for breast cancer

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ARTICLE INFO

ABSTRACT

Introduction: Despite potential advantages, application of chemotherapy in the neo-adjuvant (NAC) instead of adjuvant (AC) setting for breast cancer (BC) patients varies among hospitals. The aim of this study was to gain insight in patients' experiences with decisions on the timing of chemotherapy for stage II and III BC.
Materials and methods: A 35-item online questionnaire was distributed among female patients (age>18) treated with either NAC or AC for clinical stage II/III invasive BC in 2013–2014 in the Netherlands. Outcome measures were the experienced exchange of information on the possible choice between both options and patients' involvement in the final decision on chemotherapy timing. Chemotherapy treatment experience was measured with the Cancer Therapy Satisfaction Questionnaire (CTSQ).
Results: Of 805 invited patients, 49% responded (179 NAC, 215 AC). NAC-treated patients were younger and more often treated in teaching/academic hospitals and high-volume hospitals. Information on the possibility of NAC was given to a minority of AC-treated patients (AC, stage II:14%, stage III: 31%). Information on pros and cons of both NAC and AC was rated sufficient in about three fourth of respondents. Respondents not always felt having a choice in the timing of chemotherapy (stage II: 54% NAC vs 36% AC; stage III: 26% NAC, 54% AC).
Conclusion: The need to make a treatment decision on NAC was found to be made explicit in only a small number of adjuvant treated patients, in particular in BC stage II. Less than half of the respondents felt they had a real choice.

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1. Introduction

Breast cancer (BC) care consists of a multidisciplinary approach of surgery, radiation, and systemic therapy including chemotherapy [1]. Chemotherapy intents to eliminate potential existing micro-metastases, thus decreasing recurrence rates and mortality [2]; it is timed either prior to or following surgery, respectively neo-adjuvant (NAC) or adjuvant (AC), both leading to similar disease free and overall survival [1,3,4]. NAC versus AC yields several advantages. Down-staging of the primary tumour increases resectability and the possibility of breast conserving surgery (BCS) [4] and axillary preserving surgery [5]. Moreover, the response to chemotherapy can be assessed [1,3,4,6], creating a platform to study the activity of (novel) agents or therapeutic combinations in a patient-personalized way [3,4,7,8].

(Inter)national BC guidelines recommend NAC over AC for patients with locally advanced BC (stage III) aged <70 years, while

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NAC can also be considered for patients with stage II BC with a clear indication for adjuvant chemotherapy [1,9,10]. The use of NAC for early BC is increasing, but despite its advantages, NAC is still applied less frequently than AC [11]. In the Netherlands, 12% of all newly diagnosed BC patients was treated with NAC in 2014, whereas in that same year 31% of patients received AC. Also, a considerable variation (0—97%) in NAC-application between hospitals was observed [12]. Significant predictors for the use of NAC (stage III) appeared to be young age, a diagnostic MRI, large tumour size, advanced nodal disease and a negative hormone receptor status. However, not all variation could be explained by tumour and patient characteristics [13], implicating that other factors play a part in the timing of chemotherapy. Nowadays, treatment decisions are shared between the physician and patient. Important in the process of shared decision-making (SDM) is that both patient and physician are aware of a decision being required, knowing and understanding all available information on treatment options, and sharing the decision by incorporating both the physicians advice as the patient's preferences [14]. Therefore, the goal of this study was to gain insight in patients' experiences with decisions on the timing of chemotherapy for stage II and III BC.

2. Materials and methods

2.1. Study population

Fifty-two hospitals were invited to participate; nineteen were willing to cooperate. We attempted an equal distribution in hospital volume (low, middle, high) and type (general, teaching, academic), and an equal geographical scatter. Patients of these hospitals were selected from the Netherlands Cancer Registry (NCR): a nationwide registry in which all newly diagnosed cancer patients are registered, hosted by the Netherlands Comprehensive Cancer Organisation (IKNL), which includes all items for the NABON Breast Cancer Audit [12]. We selected surgically treated patients (aged 18 or older) who were diagnosed with primary invasive BC stage II/III between 2013 and 2014 and received NAC or AC. Patients with previous malignancies and/or metastases were excluded. A sub-set of 40—50 patients per participating hospital was randomly selected, with an average of 43 per hospital.

A total of 805 patients (367 NAC-treated, 438 AC-treated) were invited by a letter through their treating physician between August 24th, 2015 and January 1st, 2016 to participate in our online questionnaire. The survey was offered within a secured web-based environment named PROFILES [15]; paper questionnaires were provided on request. Completed questionnaires were collected until the 28st of February 2016. Respondents gave consent on an adjective (online) form for processing their answers and merging them to their clinical data available in the NCR. Approval from the Committee of Privacy of the NCR and the Medical Ethical Committee of the Netherlands Cancer Institute - Antoni van Leeuwenhoek were obtained for this study.

2.2. Questionnaire

The thirty-five-item questionnaire (appendix A) consisted of questions on SDM, completed with questions on the patients' experience and satisfaction with chemotherapy care in general. SDM was defined as by the study of Légaré et al.: both health care provider and patient recognise and acknowledge that a decision is required, while knowing and understanding all best available relevant evidence, taking into account both the patient's preferences and the provider's advice [14].

Questions (Q) 1 to 9 asked about general mental and physical health and timing and type of chemotherapy received. The following questions dealt with the conditions of SDM. To determine whether patients were *informed on the possible choice* between NAC and AC, patients were asked whether they received information on chemotherapy prior to surgery (Q10) and whether (Q11) and with whom (oncologist, surgeon, nurse practitioner, nurse specialised on BC, general practitioner; Q12) NAC was discussed. To assess whether *information on evidence of both options was provided*, patients were asked if pros and cons of both NAC and AC were discussed (Q13). To determine if *patient preferences* were taken into account, questions were posed on whether the patient understood on what arguments the final decision was made (Q14 to Q17, Q19). The patients experienced SDM was based on questions whether they felt they shared the decision on the timing of chemotherapy (Q18) and had enough time to make a decision (Q20). In addition, to determine the overall level of patient information we asked questions on chemotherapy treatment information in general (Q21 to Q24). To determine chemotherapy treatment experience, all questions from the Cancer Therapy Satisfaction Questionnaire (CTSQ) were included (Q25 to Q30), consisting of three domains: Expectation of Therapy (EOT), Feelings about Side Effects (FSE), and Satisfaction With Therapy (SWT) [16]. General items such as nationality, level of education, and living and working status were requested as well (Q31 to Q35). A patient panel contacted through the Dutch BC patient association (Borstkankervereniging Nederland) critically reviewed and adjusted the questionnaire in comprehensible language and added additional explanations.

2.3. Analysis

Completed questionnaires were merged with the clinical data registered in the NCR.

Generalisability of the results was determined by comparing characteristics of respondents to non-respondents (Pearson's chi-square). Furthermore, NAC-treated and AC-treated respondents were compared on patient, tumour, and treatment characteristics (Pearson's chi-square).

The answers to the questionnaire were assessed separately for stage II and III; NAC-treated compared to AC-treated patients. Conditions of SDM were chi-square tested, as well as the experience with general information on chemotherapy (Q21 to Q24). At last, treatment experience was described by calculating CTSQ-scores [17]: a score between 0 and 100 was assessed separately for each domain for respondents that answered a minimum amount of questions. Higher scores are associated with better responses (better therapy expectations, feeling less impact of side effects, and greater satisfaction with therapy). Means were calculated by the sum of all assessed scores divided by the number of respondents that a score was assessed to. Mean scores were compared using a T-test; we reported 95%-confidence intervals as well. Statistical significance was defined as a p-value <0.05 (two-sided).

All analyses were performed in STATA 14

3. Results

3.1. Respondents to questionnaire (Table 1)

A response rate of 49% (394/805) was reached; 179 (45%) NAC-treated patients versus 215 (55%) AC-treated patients. Respondents did not differ significantly from the non-respondents on patient (age), tumour (year of diagnosis, clinical stage, morphology), and hospital characteristics (volume, type). The ratio of NAC versus AC was comparable between respondents and non-respondents.

NAC-treated respondents were more often treated in a teaching

or academic hospital (including BC-specialised hospitals) and in a high-volume hospital. Moreover, they were generally younger and had a higher SES, and were more often classified with clinical stage III disease (30%) compared to AC-treated patients (7%). Also, there were more triple-negative and Her2-receptor positive tumours in the NAC-treated group. The majority of NAC-treated patients received breast conserving surgery for BC stage II (58%); AC-treated patients received a mastectomy more often (54%, all p < 0.05).

3.2. Conditions of SDM (Table 2)

For BC stage II, 98% and 84% of NAC-treated and AC-treated patients, respectively, received information on chemotherapy prior to surgery (p = 0.000). Among AC-treated patients, receiving information was more common in younger patients (p = 0.061). Further on, information was provided four times as often by the medical oncologist for NAC-treated compared to AC-treated patients respectively (Fig. 1). If information on chemotherapy was provided prior to surgery, 100% of NAC-treated patients versus 14% of AC-treated patients received information on NAC as a possible treatment option (p = 0.000); again, receiving information in the AC-group was more common in younger patients (p = 0.009). Of all respondents that received information on NAC, 85% and 63% of NAC and AC-patients, respectively, stated they received sufficient evidence on the pros and cons of both NAC and AC (p = 0.008). Eventually, NAC-patients could explain more often why she and/or her physician decided the given treatment plan (97% NAC vs 66% AC, p = 0.000).

For BC stage III, 92% and 93% of NAC and AC-treated patients, respectively, received prior to surgery any information on chemotherapy (p = 0.959). Provided information on pros and cons of NAC was stated sufficient in both groups (p = 0.947); almost every patient was able to explain why she and or her physician decided on either NAC or AC (p = 0.362) (Table 2).

3.3. The patient's opinion on SDM (Table 3, Fig. 2)

About half of all respondents with stage II BC (54% NAC, 36% AC) felt they had a real choice in their treatment plan (p = 0.004); 68% and 50% of NAC-treated and AC-treated patients, respectively, described they wanted to decide themselves or shared their decision with their physician (Fig. 2). However, patients who stated they received information on the possibility of chemotherapy (Q10) and NAC specifically (Q11) in both groups felt equally involved in making a decision (54% NAC, 58% AC, p = 0.854 (not in table)). For BC stage III, the treatment plan was already decided in 64% of NAC-treated patients and 50% of AC-treated patients (p = 0.521) (Table 3).

3.4. Experience with general information on chemotherapy

No significant differences were found in the patients' experience with general information on chemotherapy. Over 95% of all respondents received information on their chemotherapy scheme and understood this information (95% NAC, 96% AC). Over 80% of respondents was informed on side-effects of their chemotherapy (NAC 88%, AC 84%). Both groups scored very high regarding understanding the information they received on chemotherapy (94% NAC, 96% AC). Respondents felt they had the opportunity to ask questions about chemotherapy (92% NAC, 95% AC).

3.5. Treatment experience with chemotherapy (CTSQ, Fig. 3)

Significant differences between NAC-treated and AC-treated patients, respectively, were found in the treatment experience

(Fig. 3). Mean EOT-scores for both NAC-treated and AC-treated patients were high (68 NAC, 68 AC; p = 0.948), meaning that overall, respondents had a high believe in chemotherapy contributing to their cancer treatment. FSE-scores were moderate (46 NAC, 45 AC; p = 0.714), meaning respondents felt their side effects were as severe as expected beforehand. In totality, NAC-treated patients were less satisfied with their chemotherapy than AC-treated patients (40 NAC, 42 AC; p = 0.018).

4. Discussion

This study highlights important aspects in the decision-making process on the timing of chemotherapy (NAC vs AC) for early breast cancer. If information on chemotherapy was provided prior to surgery, 100% of NAC-treated patients versus 14% of AC-treated patients received information on NAC as a possible treatment option. Of those who received information on NAC, 85% and 63% of patients treated with NAC and AC, respectively, stated that they received sufficient evidence on the pros and cons of both NAC and AC.

The results of this survey confirm that the choice regarding either NAC or AC is often not discussed with patients with stage II-III breast cancer prior to treatment. This suggests that clinicians rarely express that a treatment decision needs to be made, and patients may not realize that neoadjuvant treatment is a valid choice. In order to make a decision, sufficient information and relevant evidence on pros and cons of all treatment options should be provided before the start of therapy. Patients treated with AC were less informed about this treatment decision than NAC-treated respondents, and stage II respondents were less informed than stage III respondents.

Further on, both patients' and clinicians' preferences should be incorporated in treatment plans [14]. Few AC-treated respondents with BC stage II were able to explain reasons for adjuvant timing of systemic treatment instead of neoadjuvant timing. Moreover, about half of respondents did not feel they had a choice regarding timing of systemic treatment. These results reveal the impaired role of participation of patients in SDM on NAC.

Several potential explanations are present. First, the Dutch and international breast guidelines are straightforward about the recommendation of NAC for stage III BC [1,9,10], but the evidence of NAC for stage II BC is not included in the guidelines yet, since it is based on promising preliminary data and research [18,19]. Seemingly, treatment decisions are predominantly guideline-congruent, and when guidelines are not clear, clinicians' recommendations to patients are not uniform either. Consequently, differences in clinicians' opinions may lead to variation in treatment patterns, as confirmed by the NBCA audit results and other recent studies [11,13].

Moreover, clinicians' opinions exert one of the most powerful influences over patients' preferences [20]. Also, patients are often not aware that a treatment decision is required [20]. The health professional first speaking with the patient plays an important role in how information is conveyed, whether this is a surgeon, medical oncologist, nurse practitioner, or physician assistant. This will most likely drive the treatment decision. According to our survey, most of the information about NAC was provided by medical oncologists, of whom we expect stronger support for applying NAC than from surgeons. A referral from the surgeon to the medical oncologist defines whether a patient actually will have a consultation with an oncologist. In addition, appropriate information and additional support is essential to make quality decisions. Decision support-systems may help patients allow them to be primary decision maker [21]. Thirdly, the level of training of clinicians, conference attendance, and multidisciplinary meeting groups on a regular base
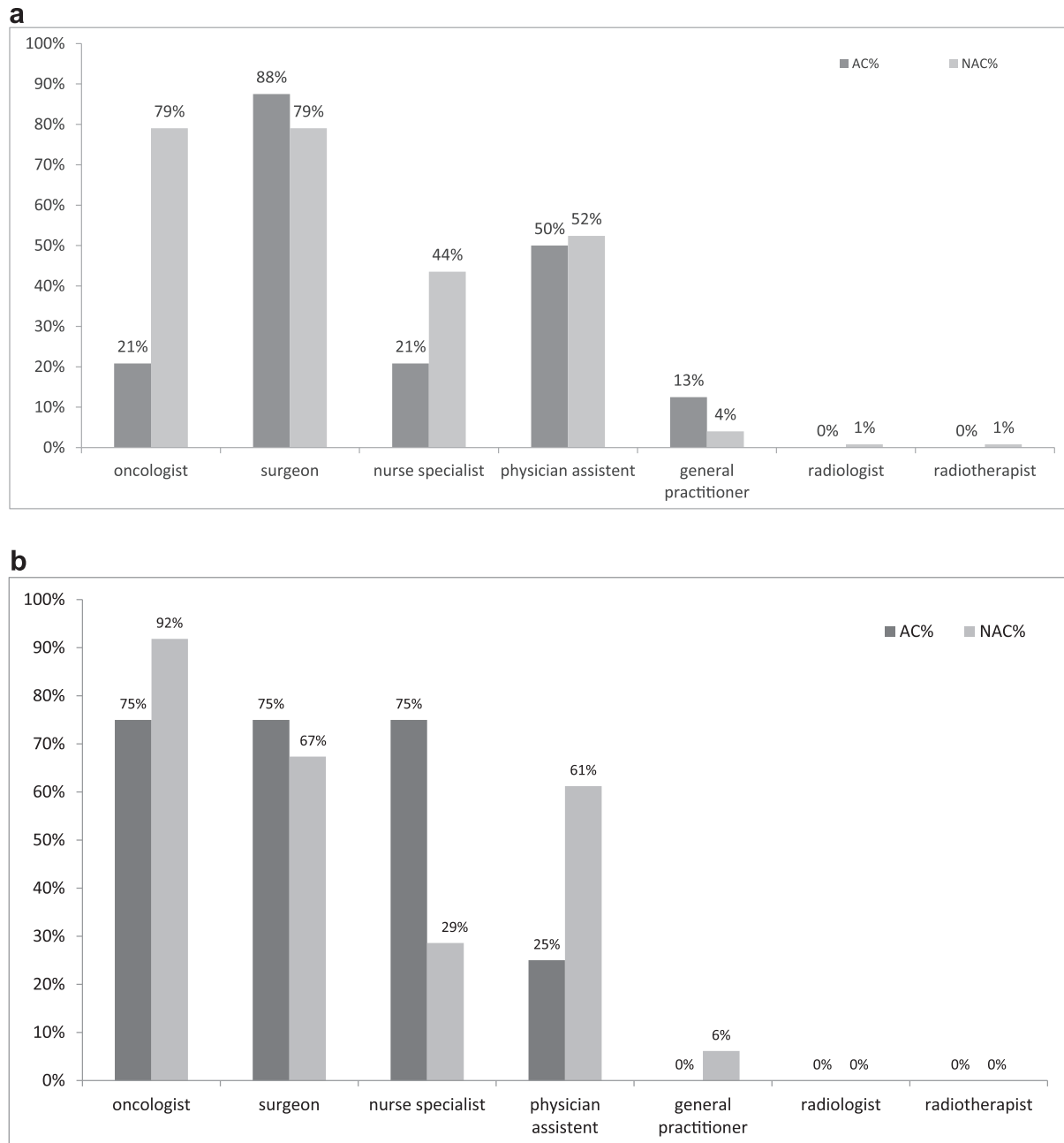
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b

Fig. 1. Information on chemotherapy provided prior to surgery by physicians during pre-surgical consultation(s), NAC vs AC, stage II (a) and stage III (b) separately (Q12).

may play a crucial role by creating more choice-awareness in preference-sensitive decisions.

Also, the preferred role of patients in preference-sensitive decisions is influenced by patients' age and education. Older and less educated patients are more likely to prefer a passive or collaborative role [22], whereas an active role is generally preferred by younger and better educated patients [23]. We observed that NAC-treated patients treated were younger and better educated, while being better informed as well. Patient's participation in their treatment plan is important because a high level of involvement is associated with improved outcome in quality of life, physical and social functioning. Patient's involvement led to high levels of satisfaction with the decision and the subsequent treatment they received [24]. Even if the fit of treatment to preferences is not enhanced, the fact that patients are involved and felt meaningful to

the situation may increase satisfaction [25]. Moreover, patients could be pleased to know whether their tumour responded or progressed on NAC, which can be valuable contribution under conditions of uncertainty.

Finally, the most common explanations for the application of NAC in stage II and stage III patients were tumour size and axillary metastases. These explanations correspond with reported results from cancer registries [11,13]. While NAC aims to downsize the tumour to improve the possibility of breast conservation surgery, it was expected that more respondents were treated with BCS after NAC [4,26]. However, in our survey the patient's desire for BCS was the major reason for NAC in only 28% of BC stage II patients. Valid options to refrain from chemotherapy (NAC or postoperative) may have been contraindications such as poor performance status or severe comorbidity. Also, it may be possible that women prefer to

Table 1
Characteristics respondents treated with NAC vs AC.

	NAC (n = 179)	(%)	AC (n = 215)	(%)	P (Chi^2)
Patient characteristics					
Age at diagnosis					0.000
<40	19	11%	14	7%	
40–49	74	41%	65	30%	
50–59	55	31%	58	27%	
60+	31	17%	78	36%	
Comorbidities					0.987
None	119	66%	140	65%	
1	48	27%	59	27%	
2 or more	10	6%	13	6%	
Missing	2	1%	3	1%	
Socio-economic status (SES)[a]					0.008
High	65	36%	55	26%	
Medium	73	41%	82	38%	
Low	41	23%	78	36%	
Education					0.093
Secondary school (low level) or lower	19	11%	43	20%	
Secondary school (medium level)	38	21%	49	23%	
Secondary school (high level)	22	12%	26	12%	
Intermediate vocational training (MBO)	39	22%	41	19%	
Higher vocational training (HBO) and university	58	32%	50	23%	
Other/unknown	3	2%	6	3%	
Tumour characteristics					
Stage (short), clinical					0.000
II	126	70%	201	93%	
III	53	30%	14	7%	
Hormone receptor status (based on biopsy supplemented with post-OK information)					0.028
Triple negative	33	18%	29	13%	
Hormone-negative, Her2-positive	15	8%	14	7%	
Hormone-positive, Her2-positive	29	16%	23	11%	
Hormone-positive, Her2-negative	99	55%	149	69%	
Unknown	3	2%	0	0%	
Treatment characteristics					
Type of surgery (based on final surgery)					
Stage II (clinical)					0.032
Breast Conserving/Lumpectomy	73	58%	92	46%	
Mastectomy	53	42%	109	54%	
Stage III (clinical)					0.124
Breast Conserving/Lumpectomy	14	26%	1	7%	
Mastectomy	39	74%	13	93%	
Hospital characteristics					
Hospital type					0.026
General	47	26%	79	37%	
Teaching or academic (incl. BC specialised hospital)	132	74%	136	63%	
Hospital surgical volume[b]					0.000
Low	58	32%	112	52%	
Middle	77	43%	75	35%	
High	44	25%	28	13%	

[a] Socio-economic status (SES) of the patients was based on four-digit postal code at time of surgery; SES scores are provided by the Netherlands Institute for Social Research (Social Cultural Planbureau) and divided into three groups based on the delivered rank numbers: low (1st-3rd deciles), intermediate (4th-7th) and high (8th-10th) SES.

[b] Hospitals were categorised by surgical volume for primary breast cancer, defined as the mean annual number of BC surgeries during the period 2011–2015; categorised as low (<150), medium (150–300), and high (300<) volume.

Table 2
Conditions of Shared Decision-Making (SDM), NAC vs AC; separate for stage II and III.

Q		NAC	(%)	AC	(%)	P (Chi^2)
	Stage II (n=126 NAC, 201 AC)					
10	Patients received information on chemotherapy in general before surgery (n = 126 NAC, 201 AC)	124	98%	169	84%	0.000
11	Patient was given information about NAC (n = 124 NAC, 169 AC)	124	100%	24	14%	0.000
13	Patient received sufficient information on pros and cons of both AC and NAC (n = 124 NAC, 24 AC)	106	85%	15	63%	0.008
14, 16	Patient was able to explain why she and/or the physician chose for either NAC or AC (n = 126 NAC, 201 AC)	122	97%	132	66%	0.000
	Stage III (n=53 NAC, 14 AC)					
10	Patients received information on chemotherapy in general before surgery (n = 53 NAC, 14 AC)	49	92%	13	93%	0.959
11	Patient was given information about NAC (n = 49 NAC, 13 AC)	49	100%	4	31%	0.000
13	Patient received sufficient information on pros and cons of both AC and NAC (n = 49 NAC, 4 AC)	36	73%	3	75%	0.947
14, 16	Patient was able to explain why she and/or the physician chose for either NAC or AC (n = 53 NAC, 14AC)	50	94%	14	100%	0.362

undergo surgery first, but these considerations should be clearly discussed.

Overall, the results of our study showed that general experience (CTSQ) with chemotherapy in terms of side effects was scored equal
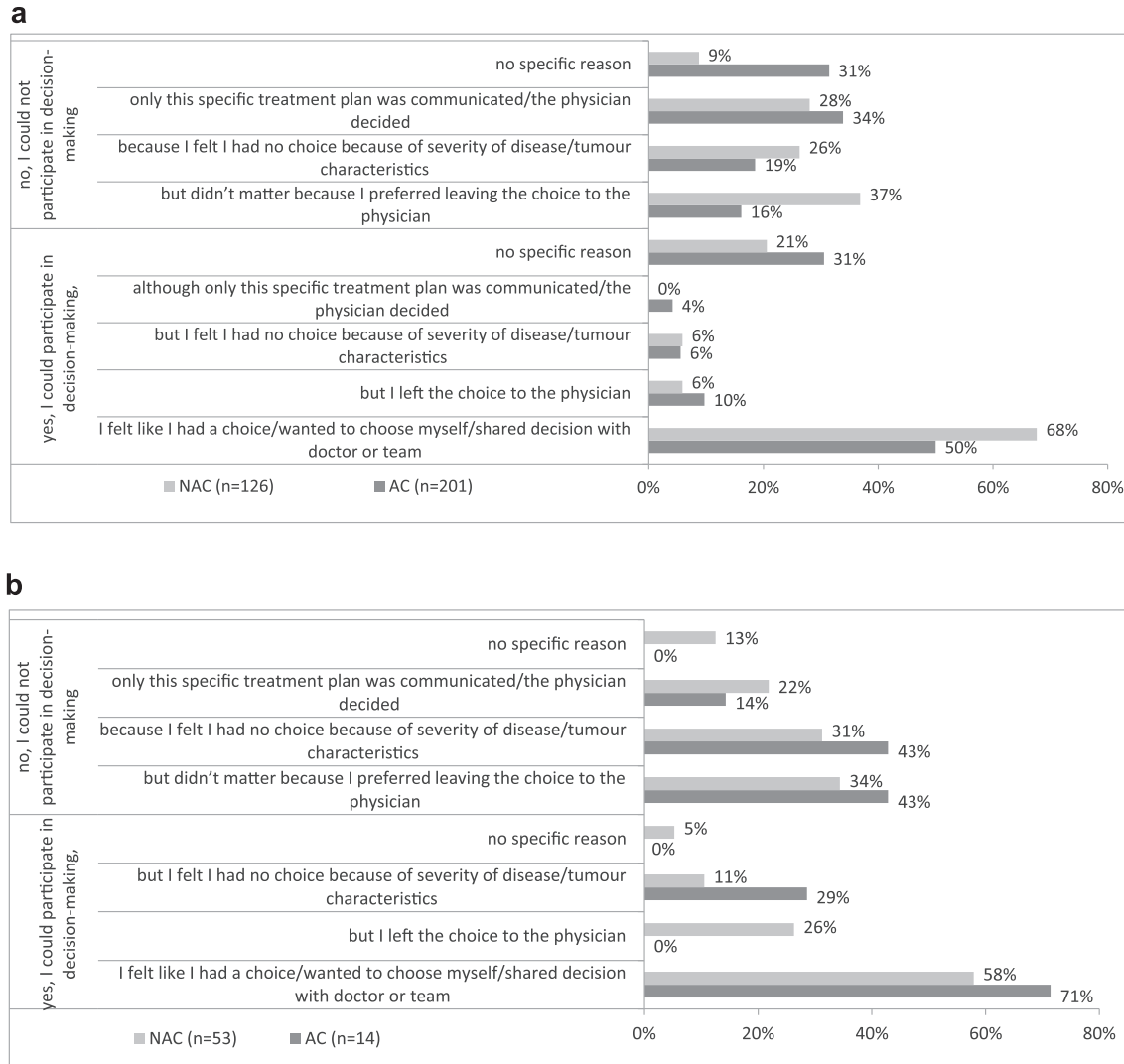
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Fig. 2. The patients opinion on SDM, separate for stage II (a) and III (b) (Q18, categorization of free text fields).

Table 3
The patients opinion on Shared Decision-Making (SDM), NAC vs AC; separate for stage II and III.

Q		NAC (n = 126)	(%)	AC (n = 201)	(%)	P (Chi2)
	Stage II (n=126 AC, 201 AC)					
18	Patient felt she did have a choice in either choosing for NAC or AC (n = 126 NAC, 201 AC)	68	54%	72	36%	0.008
20	Patient felt she had enough time to decide on either NAC or AC (n = 68 NAC, 72 AC)	67	99%	72	100%	0.302
	Stage III (n=53 NAC, 14 AC)					
18	Patient felt she did have a choice in either choosing for NAC or AC (n = 53 NAC, 14AC)	19	36%	7	50%	0.521
20	Patient felt she had enough time to decide on either NAC or AC (n = 19 NAC, 7 AC)	19	100%	7	100%	0.923

in both groups, but significant differences between groups were found in final satisfaction with care; NAC-treated patients seem to be less satisfied. The most likely explanation for this result, is the difference in approach in NAC-treated patients, in which NAC is commonly being used for down-staging of the tumour to increase resectability and enable BCS. When the response to chemotherapy appears to be disappointing and BCS does not seem possible, satisfaction could be less. Also, mostly young women receive NAC, which will have a big impact on their daily lives. However, these negative perceptions reiterate the importance of counselling support, communication, and expectation management.

4.1. Strengths and limitations

To our knowledge, this is the first study reflecting patients' experiences with decisions on the timing of chemotherapy for early BC. Previous literature focused mainly on experiences with decisions on adjuvant therapies for BC [27,28]. In the context of an increasing trend in NAC use [11,26], insight in patients' experience in SDM on NAC is extremely relevant.

Because of the connection between the clinical cancer registry and the patient reported experiences, this study is unique in design. We reached a high response rate of almost 400 respondents (49%) and selected a homogeneous comparable population compared to
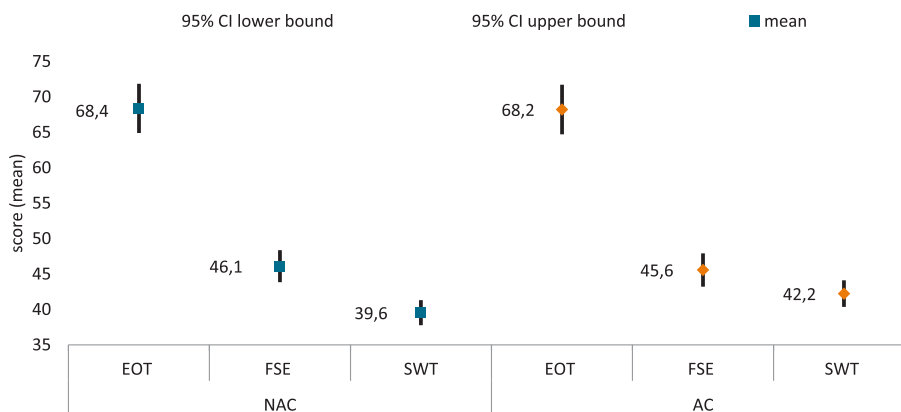
Fig. 3. Treatment experience, mean CTSQ-scores per domain* and chemotherapy treatment, incl. 95% lower and upper confidence interval for NAC and AC separately (n = 179 NAC, 215 AC).
*domains: Expectation of Therapy (EOT), Feelings about Side Effects (FSE), and Satisfaction With Therapy (SWT); range 0 (low score) to 100 (high score).

non-responders. The absolute number of BC stage III respondents was small, but because of the strict indication of NAC for these patients, this group was less relevant to discuss. Participation was opt-in, leading to selection bias in which those who responded were probably more critical on SDM then non-responders; providing paper questionnaires on request could lead to an underrepresentation of patients with lack of computer skills or access. Also, recall bias is a known limitation of all survey studies. Idem, creating a patient-comprehensible questionnaire is a difficult task. We were favoured by input from the Dutch patient association on breast cancer. Besides, we emphasize the fact that patient-reported data is based on the experience of patients, rather than a factual reflection of how decisions on chemotherapy timing were made. Furthermore, unfortunately, the numbers of respondents per hospital were too small to analyse intra-hospital variation in SDM; this would be interesting for further research.

5. Conclusion

In conclusion, our study revealed that the need to make a treatment decision on the timing of chemotherapy (NAC vs AC) for early breast cancer was discussed with only a small number of patients, in particular in BC stage II. Less than half of the respondents felt they had a real choice. Clinicians' opinions exert one of the most powerful influences over patients' preferences. National guidelines that are frequently updated and a continuous audit system integrating detection and real-time feedback will help in providing clear guidance to physicians for chemotherapy treatment timing with decision-making as a result of team work of all involved disciplines. By understanding patient preferences and incorporating them into treatment decisions, it will be possible to reduce unwarranted variations and deliver appropriate patient-centred care.

Disclosures

The authors report no conflict of interest.

Ethical approval

Approval from the Committee of Privacy of the Netherlands Cancer Registry was obtained for this study. The Medical Ethical Committee of the Netherlands Cancer Institute - Antoni van Leeuwenhoek declared that the Medical Research Involving Human Subjects Act (WMO) did not apply for this study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.breast.2017.10.016.

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