Patient Education and Counseling 101 (2018) 2111–2115

Contents lists available at ScienceDirect

Patient Education and Counseling

journal homepage: www.elsevier.com/locate/pateducou

# Current decisions on neoadjuvant chemotherapy for early breast cancer: Experts' experiences in the Netherlands

P.E.R. Spronk[a,*], K.M. de Ligt[b], A.C.M. van Bommel[a], S. Siesling[b,c], C.H. Smorenburg[d], M.T.F.D. Vrancken Peeters[e], On behalf of the NABON Breast Cancer Audit

[a] Department of Surgery, Leiden University Medical Centre, Leiden, The Netherlands
[b] Department of Research, Comprehensive Cancer Centre the Netherlands (IKNL), Utrecht, The Netherlands
[c] Department of Health Technology and Services Research, MIRA Institute for Biomedical Science and Technical Medicine, University of Twente, Enschede, The Netherlands
[d] Department of Medical Oncology, Antoni van Leeuwenhoek, Amsterdam, The Netherlands
[e] Department of Surgery, Antoni van Leeuwenhoek, Amsterdam, The Netherlands

ARTICLE INFO

*Article history:*
Received 27 January 2018
Received in revised form 3 July 2018
Accepted 17 July 2018

*Keywords:*
Neoadjuvant chemotherapy (NAC)
Early breast cancer
Experts' opinions

ABSTRACT

*Purpose:* To evaluate the opinion of surgical and medical oncologists on neoadjuvant chemotherapy (NAC) for early breast cancer.
*Methods:* Surgical and medical oncologists (N = 292) participating in breast cancer care in the Netherlands were invited for a 20-question survey on the influence of patient, disease, and management related factors on their decisions towards NAC.
*Results:* A total of 138 surgical and medical oncologists from 64 out of 89 different Dutch hospitals completed the survey. NAC was recommended for locally advanced breast cancer (94%) and for downstaging to enable breast conserving surgery (BCS) (75%). Despite willingness to downstage, 64% of clinicians routinely recommended NAC when systemic therapy was indicated preoperatively. Reported reasons to refrain from NAC are comorbidities (68%), age >70 years (52%), and WHO-performance status ≥2 (93%). Opinions on NAC and surgical management were inconclusive; while 75% recommends NAC to enable BCS, some stated that BCS after NAC increases the risk of a non-radical resection (21%), surgical complications (9%) and recurrence of disease (5%).
*Conclusion:* This article emphasizes the need for more consensus among specialists on the indications for NAC in early BC patients. Unambiguous and evidence-based treatment information could improve doctor-patient communication, supporting the patient in chemotherapy timing decision-making.


## 1. Introduction

Neoadjuvant chemotherapy (NAC) is an important initial strategy for the management of operable breast cancer (BC). In accordance with international guidelines, the Dutch national breast cancer guideline recommends NAC as an option for all patients aged <70 with an indication for systemic treatment, as similar overall and disease-free survival rates were demonstrated between preoperative and postoperative application of chemotherapy [1–4]. These guidelines disclose that NAC may be used for large tumours (T3; >5 cm) to increase resectability and the rate of breast conserving surgery and axillary preserving surgery [5]. Besides, chemotherapy prior to breast surgery remains a valuable therapeutic approach for the assessment of biological anti-tumour activity and clinical efficacy of new treatments [6]. Furthermore, administration of NAC creates a time frame for testing on hereditary breast cancer and planning the final type of surgery, for example reconstruction surgery.

Despite these arguments in favour of NAC, large national and international variation in the application of NAC is observed between hospitals [7,8]. Previous research based on data from the NABON Breast Cancer Audit (NBCA) revealed that most variation between hospitals consists in the treatment of BC stage IIB with a national average of 40% NAC use. For BC stage III, the national average is 80%.

After adjustment for patient and tumour factors associated with the use of NAC, including hospital study participation, a considerable unaccountable variation still remained between all 89 Dutch hospitals [9,10].

* Corresponding author at: Dutch Institute for Clinical Auditing (DICA), Department of Surgery, Leiden University Medical Centre, Poorgebouw Zuid 1e etage, Rijnsburgerweg 10, 2333 AA Leiden, The Netherlands.
*E-mail address:* p.e.r.spronk@lumc.nl (P.E.R. Spronk).

https://doi.org/10.1016/j.pec.2018.07.012
0738-3991/

Additional factors, such as clinician preferences and the level of shared decision-making, may play a role in the application of NAC [11]. Since it has been demonstrated that clinicians' treatment recommendations exert one of the most powerful influences over patients' preferences, the clinicians' opinion on NAC is therefore of great importance [12]. Some specialists adhere firmly to their personal treatment preferences which may lie outside evidence of best practice or safety [13]. Consequently, differences in surgeons and medical oncologists' opinions may lead to unwanted variation in treatment patterns. As options of chemotherapy timing are in equilibrium for overall and disease-free survival, but NAC also yields several advantages, it is important to gain insight in the observed variation of NAC application, as each patient indicated for NAC deserves a choice in chemotherapy timing. The aim of this study is to evaluate the current opinion of surgical and medical oncologists in the Netherlands on the use of NAC and their decisions towards NAC in early breast cancer.

## 2. Methods

### 2.1. Participants

On November 11, 2015, an invitation for an online survey was sent by mail to 575 surgical and medical oncologists, invited by the network of the NABON Breast Cancer Audit (NBCA), covering all Dutch hospitals that are involved in breast cancer care. A reminder was sent to non-respondents 3 weeks later and the survey was closed on January 8th, 2016.

Demographics of participating hospitals were derived from the NBCA dataset. The surgical volume of a hospital was defined as the mean annual number of breast cancer surgeries during the period 2011–2015; divided into low-volume (<150), mid-range (150–300) and high-volume (>300) categories. Type of hospital was described as academic, teaching, and general hospitals. Academic hospitals are part of a university, and both academic and teaching hospitals provide medical training to surgical residents.

### 2.2. Survey

The survey was developed by a multidisciplinary taskforce, including a medical oncologist, a breast cancer surgeon, a clinical epidemiologist and medical researchers. Hereafter, the survey was pre-tested and modified based on the obtained feedback. The survey consisted of 20 questions about (contra) indications and considerations for NAC and general information about the survey participants. Part one of the survey consisted of eight questions about commonly accepted indications and contraindications of NAC on the following categories: tumour characteristics (tumour size, stage and biology), patient characteristics (age, performance status and comorbidities) and clinical disease management (genetic testing and timing of final surgery) (supplement 1). The 5-point Likert scale was used to allow the respondent to express how much they agree or disagree. Part two of the survey consisted of four questions about other possible considerations that could influence the use of NAC (evidence in overall and disease-free survival benefit of NAC, axillary conservation surgery, risk of complications, risk of non-radical resections), using a yes/no scale. Throughout the survey there was the ability to write and add comments in the responses. To get an idea of the level of experience per specialist, demographic data, numbers of years in specialty, numbers of patients treated, and questions on study participation were included in the survey.

### 2.3. Statistical analysis

Frequencies and percentages were used to display responses to individual questions. Differences between surgical and medical oncologists' responses were analysed using Pearson chi-square. Statistical significance is defined as a two-sided p value <0.05. All

**Table 1**
Respondents' and affiliated hospital demographics.

| | Surgeons (N = 70) | Oncologists (N = 68) | Hospitals (N = 64) | *P-value* |
|---|---|---|---|---|
| Sex | | | | |
| Male | 40 | 28 | | *0,106* |
| Female | 30 | 40 | | |
| n of yrs in practice | | | | |
| <10 | 27 | 27 | | *0,774* |
| 10–19 | 32 | 27 | | |
| 20+ | 11 | 14 | | |
| n of patients per specialist/year | | | | |
| <50 | 8 | 24 | | *0,001* |
| 50–99 | 23 | 25 | | |
| 100+ | 32 | 15 | | |
| n of patients per specialist included in NAC studies/year | | | | |
| <10 | 21 | 12 | | *0,001* |
| >10 | 39 | 52 | | |
| Volume of hospital[a] | | | | |
| <150 | 27 | 29 | 31 | *0,578* |
| 150–300 | 23 | 25 | 22 | |
| >300 | 20 | 14 | 11 | |
| Type of hospital[a] | | | | |
| General- | 19 | 22 | 24 | *0,281* |
| Teaching hospital- | 43 | 33 | 34 | |
| Academic- | 8 | 13 | 6 | |

[a] Derived from the NBCA.

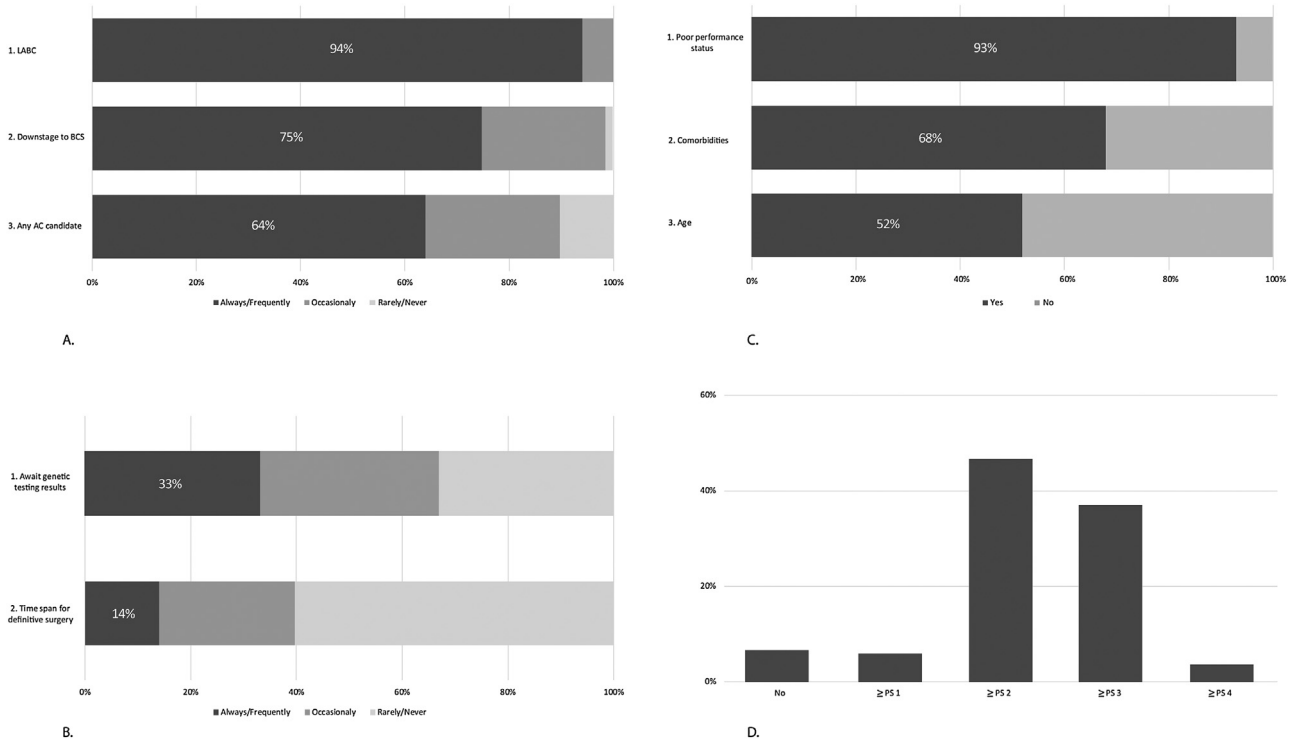


**Fig. 1.** A. Reported indications (tumour characteristics) for recommending NAC. B. Reported indications (clinical management factors) for recommending NAC. C. Reported contraindications (patient characteristics) for recommending NAC. D. Most common reported contraindication: performance status ≥2.

analyses are performed in PASW Statistics version 24 (SPSS inc Chicago, IL, USA).

## 3. Results

A total of 292 clinicians opened the online program, of whom 138 clinicians from 64 out of 89 Dutch hospitals completed the survey, leading to a response rate of 473%. Of 138 respondent clinicians, 70 surgical oncologists (43% female, 57% male) and 68 medical oncologists (59% female, 41% male) participated in the survey. The respondents had been in clinical practice for a median of 12 years (range 1–35). The number of annually treated breast cancer patients varied from 50 patients for medical oncologists (range 15–110) to 70 patients for surgical oncologists (range 30–110). The majority of clinicians included more than 10 patients in neoadjuvant chemotherapy trials per year. This survey represented two-third of Dutch hospitals; 22 hospitals had only one representative and 42 hospitals were represented by 2–7 representatives. Medical oncologists and surgical oncologists were evenly represented according to type and volume of hospitals (Table 1).

### 3.1. Survey

Respondents rated locally advanced breast cancer (LABC) as the most distinguished indication for NAC (94%). The second commonly accepted indication is down staging of the tumour to enable breast conserving surgery (75%). Of all respondents, 64% "always to frequently" recommended NAC if systemic therapy is indicated preoperatively, based on known clinical tumour characteristics (Fig. 1A). Reported reasons to refrain from NAC were WHO-performance status ≥2 (93%), comorbidities (68%), and age >70 years (52%) (Fig. 1C and D). A WHO-performance score of ≥2, which implies an inability to carry out any work activities, was reported as the most common contraindication. Age by itself was no contraindication according to 48% of respondents. But if so, patients aged <70 seemed to be the main reason for restrained application of NAC. Clinical management factors, such as the time necessary for testing on hereditary breast cancer or to plan the final type of reconstructive surgery, were less frequently denominated as indications for NAC (Fig. 1B).

In the second part of the survey, clinicians were asked about other considerations that could influence the use of NAC (Table 2).

**Table 2**
Agreement with statements on NAC by responding surgeons and medical oncologists.

| | YES | Surgeons (N = 70) | Oncologists (N = 68) | *P-value* |
|---|---|---|---|---|
| "NAC improves the chance of achieving axillary conservation surgery" | 63% | 708% (46) | 629% (39) | 0346 |
| "NAC increases the risk of surgical complications" | 9% | 133% (8) | 6,9% (4) | 0247 |
| "Breast conservation surgery after NAC increases the risk of a non-radical resection" | 21% | 292% (19) | 158% (9) | 0078 |
| "Breast conservation surgery after NAC increases the risk of recurrence" | 5% | 6,5% (4) | 4,8% (3) | 0697 |
| "There is no evidence for an overall and disease-free survival benefit of NAC compared to AC" | 60% | 623% (33) | 828% (48) | 0015 |

More than half of the respondents (60%), especially medical oncologist (83%), stated that the evidence in overall and disease-free survival benefits of NAC compared to adjuvant chemotherapy is not established yet (p-value: 0015). While in the first part of the survey 75 percent of the respondents mentioned increased breast conservation rate as an indication for NAC, a concern about non-radical resections is raised by 21% of the respondents (surgeons 292%, medical oncologists 158%, p-value:0.078). A minor consideration in performing surgery after NAC was the increased chance of surgical complications (9%). Finally, in a relative high percentage of clinicians (63%), NAC is also being used to enable axillary conserving surgery.

In added comments, a frequently described benefit of neoadjuvant therapy was the extra time for patient work-up for surgery, for example in case of controlling diabetes or smoking cessation. Reported barriers for recommending NAC were lack of patient cooperation, logistic challenges (for example a far travel distance to the hospital), a term pregnancy, oocyte preservation, or a patient's desire to undergo surgery first.

## 4. Discussion

This survey depicts the opinion of 138 Dutch surgical and medical oncologists from 64 out of 92 hospitals in the Netherlands on NAC in BC. Despite an international trend of increasing implementation for NAC in patients with early BC and the relatively high standard of care in the Netherlands, considerable variation in the use of NAC still exists between hospitals.

Respondents rated LABC as the most distinguished indication for NAC, in accordance with Dutch and international breast cancer guidelines [12]. In addition, the St. Gallen Breast Cancer Conference, that focuses exclusively on the primary therapy of early breast cancer, recommends to consider NAC based on tumour biology [14,15]. Our survey demonstrates that only 64% of clinicians recommends NAC instead of adjuvant chemotherapy when systemic therapy is indicated based on tumour biology. The actual NAC use is even lower based on NBCA-data (40% in BC stage II). With the increased evidence that subgroups of patients that achieve pCR after NAC do have a better prognosis in terms of disease-free and overall survival, NAC should nowadays be considered as a preferred option in the treatment of high risk triple negative BC and HER2 BC [3,4,16].

Another commonly accepted indication for NAC – confirmed by our survey - is to increase the chance of breast conservation surgery (BCS) without compromising the local recurrence rate. The ESMO guidelines on primary breast cancer advice primary systemic therapy in locally advanced and large operable cancers to allow for achieving operability or decreasing the extent of surgery [17]. In our survey, 75% of respondents recommend NAC to enable BCS. Contradictory, a relatively high percentage of 21% of respondents argued that BCS after NAC increases the risk of non-radical (i.e. resection with positive margins) resections. The restraint to use NAC to enable BCS may arise from the challenge for surgeons to determine the extent and original location of the residual lesion after NAC. More recently than our survey, a nationwide Dutch pathology study showed tumor-involved margins in 24.3% patients after BCS after NAC, compared to 103% after primary BSC [18]. According to Dutch National guidelines, a tumor-free margin is defined as the absence of tumor cells at the inked margins. Although surgical experiences have been improved by the introduction of iodine-125 seeds and ultrasound guided surgery, monitoring and localization techniques are still under research [19]. It is likely that clinicians' decisions towards NAC are mainly driven by surgical management goals, rather than tumour biology and survival.

Other incentives to consider NAC, such as time necessary for testing on hereditary breast cancer, are less frequently denominated as indication of importance. Only 33% of the clinicians recommends NAC to await genetic testing results, while the discovery of a BRCA1/2 mutation may influence treatment strategies. Also, extra time for patient work-up to plan the final type of reconstructive surgery is less frequently considered important. However, NAC has the potential for improving cosmetic outcomes in oncoplastic surgery [20]. Another important consideration described by clinicians in favour of chemotherapy prior to breast surgery is the possibility to asses anti-tumour activity and clinical efficacy of new treatments in neoadjuvant chemotherapy trials [21].

The survey also revealed concerns that prevented clinicians from recommending NAC. A patients' WHO-performance status of $\geq$2 was stated most frequently as reason to refrain from NAC, rather than advanced age. This is consistent with the idea that older patients, when selected correctly, can be treated safely with chemotherapy and that age only is no reason to refrain [22].

Although it can be questioned if these 138 experts represent the major opinion of NAC for breast cancer in the Netherlands, the main strength of this survey is that the respondents reflect practice preferences of 64 out of 89 Dutch hospitals: which means a 72% nationwide coverage, which stands for the treatment of almost 15.000 patients annually [10]. If this survey would be repeated, we expect same differences in opinions between experts' to be demonstrated. However, surveys rely heavily on the respondents' memory and opinion, thus bias should always be kept in mind when interpreting survey results.

### 4.1. Conclusion

Considerable variation exists in expert opinions on NAC for early breast cancer. This article highlights the complexity of decision making for early breast cancer patients and it emphasizes the need for more consensus among specialists on the indications for NAC in early BC patients.

### 4.2. Practice implications

The results of this survey highlight the importance of dynamic updates of reliable clinical practice guidelines, to standardize and ensure medical quality and safety. In other words: not only clinicians' awareness on multiple arguments in favour of the use of NAC could be improved, but also the sharing of considerations and experiences – as this brief report detailing clinical practices of Dutch surgical and medical oncologists - will speed up and clarify the implementation of NAC in early breast cancer. Ultimately, it is important that patients receive unambiguous and evidence-based treatment information in order to take part in a useful process of shared decision-making. The authors do not necessarily advocate that every patient should receive NAC; however, every patient eligible to NAC should receive a choice in chemotherapy timing. Another work by our group describes how patients perceived the choice in chemotherapy timing [23].

## Role of the funding source

We would like to thank the Dutch Cancer Society (KWF) for their financial support by providing the grant on "Research on (improving) quality of oncological care – 2015". The Dutch Cancer Society is a nation-wide organization for cancer related work in the Netherlands. It's supported by over 1 million donors and receives no money from the government.

## Conflict of interest

Non-declared.

## Acknowledgements

We would like to thank all surgeons and medical oncologists for their participation in the survey.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pec.2018.07.012.

## References

[1] Dutch National Breast Cancer Guideline, (2012) . Available at: http://www.oncoline.nl/mammacarcinoom [Version 2.0, 2012]..
[2] D. Holmes, A. Colfry, B. Czerniecki, et al., Performance and practice guideline for the use of neoadjuvant systemic therapy in the management of breast cancer, Ann. Surg. Oncol. 22 (10) (2015) 3184–3190.
[3] G. Von Minckwitz, M. Untch, E. Nüesch, et al., Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials, Breast Cancer Res. Treat. 125 (1) (2011) 145–156.
[4] P. Cortazar, L. Zhang, M. Untch, K. Mehta, J.P. Costantino, N. Wolmark, H. Bonnefoi, D. Cameron, L. Gianni, P. Valagussa, S.M. Swain, T. Prowell, S. Loibl, D. L. Wickerham, J. Bogaerts, J. Baselga, C. Perou, G. Blumenthal, J. Blohmer, E.P. Mamounas, J.W. Bergh, Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis, Lancet 384 (9938) (2014) 164–172.
[5] E. Barranger, J. Antomarchi, E. Chamorey, et al., Effect of neoadjuvant chemotherapy on the surgical treatment of patients with locally advanced breast cancer requiring initial mastectomy, Clin. Breast Cancer 15 (5) (2015) 1–5.
[6] A. Berruti, M.P. Brizzi, D. Generali, et al., Presurgical systemic treatment of nonmetastatic breast cancer: facts and open questions, Oncologist 13 (11) (2008) 1137–1148.
[7] S.S. Mougalian, P.R. Soulos, B.K. Killelea, et al., Use of neoadjuvant chemotherapy for patients with stage i to III breast cancer in the United States, Cancer 121 (15) (2015) 2544–2552.
[8] A.C.M. van Bommel, P.E.R. Spronk, M.-J.T.F.D. Vrancken Peeters, et al., Clinical auditing as an instrument for quality improvement in breast cancer care in the Netherlands: the national NABON Breast Cancer Audit, J. Surg. Oncol. (June) (2016) 1–7.
[9] P.E.R. Spronk, A.C.M. van Bommel, C.H. Smorenburg, et al., Variation in use of neoadjuvant chemotherapy in patients with stage III breast cancer: results of the Dutch national breast cancer audit, Breast 36 (2017) [submitted].
[10] DICA annual rapport. Available at: https://www.dica.nl/jaarrapportage-2014/nbca.
[11] M. Kunneman, E.G. Engelhardt, F.L.L. Hove, et al., Deciding about (neo-) adjuvant rectal and breast cancer treatment: missed opportunities for shared decision making, Acta Oncol. 55 (2016) 134–139.
[12] J.P. Wei, R.M. Sherry, B.L. Baisden, J. Peckel, G. Lala, Prospective hospital-based survey of attitudes of Southern women toward surgical treatment of breast cancer, Ann. Surg. Oncol. 2 (4) (1995) 360–364.
[13] L.J.M. Caldon, S.J. Walters, J. Ratcliffe, M.W.R. Reed, S. Sheffield, What influences clinicians' operative preferences for women with breast cancer? An application of the discrete choice experiment, Eur. J. Cancer 43 (July (11)) (2007) 1662–1669.
[14] M. Gnant, C. Thomssen, N. Harbeck, St. Gallen/Vienna 2015: a brief summary of the consensus discussion, Breast Care 10 (2) (2015) 124–130.
[15] Onclive 2017. Available at: http://www.onclive.com/conference-coverage/st-gallen2017/neoadjuvant-therapyfundamental-in-tnbc-and-her2-breast-cancer.
[16] P. Cortazar, C.E.Jr. Geyer, Pathological complete response in neoadjuvant treatment of breast cancer, Ann. Surg. Oncol. 22 (5) (2015) 1441–1446.
[17] C.H. Barrios, J. Bergh, F. Cardoso, et al., 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3), Ann. Oncol. 31 (2017) 244–259.
[18] J.H. Volders, M.H. Haloua, N.M.A. Krekel, Neoadjuvant chemotherapy in breast-conserving surgery – consequences on margin status and excision volumes: a nationwide pathology study, Eur. J. Surg. Oncol. 42 (July (7)) (2016) 986–993.
[19] M.K. Hayes, Update on preoperative breast localization, Radiol. Clin. N. Am. 55 (May (3)) (2017) 591–603.
[20] R. Jagsi, Y. Li, M. Morrow, et al., Patient-reported quality of life and satisfaction with cosmetic outcomes after breast conservation and mastectomy with and without reconstruction, Ann. Surg. 261 (6) (2015) 1198–1206.
[21] L.J. Esserman, D.A. Berry, A. Demichele, et al., Pathologic complete response predicts recurrence-free survival more effectively by cancer subset: results from the I-SPY 1 TRIAL—CALGB 150007/150012, ACRIN 6657, J. Clin. Oncol. 30 (September (26)) (2012) 3242–3249.
[22] L. Heijmen, H.W. van Laarhoven, C.J. Punt, et al., Encouraging results in older patients receiving chemotherapy: a retrospective analysis of treatment guideline adherence in daily practice, Geriatr. Gerontol. Int. 12 (1) (2012) 80–85.
[23] K.M. Ligt, De, P.E.R. Spronk, A.C.M. Bommel, Van, et al., Patients' experiences with decisions on timing of chemotherapy for breast cancer, Breast 37 (2018) 99–106.