Breast cancer and neoadjuvant chemotherapy: indications for and limits of breast-conserving surgery

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AIM: *The aim of our study was to determine how many and what subtypes of breast cancer could be treated with breast-conserving surgery after NACT. Another outcome was to determine the applicability of MD Anderson Cancer Center nomogram to predict it.*
MATERIAL OF STUDY: *We reviewed the histological examinations of 86 performed mastectomies according to the indications to BCS after NACT. For 73 cases, collected all the necessary data, we could use the nomogram available on the MDACC website to calculate the probability of BCS and pCR.*
RESULTS: *In our experience the BCS rate would increase by 34,1%, from 3,7% to 3.,8%. Patients with Triple Negative and HER2+, ER- more than ER+, show higher rates of pCR and BCS. The MDACC nomogram predicts accurately the probability of pCR and BCS after NACT in HER2 negative cancers but not in HER2 positive ones treated with Trastuzumab. This suggests that a specific nomogram for HER2 positive carcinomas has to be developed.*
CONCLUSION: *BCS after NACT is feasible and safe in terms of LRR, DFS and OS, if patients are properly studied and selected. Indication to BCS after NACT needs of a multidisciplinary assessment considering clinical staging, biological characteristics, the radiological response pattern and the expected concordance between imaging and histology.*

KEY WORDS: Breast Cancer, Breast-conserving surgery, Neoadjuvant chemotherapy

Introduction

Neoadjuvant chemotherapy (NACT) historically was designed for locally advanced breast cancer in attempt to convert non-operable cancers into surgically resectable ones.
Recently the role of NACT was evaluated in early breast cancer [1]. In this case, the main benefit of NACT is a reduction in tumour size, which allows breast-conserving surgery (BCS) in patients who otherwise would require a mastectomy (MT). Moreover, in adjuvant chemotherapy candidates, chemotherapy anticipation allows to evaluate sensitivity to chemotherapy of neoplasia.

In National Surgical Adjuvant Breast and Bowel Project B-18 the rate of BCS was greater in the neoadjuvant group (60% vs 67%; p = 0.002); this was particularly evident in patients with tumors ≥ 5.1 cm (8% in the adjuvant group vs 22% in the neoadjuvant group)[2].
In B-18, individuals who achieved a pathological complete response (pCR) showed superior disease free survival (DFS) and overall survival (OS) outcomes compared with patients who did not achieve a pCR; after 8 years of follow-up also on NSABP B-27 pCR remained a highly significant predictor of improved DFS and OS[3].
The more aggressive subtypes, Triple Negative and HER2 positive tumours, have increased frequencies of pCR. Within the HER2 positive population, pCR was more common with the addition of Trastuzumab and for hormone receptor negative tumours (ER-) than for hormone receptor positive ones (ER+) [4,5].
In addition to the prognostic advantage, pCR is most likely associated with BCS in patients who are candidates for MT prior to neoadjuvant therapy.

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The possibility of BCS after NACT varies from 20 to 40%, depending on the histology (ductal vs lobular) and biology (HER2 positive and Triple Negative vs ER+) [6]. As in the early tumours, also for advanced neoplasia treated with BCS after NACT conservative treatment is considered appropriate if the surgical margins are free from cancer. The margins positivity is the main risk factor for ipsilateral relapse.

The recent introduction of "oncoplastic techniques" can favour the increase of BCS after NACT[7]. In fact, in patients who experience a clinical response to NACT, oncoplastic surgical techniques allow to optimize cosmetic outcomes by implementing the best principles of plastic surgery in order to achieve wide tumor-free margins[8]. Oncoplastic breast surgery remains contraindicated in multicentric disease, insufficient residual breast tissue following resection to allow reshaping and prior augmentation mastoplasty; moreover, multiple medical comorbidities and active smokers are not ideal candidates for some complex tecniques [9].

There was no statistically significant correlation between local-regional recurrence (LRR) and type of surgery performed after NACT (MT vs BCS) [10]. In addition, similar OS and DFS values were documented between the BCS group and the MT group [10]. The MD Anderson Cancer Center group proved that LRR after BCS is linked only to biological factors of the neoplasia [11]. In well-selected patients, therefore, it is possible to perform conservative surgery after NACT with low recurrence rates.

Based on the data available in the literature, absolute contraindications to BCS are: multicentric disease, inflammatory breast cancer, contraindication to radiotherapy and BRCA1/2 mutations.

BCS after NACT is indicated in unifocal disease, cT2 (> 3 cm) – T3 – T4 a,b,c cN0 and cT2 (≤ 3 cm) cN+. A borderline indication is represented by multifocal disease with good chemotherapy response.

Ideally, especially in the group of patients with operable cancers, it would be very useful to predict which could benefit from anticipating chemotherapy.

The MD Anderson Cancer Center group, in 2005, developed a nomogram for predicting residual tumour size (≤ 3 cm or > 3 cm) and probability of a patient becoming eligible for breast conservation surgery after anthracycline and/or taxane-based neoadjuvant chemotherapy [12].

Regarding the probability of eligibility for BCS the factors that showed an independent correlation, at the multivariate analysis, were: pre-NACT diameter (p 0.0007), grading (p 0.07), histotype (p 0.0005), multicentricity (P 0.01) and the ER state (p 0.04) [12].

Material and Method

Between July 2015 and June 2017, at the UOC Breast Unit of the Integrated University Hospital in Verona, 91 breast cancer patients (age range, 29-76; median 51) were subjected to surgery after NACT.

3 patients were affected by bilateral neoplasia.

From our study we excluded: 4 patients because the preoperative features of cancers were not available, 3 patients in which neoadjuvant therapy was exclusively of hormone type, 1 patients affected by occult tumour with ipsilateral lymph node metastases and 1 patient affected by relapse after mastectomy.

The study included 82 patients: 78 patients with unilateral breast cancer, 2 patients with bilateral breast cancer and 2 relapses after conservative surgery and adjuvant radiotherapy.

In total 84 malignancies were treated: 29 multicentric, 44 unifocal, 11 multifocal. About tumour size: 16 cases were T1, 43 T2, 9 T3 and 16 T4 (including seven inflammatory breast cancer, T4d). Among tumours less than 2 cm (T1), 11 cases were N+ while 5 cases were N0. In N0 group 2 cases received NACT for locally advanced contralateral neoplasia, one case for suspected muscular infiltration, another case for multicentric cancer and another one for biological aggressiveness (Infiltrating Ductal Carcinoma, Ki67 50%, HER2 +). Among the T1N+ 4 tumours were multicentric, 6 unifocal and 1 multifocal.

In one cases, in whom the contralateral neoplasia was discovered during therapy, the biological characteristics of the neoplasia were not available prior to NACT because only a cytological examination was performed. Among the remaining 83 cases: 26 were Luminal A (31.33%), 28 Luminal B HER2 negative (33.73%), 15 Luminal B HER2 positive (18.07%), 4 HER2 (4.82%) and 10 Triple Negatives (12.05%).

Ductal carcinomas were 67 (80.72%) and lobular or mixed 16 (19.28%).

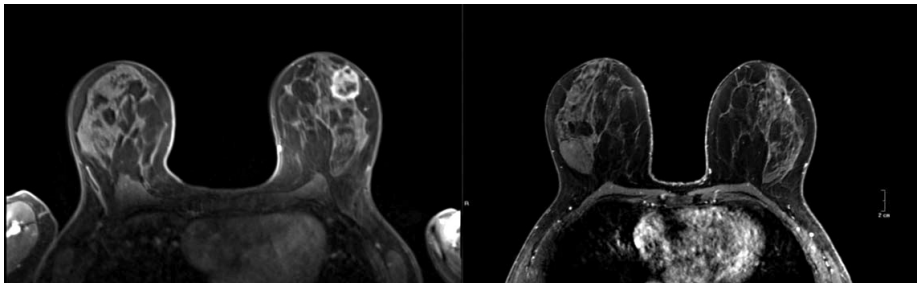

Fig. 1: MRI images before and after neoadjuvant chemotherapy in patient candidate to BCS post NACT.

All patients received neoadjuvant treatment according to AC/EC/FEC scheme for 3-4 cycles every 21 days followed by weekly Paclitaxel for 12 cycles. In cases of HER2 positivity, biological therapy with Trastuzumab was initiated prior to surgical intervention. All hormone positive cancers, except for particular contraindications, started hormone therapy at the end of chemotherapy.
In all patients the local extension of the neoplasia and the response to chemotherapy were evaluated by breast MRI that patients performed at the time of diagnosis and at the end of chemotherapy (Fig. 1).
The MD Anderson Cancer Center Nomogram is available online through the MDACC website (http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert2). After filling all fields (NACT, age, cT, initial diameter, histologic type, grading, ER status, multicentricity), the probabilities (%) of pCR, residual diameter ≤3 cm and BCS are automatically provided.
In our case we could use this nomogram in 73 of 89 malignancies; 3 cases were excluded because they received neoadjuvant treatment only with hormone therapy, not included in the MDACC nomogram, while others lacked at least one required data.
The distribution of the different variables in the groups was expressed as mean ± standard deviation. The data were analysed using Student's t-test. A value of $p < 0.05$ was statistically significant.

Results

In our case, histological examination documented a pCR in 18 cases, 6/18 were Triple Negative, 5/18 HER2+ ER+, 4/18 HER2+ ER- e 3/18 HER2- ER+. No Luminal cancer has got a pCR.
In our experience, among the 82 patients, 3 were subject to BCS and 79 to MT, bilateral for cancer in 2 cases and for prophylaxis in 4 ones.

We reviewed the histological examinations of performed mastectomies according to the indications to BCS after NACT. In 31 cases a conservative surgery could be performed. In the remaining 51 cases, there was no indication to a conservative surgery.
In some cases, the contraindication to conservative treatment was already present before neoadjuvant therapy: multicentricity in 29 cases, inflammatory carcinoma (T4d) in 3 cases, BRCA1/2 mutation in 2 cases, recurrence after lumpectomy followed by adjuvant radiotherapy in 2 cases. In other 15 cases, the contraindication was related to the extension of the disease after neoadjuvant therapy (diameter ≥ 3 cm); breast MRI had predetermined diameter of more than 3 cm in only 6 of these cases.
The BCS rate would increase by 34.1%, from 3,7% (3/82) to 37,8% (31/82).
In our case 17/73 (23.28%) cancers reached a pCR; according to the MDACC nomogram the average waiting was 26.71%.
In particular, in our experience, pCR in the different subtypes was: HER2– ER– (Triple Negative): 66.67% (6/9), HER2+ ER–: 66.67% (4/6), HER2– ER+: 6.67% (3/45), HER2+ ER+: 38.46% (5/13).
The results achieved according to the MDACC nomogram were: HER2– ER– (Triple Negative): 60%, HER2+ ER–: 62.50%, HER2– ER+: 15.9%, HER2+ ER+: 23.69%.
Based on the results of the nomogram between the HER2+ ER+ and the HER2– ER+ group we will not have to expect a statistically significant difference in pCR (23.69% vs 15.9% p 0.0981) (Fig. 2); in our experience, however, the two groups showed a statistically significant difference in pCR (38.46% vs 6.67% p 0.0087) (Fig. 3).
Unlike between HER2+ ER– and HER2– ER– groups was no significant difference in pCR nor according to the expected results of the nomogram (62.50% vs 60%

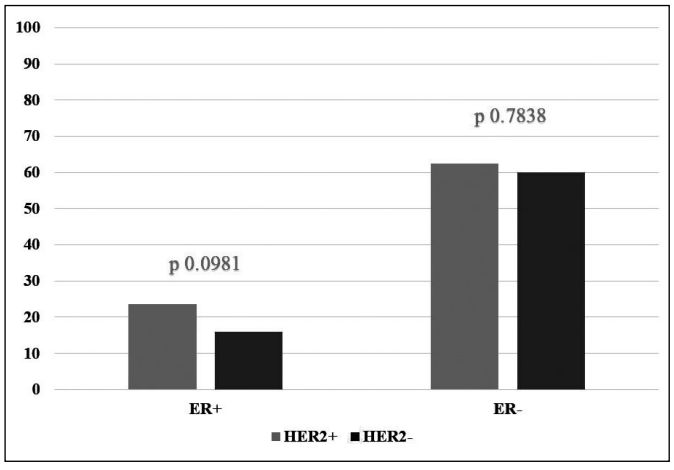

Fig. 2: pCR rates (%) in the different immunophenotype groups according to the MDACC nomogram.

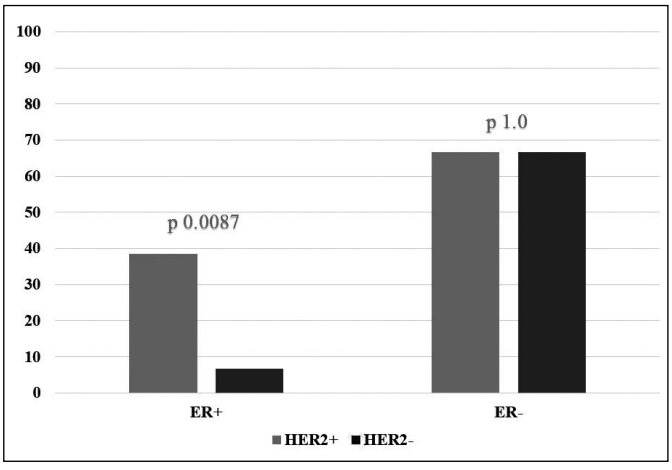

Fig. 3: pCR rates (%) in the different immunophenotypic groups in our experience.

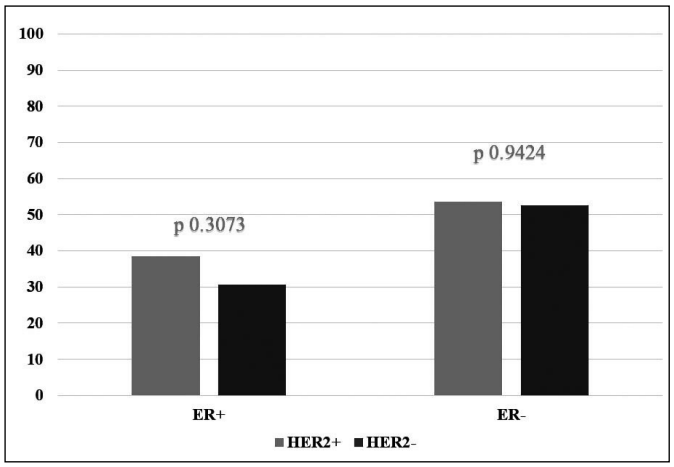

Fig. 4: BCS rates (%) in the different immunophenotypic groups in our experience.

p 0.7838) (Fig. 2) nor the results of our study (66.67% vs 66.67% p 1.0) (Fig. 3).
According to the MDACC nomogram, the average waiting for BCS was 36.23%. In our experience 32/73 (43.84%) carcinomas could have been treated with conservative surgery.
In our experience, the BCS rate in the different subtypes was: HER2– ER– (Triple Negative): 55.56% (5/9), HER2– ER+: 35.56% (16/45), HER2+ ER+: 53.85% (7/13), HER2+ ER–: 66.67% (4/6).
The results achieved according to the MDACC nomogram were: HER2– ER– (Triple Negative): 52.67% (DS 25.37), HER2– ER+: 30.57% (DS 23.86), HER2+ ER+: 38.46% (DS 18.85), HER2+ ER–: 53.66% (DS 26.97).
According to the nomogram and our experience there were no statistically significant differences in BCS, both between HER2+ ER+ and HER2– ER+ group (38.46 vs 30.57% p 0.3073 and 53.85 vs 35.56% p 0.3056) and between HER2+ ER– and HER2– ER– group (53.66% vs 52.67% p 0.9424 and 66.67% vs 55.56% p 0.6934) (Figs. 4, 5).

Discussion and Comments

When patients are properly studied and selected, BCS after NACT proved to be a feasible and safe practice in terms of loco-regional relapse, DFS and OS.
Conservative surgery after NACT may be considered in:
– Inoperable cancers (cT2 > 3 cm - cT4c ± cN) good responder to chemotherapy;
– cT1-cT2 (<3 cm) cN+. The anticipation of chemotherapy permits an early evaluation of the effectiveness of systemic therapy or brings downstage that allows a surgical conversion from MT to BCS;
– cT1-cT2 (<3 cm) cN0, where it is decided to anticipate adjuvant chemotherapy for biological aggression.
Breast-conserving surgery should not be an option in multicentric disease, inflammatory breast cancer (cT4d), if there are contraindications to radiotherapy (collagen diseases, previous thoracic radiotherapy, macromastia, pregnancy) or in BRCA1/2 mutated patients.
To indicate NACT, in addition to clinical staging, microhistological typing of the neoplasia is necessary both for therapeutic choice and for predicting therapeutic efficacy.
In surgical planning, the biological characteristics of the neoplasia, clinical and radiological response should be considered.
A good or complete pathological response is most likely associated with conservative surgery in patients who are candidates for mastectomy before starting neoadjuvant chemotherapy.
Breast cancer is not a homogenous entity and molecular subtypes behave differently, both in their imaging patterns and in clinical-biological behaviour; even within the different subtypes, the response to neoadjuvant chemotherapy can be very variable.
Triple Negative cancers are more likely to present as a mass on the initial MRI (p 0.035), whereas non-mass enhancement is more likely to be associated with luminal cancer (p 0.014)[13,14]. Following NACT, Triple Negative cancers are more likely to show concentric shrinkage with no surrounding lesions (p 0.049), whereas shrinkage with surrounding lesions is more likely with luminal cancer (p 0.004)[13].
HER positive cancers, ER+ or ER-, show both concentric shrinkage with no surrounding lesions and shrinkage with surrounding lesions (p 0.611 e p 0.145)[13].
MRI is more accurate in predicting the size of residual cancer in Triple Negative cancers as compared to luminal cancers, where there is a high incidence of underestimation of residual disease.
The MRI can underestimate the disease more than 5 mm in 50% of the luminal cancers[13].
The false negative and false positive MRI findings could be due to chemotherapy-induced vasoconstriction and chemotherapy-induced inflammatory changes, respectively.
The response to chemotherapy can also be monitored with PET/CT. MRI visualizes changes in morphology and vascularization of tumours whereas PET/CT visualizes changes in the glucose metabolism of tumours. For HER2 positive tumours, monitoring of cancer response to NACT is more accurate using MRI only. For Triple Negative tumours, there were little differences between the performance of PET/CT and MRI; this suggests that PET/CT is an appropriate alternative to MRI for patients affected by this kind of cancer with contraindications for MRI. For ER+ tumours, PET/CT shows favourable performance over MRI, and combining PET/CT with MRI could provide optimal response monitoring[15].
There were three microscopic morphological types of residual breast cancer after NACT[16]:
– Type I comprised solitary lesions in the fibrotic tumour bed with extensive lymphocyte infiltration near the cancer lesion;

– Type II involved fibrotic changes in the tumour bed, which divided the residual cancer structure into several lesions with irregular shapes and patch like shapes of different sizes;
– Type III had a main cancer lesion and one or two small satellite lesions at least 1.0 cm away from it (10 mm to about 25 mm) visible in the fibrotic cancer bed with or without scattered cancer cell structures around the cancer lesion.
Type 1 can be removed radically through conservative surgery; type 2 and type 3 pose a greater risk of positive margins and local recurrence.
It is not clear whether there is a correlation between residual type and tumour biology. In Wang's study the positive rates of ER, PR and HER2 before and after NACT were not statistically different among patients with three types of residual tumours ($P > 0.05$)[16]. It seems that the subtype most frequently associated with a Type 1 response is the Triple Negative.
The ability to predict accurately the likelihood of achieving BCS after NACT is important in deciding whether chemotherapy or surgery should be the first-line treatment in patients with operable breast cancers.
There are currently no recommended nomograms; the MD Anderson Cancer Center nomogram has proven to be a valid tool but needs some improvements, partly related to the therapeutic progress that has been made in recent years.
The MDACC nomogram predicts accurately the probability of pCR after NACT in HER2 negative cancers but does not correctly predict pCR in HER2 positive ones treated with Trastuzumab [17]. This suggests that a specific nomogram for HER2 positive carcinomas has to be developed.
This nomogram, moreover, does not distinguish the different subgroups in stage T4, considering the T4a as the T4d which represents an absolute contraindication to conservative surgery. Other factors not considered that may affect the possibility of conservative surgery are the size of the breast and the presence of contraindications to radiotherapy.
More recently the same group created a nomogram to predict pCR rates in patients with primary HER2 positive breast cancer treated with NACT [18], using five covariates: ER expression level, PR expression level, HER2/CEP17 ratio, IBC or non-IBC (T4d or not T4d), and NACT regimen (cytotoxic agents alone, Trastuzumab or Trastuzumab and Pertuzumab).
In our center, as recommended by the ASCO CAP guidelines, HER2/CEP17 ratio is evaluated by FISH only in cancers with equivocal immunohistochemistry (HER2 2+); furthermore, the report specifies only if ≥ or < 2 (cut off to determine whether HER positive or negative) and not the real ratio as required by the nomogram. It was therefore not possible to apply the new nomogram and compare it to the previous one in HER2 positive patients.

Conclusions

BCS after NACT proved to be a feasible and safe practice in terms of LRR, DFS and OS, if patients are properly studied and selected.
Patients with triple-negative and HER2 positive breast cancers have the highest rates of pCR after neoadjuvant chemotherapy. Patients with these subtypes are most likely to be candidates for less invasive surgical approaches after chemotherapy.
Indication to BCS after NACT needs of a multidisciplinary assessment considering clinical staging, biological characteristics, the presence of any contraindications to breast-conserving surgery, the radiological response pattern, the expected concordance between imaging and histology, and of the expected pathological response.

Riassunto

La chemioterapia neoadiuvante è finalizzata al primo trattamento per tumori localmente avanzati della mammella non suscettibili di intervento chirurgico radicale, ma recentemente all'International Consensus Conference del 2012 è stato riconosciuto il ruolo della chemioterapia neoadiuvante anche per tumore operabile ma candidato a chemioterapia adiuvante per caratteristiche biologiche aggressive. Inoltre avrebbe il vantaggio di offrire un test di chemiosensibilità e di aumentare i tassi di chirurgia conservativa nelle pazienti operabili ma candidate a mastectomia.
Dal Luglio 2015 al Giugno 2017 presso l'UOC Breast Unit dell'Azienda Ospedaliera Universitaria Integrata di Verona sono state sottoposte ad intervento chirurgico senologico dopo terapia neoadiuvante 91 pazienti, 3 delle quali erano affette da neoplasia bilaterale. Dopo l'esclusione di 9 pazienti la casistica comprende 82 pazienti: 78 con neoplasia primitiva della mammella unilaterale, 2 pazienti con neoplasia primitiva bilaterale e 2 recidive dopo chirurgia conservativa e RT adiuvante.
L'estensione locale della neoplasia e la risposta alla chemioterapia sono stata valutate tramite RMN mammaria che le pazienti hanno eseguito al momento della diagnosi e al termine della chemioterapia.
Abbiamo utilizzati il nomogramma MDACC in 73 di 89 neoplasie per vari motivi di esclusione, analizzando statisticamente i dati con lo Student's t-test.
In 3 pazienti la chirurgia è stata conservativa, in 79 casi la mastectomia: bilaterale in 2 casi per bilaterale e in 4 casi per profilassi. Al controllo retrospettivo su base istologica il tipo di indicazione operatoria, risulterebbe un aumento del tasso di operabilità conservativa dal 3.7% (3/82) al 37.8% (31/82). A fronte di una media delle pCR calcolata dal nomogramma MDACC del 26.71%, il 23,28% (17/73 casi) hanno raggiunto una risposta patologica completa.

La media delle BCS calcolata dal MDACC è stata 36.23%: nella nostra casistica 32/73 neoplasie (43.84%) avrebbero potuto essere trattate con chirurgia conservativa.
La scelta di una chirurgia conservativa dopo NACT attualmente dovrebbe essere fatta valutando ogni singolo caso in ambito multidisciplinare tenendo conto della stadiazione preoperatoria, delle caratteristiche biologiche, della presenza di eventuali controindicazioni a una chirurgia conservativa, del pattern di risposta radiologico, della concordanza prevista fra imaging e istologia, e della risposta patologica prevista.

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