DANISH MEDICAL JOURNAL

Original Article

Dan Med J 2020;67(12):A01200010

Neoadjuvant chemotherapy for primary operable breast cancer

Anne Krag Halberg[1*], Charlotte Dahl Gravesen[1*], Søren Cold[2] & Jeanette Dupont Jensen[2]

1) Faculty of Health Science, University of Southern Denmark, 2) Department of Oncology, Odense University Hospital, Odense, Denmark

Dan Med J 2020;67(12):A01200010

ABSTRACT

INTRODUCTION: Neoadjuvant chemotherapy (NACT) has been found useful in downstaging tumours in women with primary operable breast cancer without increasing mortality. As a result of several studies supporting this, the Danish Breast Cancer Cooperative Group implemented new guidelines for the treatment of primary operable T2 N0/N1 M0 ductal carcinomas in late 2016, treating patients with six cycles of NACT. This study aimed to conduct a quality assessment of the efficacy of the NACT regime based on real-time data from a single Danish hospital.

METHODS: A retrospective observational study was conducted at Odense University Hospital, Denmark, from the introduction of the NACT regime to December 2018. Patients were identified using the surgical department's registry. Through medical chart review, predefined outcomes were collected on tumour characteristics, surgical outcomes, treatment response and type of NACT treatment. Descriptive statistics and Fisher's exact test were used on relevant data.

RESULTS: Among the 64 patients, 67% completed a recommended NACT regime. A 55% majority underwent lumpectomy and 64% were spared axillary dissection. Complete pathological response was found in 28% of patients. After treatment, 38% of the pre-NACT N1 patients were downstaged to N0.

CONCLUSIONS: This study indicated that the NACT regime was a favourable treatment strategy for these patients. Two-thirds of patients were able to undergo a recommended NACT regime. The majority of patients were both spared axillary dissection and mastectomy.

FUNDING: none.

TRIAL REGISTRATION: not relevant.

Breast cancer is the leading type of cancer affecting women in Denmark, with more than 4,600 Danish women diagnosed annually [1, 2]. For many years, the primary treatment strategy for operable breast cancer in Denmark was surgery, potentially followed by chemotherapy, endocrine therapy, radiotherapy or a combination of these modalities [3-5]. In past decades, several studies have investigated neoadjuvant therapy for primary operable breast cancer and have found that it was possible to reduce the tumour size and to achieve a more optimal surgical result without compromising survival [6-8]. Based on these results, the Danish Breast Cancer Cooperative Group (DBCG) released new guidelines for treatment of early primary operable T2 N0/N1 M0 ductal carcinomas in late 2016. These guidelines recommended neoadjuvant chemotherapy (NACT) prior to surgery [9]. The DBCG's goal for this regime was to downstage/downsize tumours to increase the possibility of lumpectomies and axillary-sparing surgeries [9]. The present study aimed to conduct a quality assessment of the efficacy of the NACT regime using real-time data from a single Danish hospital.

METHODS

All patients referred for NACT treatment at Odense University Hospital (OUH) Denmark from the introduction of the NACT regime in 2016 to December 2018 were retrospectively identified at the end of February 2019. In agreement with current Danish guidelines on the use of personal data, a list of social security numbers for the identified patients was generated from the section for breast surgery and from the hospital pharmacy at the OUH [10].

Patients were included in the study cohort if they met the general recommendations for NACT as defined by DBCG's clinical guidelines [9]. The inclusion criteria required that patients were candidates for adjuvant chemotherapy, were classified as tumour stage T2 (2-5 cm in diameter on ultrasound imaging (UL)), were nodal stage N0-N1 and had histologically verified invasive breast cancer of non-lobular type [9]. Patients were excluded if they had locally advanced breast cancer, had not completed surgery at the beginning of the data collection (28/2/2019) or had received more than six cycles of chemotherapy. In accordance with DBCG guidelines, the initial tumour size and N-stage were assessed at baseline using UL, MRI and clinical breast palpation. If lymphatic metastasis was suspected, fine-needle aspiration (FNA) and insertion of a lymphatic coil was performed. Patients were assessed for tumour and axillary response to NACT with MRI and clinical examination after two series of NACT [9].

Patients were categorised into three groups based on clinical subtypes according to their oestrogen (ER) and human epidermal growth factor receptor 2 (HER2) status. The three subtypes were ER+ (ER+ and HER2–), HER2+ (HER2+ and either ER+ or ER–) and triple negative (TNBC) (ER– and HER2–) (**Table 1**). Patients were also categorised into three different regime groups according to their NACT. The standard NACT regime (regime A) consisted of three cycles of epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2) (EC) administered every three weeks, followed by three cycles of weekly administered paclitaxel (80 mg/m^2 on days 1-8 and 15). In the case of minimal or no response after two cycles of EC, patients were converted to paclitaxel and received a total of two cycles of EC and four cycles of paclitaxel (regime B). Regime C included all aberrant treatment courses where patients were treated with different types of chemotherapy agents or received a varying number of treatment administrations. For HER2+ patients, trastuzumab and pertuzumab were administered concomitantly with paclitaxel every three weeks.

TABLE 1 / Baseline patient characteristics.

Differentialdiagnose	Symptomer
All patients, N	64
Age, median (range), yrs	51 (25-78)
Clinical subtypes, n (%)	
ER+: HER2-	24 (38)
HER2+: ER+/ER-	18 (28)
TNBC: ER-, HER2-	22 (34)
Initial tumour diameter	
UL:[a]	
Mean (range), mm	26.8 (17-42)
⟨ 20 mm, n	2
21-50 mm, n	62
⟩ 50 mm, n	0
Palpated:[b]	
Mean (range), mm	32.6 (20-60)
⟨ 20 mm, n	0
21-50 mm, n	59
⟩ 50 mm, n	3
Unknown, n	2
MRI:[b]	
Mean (range), mm	31.5 (17-85)
⟨ 20 mm, n	3
21-50 mm, n	56
⟩ 50 mm, n	3
Unknown, n	2
Suspected lymphatic metastasis, n	26
Verified N1 pre-NACT-FNA, n	16

ER = oestrogen receptor; FNA = fine-needle aspiration; HER = human epidermal growth factor receptor; N1 = spread to 1-3 lymph nodes; NACT = neoadjuvant chemotherapy; TBNC = triple negative breast cancer; UL = ultrasound imaging.
a) Inclusion criteria for tumour diameter is determined by UL.
b) Tumour diameters can vary due to inflammation after biopsies and coil insertion prior to measurement.

The outcome variables were surgical (mastectomy or lumpectomy) and axillary (dissection or sparing) outcome, treatment response and type of completed NACT regime. These outcome variables were also evaluated based on clinical subtypes. All patients were subject to sentinel lymph node procedure (SLN) following NACT to assess whether there was metastatic spread to the axilla. N1 was defined by the guidelines as the presence of any number of malignant cells in the SLN. Following these guidelines, all SLN-N1 patients should undergo axillary lymph node dissection (ALND) [9]. Treatment response on surgical tissue was evaluated using the modified Miller-Payne classification. Grade I/complete pathological response (pCR) meant that no remaining malignant cells in the removed tissue were left [9]. Grade II-IV were defined according to the amount of remaining tumour mass [9]. Descriptive statistics were used on relevant data variables. Fisher's exact test was used to calculate

statistical differences between stratified groups. $p < 0.05$ were considered significant.

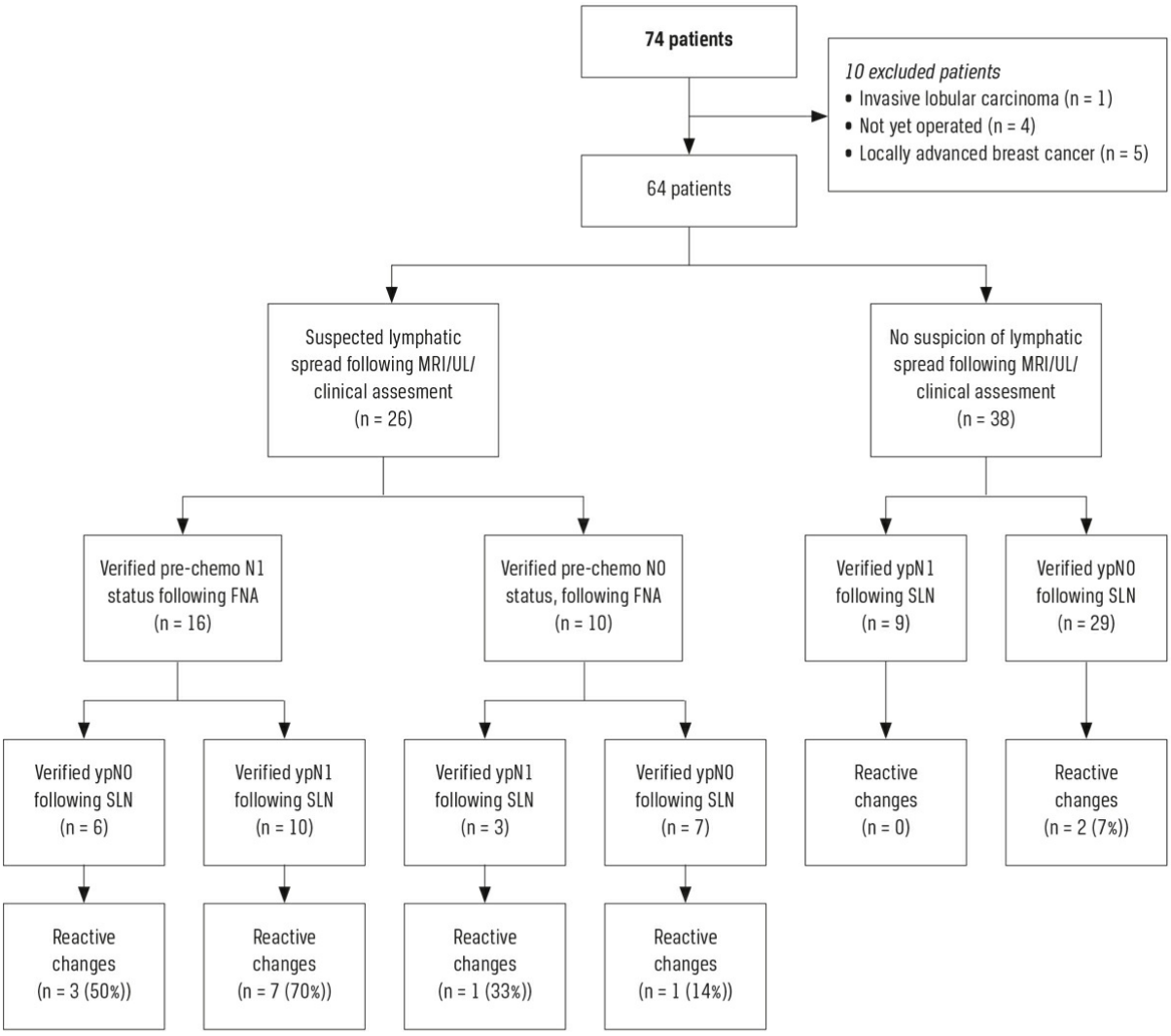
Trial registration: not relevant.

RESULTS

Patient characteristics

From September 2016 to December 2018, 74 patients diagnosed with breast cancer at the OUH were registered as NACT candidates. Ten patients were excluded after completing a medical chart review (**Figure 1**), and ultimately 64 patients were included in the cohort. Patient and tumour characteristics are summarised in Table 1. Lymphatic metastasis was suspected following initial UL, MRI or clinical assessment in 26 patients, deeming FNA and insertion of a lymphatic coil necessary. Malignant cells were cytologically verified in the suspected lymph node in 16 of these patients who were hence diagnosed as N1 pre-NACT. No malignant cells were found in the remaining ten patients' FNA.

FIGURE 1 / Cohort nodal status.



FNA = fine-needle aspiration; N0 = no spread to lymph nodes; N1 = spread to 1-3 lymph nodes; NACT = neoadjuvant chemotherapy; SLN = sentinel lymph node procedure; UL = ultrasound imaging; ypN0 = N0 post-NACT; ypN1 = N1 post-NACT.

Neoadjuvant chemotherapy regime

Among the 64 patients in this cohort, 30 patients completed regime A and 13 completed regime B, resulting in 67% of all patients completing six full cycles of NACT. Hence, these patients were treated according to the DBCG's recommendations (regime A + regime B). The remaining 21 patients had aberrant courses of treatment (**Table 2**). Nine patients were ER+, seven were HER2+ and five were TNBC. Among these 21 patients, 14% were treated with different chemotherapy agents and 86% received a varying number of treatment administrations, primarily due to neuropathy following paclitaxel. Stratification by clinical subtype produced recommended regimes (regime A + regime B) completed by 62% of the ER+, 61% of the HER2+ and 77% of the TNBC patients, whereas the remainder in each group had aberrant treatment courses. Four patients with aberrant regimes experienced tumour progression or so little regression that NACT was discontinued and the patients underwent surgery. All four patients were ER+ and none had experienced a relapse at the most recent follow-up at the OUH. Categorised by HER2+/HER2–, recommended regimes were completed by 67% of HER2+ patients and 65% of HER2– patients. A statistical difference was found, illustrating that HER2– patients favoured regime A and HER2+ patients favoured regime B ($p < 0.001$).

TABLE 2 / Distribution of neoadjuvant chemotherapy regimes among all patients and subtypes. The values are n (%).

	Regime A[a]	Regime B[b]	Regime C[c]
All patients	30 (47)	13 (20)	21 (33)
Clinical subtypes			
ER+: HER2–	13 (54)	2 (8)	9 (38)
HER2+: ER+/ER–	4 (22)	7 (39)	7 (39)
TNBC: HER2–, ER–	13 (59)	4 (18)	5 (23)
HER2-status			
HER2+	4 (22)	8 (45)	6 (33)
HER2–	25 (54)	5 (11)	16 (65)

EC = epirubicin (90 mg/m²) and cyclophosphamide (600 mg/m²); ER = oestrogen receptor; HER = human epidermal growth factor receptor; TBNC = triple negative breast cancer.
a) 3 cycles EC and 3 cycles of paclitaxel.
b) 2 cycles EC and 4 cycles of paclitaxel.
c) All aberrant treatment courses: different chemotherapy agents or varying number of administrations, ± of anti-HER2 agents in accordance with HER2 status.

Surgical and axillary outcomes

After completion of NACT, 55% of patients underwent lumpectomy and 45% mastectomy (**Table 3**). A total of 22 patients were N1 post-NACT (ypN1) and 20 of these patients underwent ALND. One patient rejected the surgery, and another was too fragile to undergo the procedure. Three N0 post-NACT (ypN0) patients were subjected to

ALND because the lymphatic coil could not be identified at the SLN, and therefore guidelines deem dissection necessary. Ultimately, 36% of the patients had ALND after NACT, whereas 64% were spared. After NACT, six of the 16 pre-NACT N1 patients were found to have no malignant cells in the SLN and thus 38% were downstaged from N1 to N0 owing to NACT. Only three of the six patients were spared ALND owing to missing coil identification in the SLN. Three of the ten patients who underwent FNA pre-NACT and were found to be N0 were SLN ypN1. Nine of the 38 patients without suspected lymphatic spread before treatment were SLN ypN1 (Figure 1).

TABLE 3 / Treatment results. The values are n (%).

		Stratified				
	All patients, n	pCR	Grade II-IV	ER+: HER2-	HER2+: ER±	TNBC: HER2-, ER-
Surgical outcome						
Mastectomy	29 (45)	5 (28)[a]	24 (52)[b]			
Lumpectomy	35 (55)	13 (72)	22 (48)			
Axillary outcome						
ALND +	23 (36)					
ALND-	41 (64)					
Pathological treatment response						
pCR	18 (28)[c]			2 (8)	9 (50)	7 (32)
Grade II-IV	46 (72)			22 (92)	9 (50)	15 (68)

ALND = axillary lymph node dissection; ER = oestrogen receptor; HER = human epidermal growth factor receptor; N0 = no spread to lymph nodes; NACT = neoadjuvant chemotherapy; pCR = complete pathological response; SLN = sentinel lymph node; UL = ultrasound imaging; ypN0 = N0 post-NACT.
a) 2 patients had primary reconstructive surgery due to young age, 1 patient had a high-risk mutation, 1 patient's tumour location did not cosmetically permit lumpectomy, 1 patient requested a mastectomy.
b) 3 patients had high-risk mutations.
c) 17 out of 18 pCR patients also had total pCR = pCR + SLN ypN0.

Treatment response

In this cohort, 28% of patients had pCR in the breast tissue and the remaining 72% of the patients were grade II-IV. Lumpectomies were performed on 13 (72%) of the patients with pCR.

When stratified by clinical subtype, pCR was found in 8% of the ER+, 50% of the HER2+ and 32% of the TNBC patients. Lymph nodes from SLN were pathologically assessed for presence of reactive changes due to NACT. Fourteen patients presented with reactive changes, whereas 50 patients had no reactive changes on their SLN (Figure 1).

DISCUSSION

The new DBCG guidelines for NACT were introduced in 2016 with the aim of downstaging and downsizing large primary operable tumours in order to enable breast-conserving surgery and axillary sparing [9]. This study aimed to investigate the efficacy of the NACT regime. Similar to the lumpectomy rate found in this study, a 2018 meta-analysis found an average post-NACT lumpectomy rate of 57% across 16 randomised trials [11]. There has been some dispute as to whether the rate of lumpectomies is a relevant outcome for the effect of NACT on breast cancer. Hage et al proposed that the final surgical procedure does not reflect the number of patients already eligible for conservative surgery prior to treatment, and concluded that it is therefore an inaccurate measure of

the impact of NACT [12]. Ideally, this study would have included the initial surgical intention for each patient, so that a rate of surgical conversion could have been calculated. Unfortunately, this information was available for 16 patients only. Some patients had mastectomies due to mutations in the breast cancer genes (BRCA1 or BRCA2), which is not accounted for in the surgical outcome rates. The frequency of pCR across clinical subtypes in this study was similar to the frequency found in the 2014 pooled analysis by Cortazar et al, with higher rates of pCR in TNBC and HER2+ patients, and lower rates in ER+ patients [13]. The four patients in this study with poor NACT responses were of the ER+ subtype, which is in line with the lower tumour response rates for this tumour subtype found by Cortazar et al [13].

Another purpose of NACT is to potentially reduce the need for ALND. In this study population, only 36% were subjected to ALND following NACT. Thus, the majority of patients were spared axillary dissection. Comparative rates of ALND in the NACT setting are sparsely reported in the existing literature, as it is not a commonly used endpoint for evaluation of NACT. Even so, the present study deemed it important to analyse the ALND rates, as axillary-sparing surgery is one of the main goals of the DBCG [9]. The rate of ALND is influenced by the presence of lymphatic metastasis following NACT [9]. The ability of NACT to convert N1 patients to N0 is, therefore, a relevant measure of the efficacy of the treatment, since this ability decreases the need for axillary dissection. In a 2017 study, Man & Cheung found that the proportion of N0 patients increased from 15% to 43% at the end of the NACT period; thus, they reported a similar N-stage conversion fraction to the one found in our study [14]. Of note, some of the pre-NACT N1 patients who presented as ypN0 were without reactive changes in their SLN (Figure 1). This is explained in the DBCG's pathology guidelines, as lymph nodes without tumour cells prior to NACT can present with fibroses post-NACT, just as lymph nodes with prior tumour cells can present without reactive changes post-NACT [15].

Another perspective in the evaluation of NACT is the possibility of individualising chemotherapy treatment. Almost two-thirds of the cohort were able to complete the recommended six-cycle regime, confirming that the majority of patients can adhere and do respond to the proposed treatment. Although the present cohort was small, our findings do suggest that HER2+ patients are at an increased risk of not responding sufficiently to EC. Whether HER2+ breast cancer responds less to EC compared with HER2– breast cancer is poorly described in the available literature. On the contrary, multiple trials have examined the effect of anti-HER2 agents on HER2+ breast cancer in the neoadjuvant setting, finding an improvement in pCR with the addition of trastuzumab and pertuzumab given concomitantly with chemotherapy [16-18]. The findings in the present study lay the ground for suggesting that the NACT DBCG guidelines be changed in favour of initiating treatment with paclitaxel and anti-HER2 treatment before EC for HER2+ patients; however, this should be confirmed on a larger cohort.

This study had several limitations. The retrospective observational design must be considered one of the main weaknesses since all findings and results depend on pre-existing data which may contain errors or missing information. There is also a risk of reviewer bias as the authors were not blinded. Furthermore, the possibility of selection bias must be considered as some NACT candidates might be subjected to primary surgery instead of NACT because of surgical or personal preferences on the part of either the patient or the treating surgeon/oncologist. This study was conducted on a small cohort of patients, which makes it difficult to control for potential confounders. Since this study only included breast cancer patients treated at one hospital, these findings may not apply to all breast cancer patients. As the DBCG guidelines are used nationwide, additional studies could be conducted on a national basis to further investigate the outcome of NACT in Denmark.

CONCLUSIONS

The overall objective of the DBCG NACT regime was to increase the possibility of lumpectomy and reduce the need for ALND. The present study found more patients undergoing lumpectomies than mastectomies following

NACT. The majority of the patients in this cohort were spared axillary dissection, and more than one third of N1 patients were downstaged. Unfortunately, these results do not directly allow us to conclude that the possibility for lumpectomies post NACT was increased as all patients were not given a pre-NACT surgical intent, and therefore it remains unknown for this cohort if the DBCG objective was achieved. Two-thirds of the patients were able to undergo a DBCG-recommended regime of chemotherapy prior to surgery. The findings of this study indicate that the NACT regime is a favourable treatment strategy for these patients.

Correspondence: *Charlotte Dahl Gravesen*. E-mail: charlotte@gravesen.us

Accepted: 10 September 2020

Conflicts of interest: none. Disclosure forms provided by the authors are available with the full text of this article at Ugeskriftet.dk/dmj

*) Contributed equally

LITERATURE

1. Hansen NK, Kejs AMT. Statistik om brystkræft. Kræftens Bekæmpelse. www.cancer.dk/brystkraeft-mammacancer/statistik-brystkraeft/?gclid=CjwKCAjwqqrmBRAAEiwAdpDXtHs7VIkyxMs3IsgPchFDJo4SWVEc--n4bNw_YR83uVkBCqfN_vniZBoC5BEQAvD_BwE (8 Apr 2019).
2. Gaardsted AM, Engholm G. De hyppigste kræftformer. Kræftens Bekæmpelse. www.cancer.dk/hjaelp-viden/fakta-om-kraeft/kraeft-i-tal/de-hyppigste-kraeftformer/?gclid=CjwKCAjwqqrmBRAAEiwAdpDXtHrLXn5uYCE0FvCxgiprm9mZNwqLwvI29rU29yubUxYzncXLtXatbxoCoeIQAvD_BwE (2 Apr 2019).
3. Kirurgisk behandling. Danish Breast Cancer Cooperative Group, 2011. www.dbcg.dk/PDF%20Filer/Kap_4_Kirurgisk_behandling_03.04.13.pdf (3 Apr 2013).
4. Nørgaard A, Nielsen AH, Jylling AMB et al. Pakkeforløb for brystkræft for fagfolk. In: Danish Health Authority. sst.dk (17 Nov 2019).
5. Jakobsen AS. Behandling af brystkræft. Kræftens Bekæmpelse. www.cancer.dk/brystkraeft-mammacancer/behandling-brystkraeft/(25 Feb 2019).
6. Wolmark N, Wang J, Mamounas E et al. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Nat Can Inst Monograp 2001:96-102.
7. Bear HD, Anderson S, Smith RE et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2006;24:2019-27.
8. Boddington C, Bradley R, Burrett J et al. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol 2018;19:27-39.
9. DBCG's Redaktionsgruppe. Neoadjuverende kemoterapi ved brystkræft mhp. down-sizing og down-staging. Danish Breast Cancer Cooperative Group, 2016. http://dbcg.dk/PDF%20Filer/Kap7_Neoadj_KT_ved_brystkraeft_mhp_down-sizing_og_down-staging_04.10.2016.pdf (10 Apr 2016).
10. Borch-Johnsen K, Borre M, Emmeluth C et al. Retningslinjer for videregivelse af personoplysninger fra de støttede, landsdækkende kliniske kvalitetsdatabaser. In: Kvalitetsudviklingsprogram RKKP 2018:3-6.
11. Criscitiello C, Golshan M, Barry WT et al. Impact of neoadjuvant chemotherapy and pathological complete response on eligibility for breast-conserving surgery in patients with early breast cancer: a meta-analysis. Eur J Cancer 2018;97:1-6.
12. Hage AN, Capriccioso C, Brennan J et al. Impact of neoadjuvant chemotherapy on surgical outcomes among patients with hormone receptor positive breast cancer. J Surg Oncol 2017;116:665-70.
13. Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164-72.

14. Man VC, Cheung PS. Neoadjuvant chemotherapy increases rates of breast-conserving surgery in early operable breast cancer. Hong Kong Med J 2017;23:251-7.
15. Patologi. Danish Breast Cancer Cooperative Group, 2020. www.dmcg.dk/siteassets/forside/kliniske-retningslinjer/godkendte-kr/dbcg/dbcg_patologiprocedure_rkkp_admgodk300420x.pdf (31 Apr 2020).
16. Buzdar AU, Ibrahim NK, Francis D et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 2005;23:3676-85.
17. Hamy AS, Belin L, Bonsang-Kitzis H et al. Pathological complete response and prognosis after neoadjuvant chemotherapy for HER2-positive breast cancers before and after trastuzumab era: results from a real-life cohort. Br J Cancer 2016;114:44-52.
18. Gianni L, Pienkowski T, Im YH et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:25-32.