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Neoadjuvant chemotherapy for breast cancer in Italy: A Senonetwork analysis of 37,215 patients treated from 2017 to 2022

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ABSTRACT

Background: Adoption of neoadjuvant chemotherapy (NACT) in the "real world" has been poorly investigated. Aim of this study was to examine the rate of NACT in Italy, trends over time and determinants of therapeutic choices.

Methods: Senonetwork, the recognized network of Breast Centers in Italy, has developed a voluntary national data warehouse with the aim to monitor and improve treatments quality. A retrospective analysis was conducted among 58,661 breast cancer (BC) patients treated between 2017 and 2022 by 24 high-volume Breast Centers participating in the project.

Results: After subset exclusion, 37,215 primary BC patients were analysed, 32,933 underwent primary-breast-surgery and 4,282 underwent NACT. From 2017 to 2022, the overall NACT incidence increased particularly for HR-/HER2+, Triple-Negative, and HR+/HER2+ BC ($p < 0.001$). In cN + patients the recommendation to axillary lymph-node dissection after NACT decreased over time along with an increase of <4 lymph-nodes removed ($p < 0.001$). Immediate breast reconstruction and indication for nipple sparing mastectomy increased significantly over time (OR = 1.10, $p = 0.011$ and OR 1.14, $p < 0.001$, respectively). On multivariate analysis, there was a trend towards an increased adoption of conservative treatment for HR-/HER2+ ($p = 0.01$) and Triple Negative tumors ($p = 0.06$). Implementation of NACT varied significantly among Breast-Centers from 3.8 to 17.7 % ($p < 0.001$).

Conclusion: The impact of NACT on the subsequent surgical management is substantial and continues to evolve over time, resulting in less-extensive surgery. Even among high-volume Centers NACT implementation rate is still highly variable. Although we registered a significant increase in its use during the study period, these results need to be further improved.

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1. Introduction

Over the last few decades neoadjuvant chemotherapy (NACT) has been increasingly adopted for breast cancer (BC) patients, along with the introduction of multidisciplinary approaches and the use of targeted therapies and tailored drug regimens [1–3].

Several randomised trials and one meta-analysis demonstrated equivalent survival rates for patients with stage I-III disease treated with either NACT or adjuvant chemotherapy [4–10]. However, it is now recognized that in some clinical settings NACT represents a superior alternative to primary breast surgery (PBS), because it optimizes both surgical and oncological strategies, leading to more personalized treatments and to a better outcome [11–16]. One of the main purposes of NACT is to downstage both the primary breast tumour [17,18], allowing in most instances a reduction of the volume of surgical resection with better cosmetic outcomes [10,19], and the lymph nodes status [20,21], with the aim to decrease surgical-related morbidity without compromising oncological outcomes [22–26]. In addition, analysis of the residual cancer burden has been associated with both local control and the risk of systemic relapse, so that escalating oncological strategies can be implemented to improve outcome in cases of incomplete response [27–30]. However, actual implementation of NACT and patterns of surgical care in this setting are largely unknown in most parts of the world, including in Italy. In 2017, Senonetwork, the recognized network of Breast Centers in Italy, promoted a voluntary national data warehouse (Senonet) among affiliated Breast Centers with the aim to establish a national benchmark analysis to monitor and improve the quality of treatments, and to encourage retrospective clinical research. The aim of the present study is to describe the incidence of NACT among Italian Breast Centers participating in Senonet, the trends in surgical treatments and the determinants of therapeutic strategies.

2. Material and methods

Senonetwork is the recognized network of Italian Breast Centers, affiliation of Breast Centers is voluntary and requires access criteria in terms of minimum number of new cases/year and self-declaring compliance with quality requirements. Currently, 155 Breast Centers are affiliated accounting for more than 95 % of women treated every year in Italy for BC. Senonet data warehouse began operations in 2017, and it is a registry involving 24 high-volume Breast Centers in Italy currently participating at this project, intercepting approximately 20 % of the total national incidence of BC cases. Data regarding 279 items for each patient entry are collected yearly by each Breast Center data-manager through a specialized web-based database, Databreast®. Senonet analyzes data, elaborates cumulative reports aimed to describe benchmarking activities, and issues a yearly report on the performance for each Breast Center in agreement with the Quality Indicators identified by Senonetwork [31].

A retrospective analysis was performed from Senonet data warehouse on patients with primary BC surgically treated between January 1st, 2017 and December 31st, 2022. The collected data were: patients age, menopausal status, family history of BC, genetic testing and BRCA status, breast and axillary clinical radiological assessment, tumor diameter and lymph node status, clinical and pathological stage of disease, prognostic factors of the primary tumor, type of adjuvant and/or neoadjuvant therapy, pathological response to NACT, type of breast and axillary surgery, resection margins. According to the immunohistochemical pattern, breast tumors were defined as Luminal A-like (ER + and/or PR+, HER2-, and Ki67 < 20 %), Luminal B-like (ER+, PR −/+, and Ki67 ≥ 20 %), HER2+ (ER negative, PR-, HER2+), Triple-Positive (ER+ and/or PR+, HER2+) and Triple-Negative (ER-, PR-, and HER2-) [32]. Clinical practices followed national Guidelines (Early Breast Cancer – AIOM, Italian Association of Medical Oncology), which recommends positioning of a clip in the breast tumor bed before starting NACT, while clipping of a metastatic axillary lymph node pre-NACT is allowed but not specifically recommended, along with use of a double tracer for sentinel node biopsy after systemic treatment if clinical and radiological downstaging is documented by ultrasound and MRI.

(last version updated November 20, 2023, https://www.iss.it/documents/20126/8403839/LG_C0013_AIOM_Ca-mammario-precoce.pdf).

2.1. Statistical analysis

Primary analysis was performed by comparing variables between two groups (NACT versus PBS) to assess the determinants of NACT: we performed a set of univariable analyses for the comparison with respect to patient age, tumour and nodal stages, molecular subtypes and year of treatment (all in categorical format). All the five covariates significantly correlated with NACT performance and were entered into a multivariate logistic regression model to identify the role of each in determining the choice of NACT. Heterogeneity between centers was assessed with Fisher's Test, given the small number of cases in some of them. Trends over time were checked analysing the year of treatment as a continuous variable in a multivariate logistic regression model adjusting for the other five covariates. Trend analyses were performed both on the whole dataset and on subsets based on tumour and nodal stages and molecular subtypes.

Secondary analyses were performed to identify determinants for surgical decisions in case of NACT, and to assess their trends over time: For each secondary analyses a multivariate logistic regression model was used to determine the factors influencing each surgical decision: all models included year of treatment as a categorical variable (continuous for trend analyses), age and molecular subtype as covariates; tumour and nodal stage were included as covariates only when not used for the subset selection.

All statistical analyses were performed using R version 4.3.2 (©TheRFoundation). Statistical significance was set at $p < 0.05$. Data collected into Senonet are regulated following the general principles of the European rule for the treatment of personal data (GDPR 679/2016 and D.lgs 196/03). Data extracted from Senonet for statistical analysis, being anonymous data, are non-subjects to GDPR rules and no other action or authorization is required from the Breast Centers that have already joined the Quality Control Project by signing the project documents and agreements.

3. Results

Among 58,661 BC patients diagnosed and treated between January 2017 and December 2022 in the 24 Breast Centers participating in Senonet, a total of 37,215 women with primary invasive and non-metastatic BC were analysed after subset exclusion (Fig. 1).

Patients' and tumors' characteristics, and multivariable analysis of determinants of NACT vs. PBS are described in Table 1.

3.1. Determinants of NACT

The overall incidence of NACT increased significantly from 2017 to 2022 (OR = 1.07; $p < 0.001$). Women who received NACT were younger ($p < 0.001$) and their tumor subtypes were more frequently represented by HR-/HER2+ (OR = 10.6, $p < 0.001$) and Triple-negative subtypes (OR = 7.89, $p < 0.001$) (Table 1). We documented a significant association between increasing tumor diameter >1 cm, nodal involvement and implementation of NACT ($p < 0.001$) (Table 1).

3.2. Trends over time

During the study period, a significant increase in the incidence of NACT was observed among HR-/HER2+, Triple-negative and Triple Positive BC subtypes, from 40 % to 57 % (OR = 1.34, $p < 0.001$), from 32 % to 45 % (OR = 1.26, $p < 0.001$), and from 31 % to 37 % (OR =

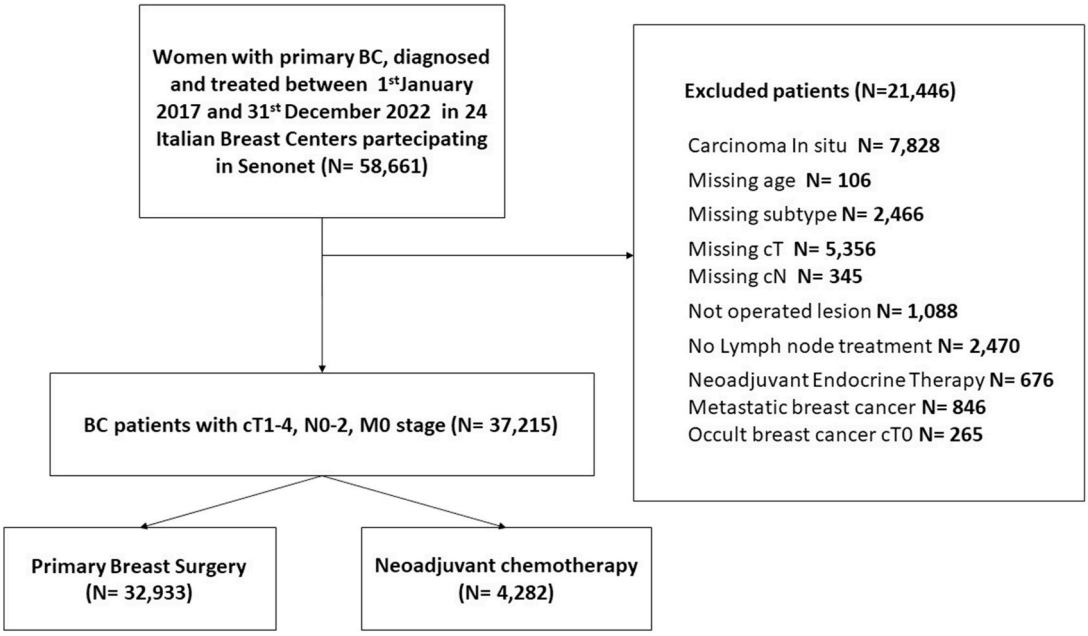

Fig. 1. Flowchart of patients selection.

1.15, $p < 0.001$), respectively (Fig. 2).

3.3. Trends in cN0 and cN + patients

Among 19,282 cT1N0 cases, a significant increase in NACT indications for HR-/HER2+, Triple-negative and HR+/HER2+ subtypes was observed, from 8 % to 36 % (OR = 1.47, $p < 0.001$), 7 %–34 % (OR = 1.49, $p < 0.001$), and 10 %–18 % (OR = 1.18, $p = 0.006$), respectively (Fig. 3A).

Among 5,443 patients with cT2-4N0 tumors, the incidence of NACT for patients with HR-/HER2+ and Triple-negative subtypes increased significantly over time from 30 % to 52 % (OR = 1.40, $p < 0.001$), and from 23 % to 26 % (OR = 1.13, $p = 0.04$), respectively (Fig. 3B).

Among 6,073 BC patients with cT1N + disease the indication for NACT increased significantly both for Triple-negative and Triple positive subtypes, from 55 % to 57 % (OR = 1.21, $p = 0.03$) and from 51 % to 41.5 % (OR = 1.23, $p = 0.01$) respectively, and with a trend to significance for HR-/HER2+ subtype (OR = 1.25, $p = 0.054$) (Fig. 3C).

Among 6,417 patients with tumors ≥ cT2 cN+ a significant increase of implementation of NACT was observed for HR-/HER2+ and Triple Positive subtypes from 40 % to 57 % (OR = 1.30, $p = 0.009$), and from 31 % to 37 % (OR = 1.21, $p = 0.004$), respectively (Fig. 3D).

3.4. Determinants of surgical decisions after NACT

3.4.1. Breast conservative surgery vs. Mastectomy

There was no increase in the adoption of breast conservative surgery (BCS) after NACT over time, from 292/701 cases in 2017 (42 %) to 250/493 in 2022 (51 %) (OR = 1.01, $p = 0.71$). However, in a multivariate analysis, there was a significant increase in the adoption BCS for patients with Triple-negative subtype (OR = 1.3, $p = 0.004$) and HR+/HER2+ subtypes (OR = 1.27, $p = 0.01$). BCS resulted negatively associated with age <39 years (OR = 0.44, $p < 0.001$), premenopausal status (40–49 years) (OR = 0.66, $p < 0.001$), Luminal A-like subtype (OR = 0.71, $p = 0.006$), tumor size greater than 2 cm (cT2+) (OR = 0.53, $p < 0.001$) and lymph node involvement (cN+) (OR = 0.61, $p < 0.001$) (Table 2).

3.4.2. Immediate breast reconstruction vs. No breast reconstruction

Immediate breast reconstruction (IBR) increased significantly over time (OR = 1.10, $p = 0.011$). Young age (up to 39 years), premenopausal status (40–49 years) and Triple Positive subtype were significantly associated with IBR (OR = 4.45, $p < 0.001$; OR = 3.33, $p < 0.001$; OR = 1.4, $p = 0.037$, respectively). Conversely, tumor size greater than 2 cm (cT2+) (OR = 0.58, $p = 0.034$), lymph node involvement (cN+) (OR = 0.49, $p < 0.001$) and age >70 years (OR = 0.09, $p < 0.001$) resulted negatively associated with IBR. Similarly, indication for nipple sparing mastectomy (NSM) (vs. other types of mastectomy) increased significantly over time from 139/399 cases in 2017 (35 %) to 93/236 in 2022 (39 %) (OR = 1.14, $p < 0.001$).

3.4.3. Number of lymph nodes removed (≤4 vs > 4) in cN0 disease

Among 1,835 BC patients clinically staged cN0, the vast majority received SLNB after NACT (N = 1496–81.5 %). In this setting, the trend of surgical axillary staging with >4 removed lymph nodes did not change significantly over time (OR = 0.94, $p = 0.095$) but resulted negatively associated with HR+/HER2+, Triple-negative and HR-/HER2+ subtypes (OR = 0.53, $p = 0.001$; OR = 0.48, $p < 0.001$; OR = 0.41, $p < 0.001$, respectively).

3.4.4. Axillary lymph node dissections (ALND) vs. No ALND in cN + disease

Among 2436 patients with cN + disease, axillary lymph node dissection (ALND) was the most commonly performed staging procedure (Table 3). However, in the study period there was a significant increase of SLNB (only) from 23 % to 35 % (OR = 0.33, $p < 0.001$).

while (Table 3).

In cN + disease ALND was strongly associated with Luminal A-like subtype (OR = 1.71, $p = 0.03$), tumor size greater than 2 cm at diagnosis (cT2+) (OR = 1.83, $p = 0.003$) and age >70 years (OR = 1.51, $p = 0.04$). Premenopausal age (40–49 years) (OR = 0.77, $p = 0.02$) and Triple Positive, Triple-negative and HR-/HER2+ subtypes (OR = 0.35, $p < 0.001$; OR = 0.44, $p < 0.001$; OR = 0.28, $p < 0.001$, respectively) were negatively associated with ALND (Table 3).

3.4.5. SLNB with 2 tracers vs. 1 tracer in cN+/ycN0 disease

In cN + BC patients treated with SLNB procedure, the use of a double-tracer technique with the aim to localize three or more sentinel nodes increased significantly over time from 12.7 % to 25 % (OR = 1.29, $p = 0.004$). There was no correlation between the use of a single- or a double-tracer techniques and the other clinical variables taken into

Table 1
Patients' and tumors' characteristics and multivariable analysis of determinants of NACT (vs. PBS).

	Total	PBS (%)	NACT (%)	OR[a]	p-value	Missing N (%)
Total	37215	32933 (88.5 %)	4282 (11.5 %)			
Year						
2017	6629	5920 (89 %)	709 (12 %)	ref.		0 (0 %)
2018	7511	6674 (89 %)	837 (11 %)	1.08	0.25	
2019	7620	6763 (89 %)	857 (11 %)	1.13	0.08	
2020	5262	4557 (87 %)	705 (13 %)	1.6	**<0.001**	
2021	5357	4677 (87 %)	680 (13 %)	1.47	**<0.001**	
2022	4836	4342 (90 %)	494 (10 %)	1.21	0.02	
Age (years)						
Mean (years)	60.6 (20–94)	61.7 (20–94)	52.4 (23–80)		**<0.001**	
Up to 39	1571	1017 (65 %)	554 (35 %)	2.44	**<0.001**	0 (0 %)
40–49	7228	5932 (82 %)	1296 (18 %)	1.57	**<0.001**	
50–69	17668	15612 (88 %)	2056 (12 %)	ref.		
70+	10748	10372 (96.5 %)	376 (3.5 %)	0.16	**<0.001**	
Tumor stage						
T1a-b	15185	14834 (98 %)	351 (2 %)	ref.		0 (0 %)
T1c	10170	9456 (93 %)	714 (7 %)	2.75	**<0.001**	
T2+	11860	8643 (73 %)	3217 (27 %)	12.8	**<0.001**	
Nodal stage						
N0	24725	22882 (92.5 %)	1843 (7.5 %)	ref.		0 (0 %)
N+	12490	10051 (80.5 %)	2439 (19.5 %)	1.99	**<0.001**	
Biological subtype						
Luminal A	20775	20359 (98 %)	416 (2 %)	0.25	**<0.001**	0 (0 %)
Luminal B	9372	8284 (88 %)	1088 (12 %)	ref.		
HR+/HER2+	2706	1716 (63 %)	990 (37 %)	6.33	**<0.001**	
Triple negative	3054	1880 (62 %)	1174 (38 %)	7.89	**<0.001**	
HR-/HER2+	1308	694 (53 %)	614 (47 %)	10.6	**<0.001**	
Multifocal/Multicentric lesions						
Yes	21924	19933 (91 %)	1991 (9 %)			7974 (21.4 %)
No	7317	6041 (83 %)	1276 (17 %)			
Missing information	7974	6959 (87 %)	1015 (13 %)			
Tumor stage						
IA	22673	22054 (97 %)	619 (3 %)			1273 (3.4 %)
IB	10	7 (70 %)	3 (30 %)			
IIA	8511	7041 (83 %)	1470 (17 %)			
IIB	3245	1921 (59 %)	1324 (41 %)			
IIIA	789	343 (43.5 %)	446 (56.5 %)			
IIIB	587	265 (45 %)	322 (55 %)			
IIIC	127	29 (23 %)	98 (77 %)			
Histologic type						
Ductal	26157	23850 (91.2 %)	2307 (8.8 %)			1999 (5.3 %)
Lobular	5110	4949 (96.8 %)	161 (3.2 %)			
Other	3949	3744 (94.8 %)	205 (5.2 %)			
Tumor grade						
G1	4102	4040 (98.5 %)	62 (1.5 %)			287 (0.8 %)
G2	21151	19672 (93 %)	1479 (7 %)			
G3	11675	9103 (78 %)	2572 (22 %)			

Abbreviations: *BC = breast cancer; PBS = primary breast surgery; NACT = neoadjuvant chemotherapy; T2+: tumor size* > 2 cm *in diameter.*
[a] Calculated with a multivariable model adjusting also for center.

consideration in the multivariate analysis.

3.5. Variability among breast centers participating in senonet

There was a significant variability for the indication to NACT among the 24 participating Breast Centers (range 4–18 %) (Fisher test: $p < 0.001$) (Fig. 4).

A significant variation among Breast Centers was also observed for the adoption of BCS (range 30–100 %) ($p < 0.001$), NSM (range 0–56 %) ($p < 0.001$) and IBR (49–100 %) ($p < 0.001$) after NACT. In addition, there was a considerable heterogeneity regarding the use of ALND after NACT both for patients with cN0 (range 0–100 %) ($p < 0.001$) and cN + disease at diagnosis (range 50.5–100 %) ($p < 0.001$).

4. Discussion

Only few studies describe the current implementation of NACT among BC patients at a national level in the "real world", and this is the first Italian investigation on this topic analysing a large cohort of patients. Although we documented a significant increase in the incidence of NACT among Italian Breast Centers participating in Senonet over time, we registered a rate of roughly 10 %, which is low if compared to other national experiences reported in literature. This is particularly significant, considering that Senonet is a voluntary registry which is powered by 24 high-volume Breast Centers and most of them obtained the European Breast Centers Certification (BCCERT) based on the Eusoma requirements [33,34].

A national cancer audit of 114,700 patients treated in the Netherlands between 2011 and 2020 indicated that 21 % of these women were managed with NACT. Similarly, a national French survey among surgeons in institutions caring for 26 % of the total national incidence of BC cases revealed that roughly 16 % of women treated for this reason underwent surgery after NACT, although with a wide-range variation among different centers from 2 to 30 % [35–38]. Finally, data from the National Cancer Database (NCDB) in the USA showed that the overall incidence of NACT significantly increased from 15.7 % in 2010 to 26 % in 2015 for all BC-subtypes, and particularly for HR-/HER2+ and Triple-negative tumors [12,15]. Only one other report, although with a limited number of cases, was conducted so far in Italy, documenting that 14 % of 1,276 stage I-III BC patients enrolled in a

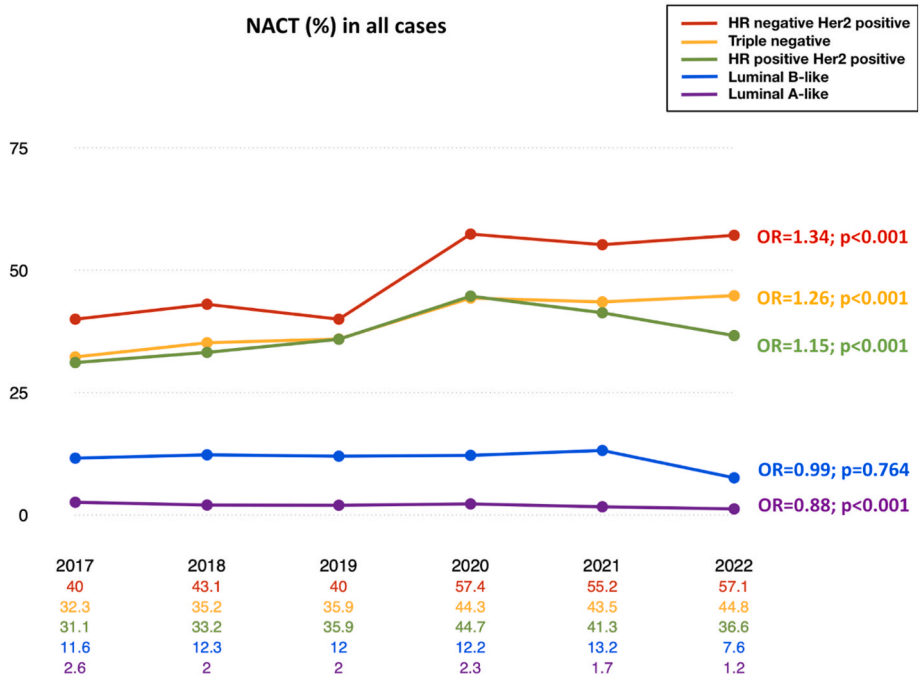

Fig. 2. Incidence of NACT per year from 2017 to 2022, in different molecular subtypes of breast cancer patients. **Abbreviations:** *NACT = neoadjuvant chemotherapy*.

prospective/observational/multicenter study received NACT in the years 2018–2021 [39].

As observed in previous reports [40–42], clinicopathologic factors predictive of NACT in our study included young age, larger tumor diameter and lymph node involvement at diagnosis. Among BC patients with tumor size >2 cm or presenting with positive lymph nodes, 27 % and 20 % of the patients received NACT, respectively. On multivariate analysis, we identified that patients with age >70 years had a lower likelihood of receiving NACT, probably due to the increased risk of toxicity and associated comorbidities [43]. As previously reported [42], we documented, a significant higher rate of NACT specifically for more aggressive bioprofiles, with 54 %, 43 % and 35 % of our patients with HR-/HER2+, Triple-negative and Triple-positive BC cases, respectively, being so treated. It is well known that these subtypes are associated with high-rates of pathologic complete response (pCR), reaching 60 % in some studies [12,27–30], and that the latter is a highly significant prognostic marker for both disease-free survival and overall survival [13].

In our study the incidence of NACT in cN0 disease for both HR-/HER2+ and Triple-negative subtypes increased over time, and recent studies documented a prognostic advantage of NACT in this setting [44–46]. Similarly, the addition of immunotherapy to standard neo-adjuvant regimens for early-staged Triple-negative BC patients has been associated to a higher pCR rate and, at a median follow-up of more than 5-years, to a clinically significant improvement of event-free-survival [47–49]. Conversely, residual disease after NACT directs further therapeutic strategies in patients with Triple-negative and HR-/HER2+ BC patients, and this may explain in part the observed increase in NACT rate for these patients in our study [50,51].

The majority of patients in the present study received mastectomy after NACT. In addition, we found that tumor size greater than 2 cm and lymph node involvement were negatively associated with BCS, a notion previously reported but that should be better analysed if one considers that most of such patients reach a pCR [52]. While CALGB 40601 and 40603 trials for HR-/HER2+ and Triple-negative BC patients [53,54] documented that many patients deemed ineligible for BCS can be converted to be eligible after NACT, still a high-proportion of these women undergo mastectomy, in contemporary reports. In addition, a secondary analysis of the BrighTness multicentric randomized trial on patients with Triple-negative BC reported that, while 76.5 % of these women were registered as BCS eligible pre-NACT and roughly 50 % of those ineligible clinically pre-NACT converted to be eligible, yet only 68 % of patients effectively received BCS despite that the pCR rate was 50 %, whatever surgical strategy was employed [55]. We acknowledge the fact that choosing the best surgical option after NACT is often a clinically-difficult and a personal multi-faced issue, and that this requires a deep discussion and an open confrontation between patient and her team. In literature, type of breast surgery performed is clearly influenced by several factors including surgeon's attitude and counselling [52,56], degree of diagnostic investigations [57] and patient's preference [58,59]. The latter is a complex-balance conditioned by several aspects such as age, marital status, education and cultural level [59] and type of disease itself. These considerations need to be better evaluated by the surgical and oncological community, taking in account that the pCR rate is progressively increasing and that one recent retrospective study shows that local recurrence rate is low in this subset of patients, regardless of the type of the local surgical approach [60]. We are in the process of further analysing data to study the association between pCR and mastectomy or ALND and we will present these data in a further paper. In the meanwhile, our results confirm that after NACT Breast Centers adopted less aggressive axillary staging strategies, with a decrease both for ALND rate and the number of removed lymph nodes. According to national and international guidelines, it is well accepted that patients clinically staged cN0 can be safely managed with SLNB-only if a pN0 status is confirmed. For patients with cN + disease a complete down-staging in the lymph nodes can occur in more than 50 % of cases, particularly for HR-/HER2+ disease [61–63]. The accuracy of SLNB in clinically node-positive patients who convert to clinically node-negative has been evaluated in several studies [64–67], documenting that SLNB is feasible in case of lymph nodes clinical and radiological response, particularly if a double-tracer is used and if at least 3 lymph nodes are biopsied. This is associated with a reduced false negative rate below 10 % [68]. Our study documented a significant increase in the adoption of double-tracer use with SLNB in cN + cases. In this cohort, the adoption of SLNB-only after NACT significantly increased from 23 % to 35 % in the study period, reflecting an increased

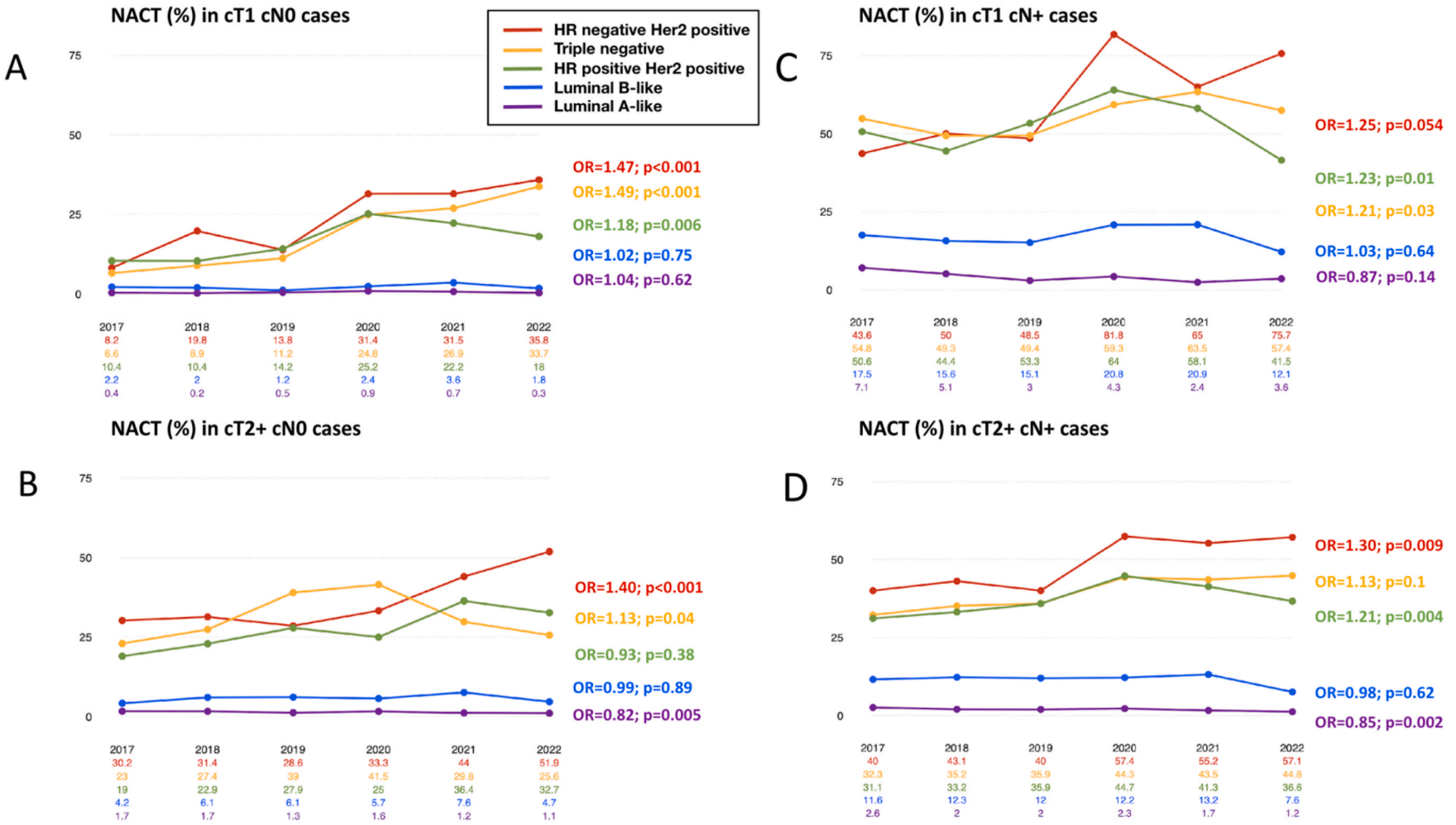

Fig. 3. Incidence of NACT per year from 2017 to 2022, in different molecular subtypes: **A** in cT1 cN0 cases; **B** in cT2+ cN0 cases; **C** in cT1 cN + cases; **D** in cT2+ cN + cases. **Abbreviations:** *NACT = neoadjuvant chemotherapy; cT2+: tumor size* > 2 cm *in diameter*.

Table 2
Determinants of BCS versus mastectomy after NACT.

	Total	Mastectomy (%)	BCS (%)	Multivariable	
				OR	p
Total	4252	2295 (54 %)	1957 (46 %)		
Year					
2017	701	409 (58 %)	292 (42 %)	ref	
2018	834	493 (59 %)	341 (41 %)	0.98	0.85
2019	849	464 (55 %)	385 (45 %)	1.1	0.38
2020	701	349 (50 %)	352 (50 %)	1.05	0.71
2021	674	337 (50 %)	337 (50 %)	1.05	0.71
2022	493	243 (49 %)	250 (51 %)	1.01	0.93
Age (years)					
Up to 39	550	376 (68 %)	174 (32 %)	0.44	**<0.001**
40–49	1290	765 (59 %)	525 (41 %)	0.66	**<0.001**
50–69	2041	985 (48 %)	1056 (52 %)	ref	
70+	371	169 (46 %)	202 (54 %)	1.15	0.23
Clinical tumor stage					
cT1a-b	348	148 (42 %)	200 (58 %)	ref	
cT1c	709	271 (38 %)	438 (62 %)	0.97	0.84
cT2+	3195	1876 (59 %)	1319 (41 %)	0.53	**<0.001**
Clinical nodal stage					
cN0	1829	819 (45 %)	1010 (55 %)	ref	
cN+	2423	1476 (61 %)	947 (39 %)	0.61	**<0.001**
Biological Subtype					
Luminal A-like	409	257 (63 %)	152 (37 %)	0.71	**0.006**
Luminal B-like	1083	655 (60.5 %)	428 (39.5 %)	ref	
HR+/HER2+	985	499 (51 %)	486 (49 %)	1.27	**0.01**
Triple negative	1167	578 (49.5 %)	589 (50.5 %)	1.3	**0.004**
HR-/HER2+	608	306 (50 %)	302 (50 %)	1.23	0.06

Abbreviations: BCS = breast conservative surgery; cT2+: tumor size > 2 cm in diameter.

Table 3
Determinants of axillary dissection versus SLNB (only) in cN + disease after NACT.

	Total	SLNB (only) (%)	ALND (%)	Multivariable	
				OR	p
Total	2436	706 (29 %)	1730 (71 %)		
Year rowhead					
2017	439	101 (23 %)	338 (77 %)	ref	
2018	531	143 (27 %)	388 (73 %)	0.79	0.16
2019	517	156 (30 %)	361 (70 %)	0.61	**0.003**
2020	366	112 (31 %)	254 (69 %)	0.39	**<0.001**
2021	344	111 (32 %)	233 (68 %)	0.33	**<0.001**
2022	239	83 (35 %)	156 (65 %)	0.33	**<0.001**
Age (years)rowhead					
Up to 39	314	103 (33 %)	211 (67 %)	0.82	0.19
40–49	756	242 (32 %)	514 (68 %)	0.77	**0.02**
50–69	1146	318 (28 %)	828 (72 %)	ref	
70+	220	43 (19.5 %)	177 (80.5 %)	1.51	**0.04**
Clinical tumor stage rowhead					
cT1a-b	158	54 (34 %)	104 (66 %)	ref	
cT1c	288	105 (36.5 %)	183 (63.5 %)	1.03	0.91
cT2+	1990	547 (27.5 %)	1443 (72.5 %)	1.83	**0.003**
Biological Subtyperowhead					
Luminal A-like	252	25 (10 %)	227 (90 %)	1.71	**0.03**
Luminal B-like	739	142 (19 %)	597 (81 %)	ref	
HR+/HER2+	555	212 (38 %)	343 (62 %)	0.35	**<0.001**
Triple negative	537	187 (35 %)	350 (65 %)	0.44	**<0.001**
HR-/HER2+	353	140 (40 %)	213 (60 %)	0.28	**<0.001**

Abbreviations: ALND = axillary lymph nodes dissection; cT2+: tumor size > 2 cm in diameter.

comfort with the use of SLNB in this setting. This was more pronounced in patients with HR-/HER2+ and Triple-negative disease, in accordance with data from the NCDB [69,70].

For cN + patients with Luminal A-like and Luminal B-like bioprofiles, our study shows that the incidence of ALND maintained high over time, probably due to their lower response rate to NACT [12,13,27–30],

Of particular importance, our data shows a significant variability of surgical treatment after NACT even among a selected group of high-volume/highly-specialized Breast Centers, following the same national guidelines. This underscores the need to share attitudes and protocols to improve homogeneity of approaches in this setting. To further improve results at a national level, Senonet issues a yearly report for each Breast Center on the outcome according to quality indicators, and compares performance of each Center with the national benchmark.

There are some weaknesses of our study. First, this was a retrospective review of a multicentric registry, and some items in the datasets were missing for incomplete data entry. Second, the analysis was limited to Breast Centers participating to Senonet, and it does not represent, therefore, a complete national picture. Third, bioprofiles are approximated on clusters based on available immunohistochemical data and do not consider genomic-assays.

Nevertheless, this is the first report from Italy on this topic analysing a high number of cases from a prospectively maintained data warehouse, and it represents, therefore, a clear indication on how the clinical approach is evolving at a national level in this setting.

5. Conclusions

Although this study indicates that implementation of NACT has increased among Italian Breast Centers over recent years, the rate remains low if compared with other national reports. The impact of NACT on the subsequent surgical management is substantial and continues to evolve over time, with less extensive surgery if not needed. We found a high variability among Breast Centers, and this underscore the need to further improve the adoption of current recommendations. Health-systems should monitor implementation of NACT as clinical outcome and study ways to further improve results at a national and regional level.

The Journal policies have been reviewed by all the Authors.

Ethics

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript is in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.

CRediT authorship contribution statement

A. De Luca: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **M.I. Amabile:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **F. Santori:** Writing – original draft, Investigation, Data curation. **S. Di Matteo:** Writing – original draft, Investigation, Data curation. **M. Tomatis:** Writing – review & editing, Writing – original draft, Validation, Software, Formal analysis, Data curation, Conceptualization. **A. Ponti:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **F. Frusone:** Writing – review & editing, Writing – original draft, Methodology. **M. Taffurelli:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **C. Tinterri:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **L. Marotti:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **M. Calabrese:** Writing – review & editing, Writing – original draft. **C. Marchiò:** Writing – review & editing, Writing – original draft, Methodology. **F. Puglisi:** Writing – review & editing, Writing – original

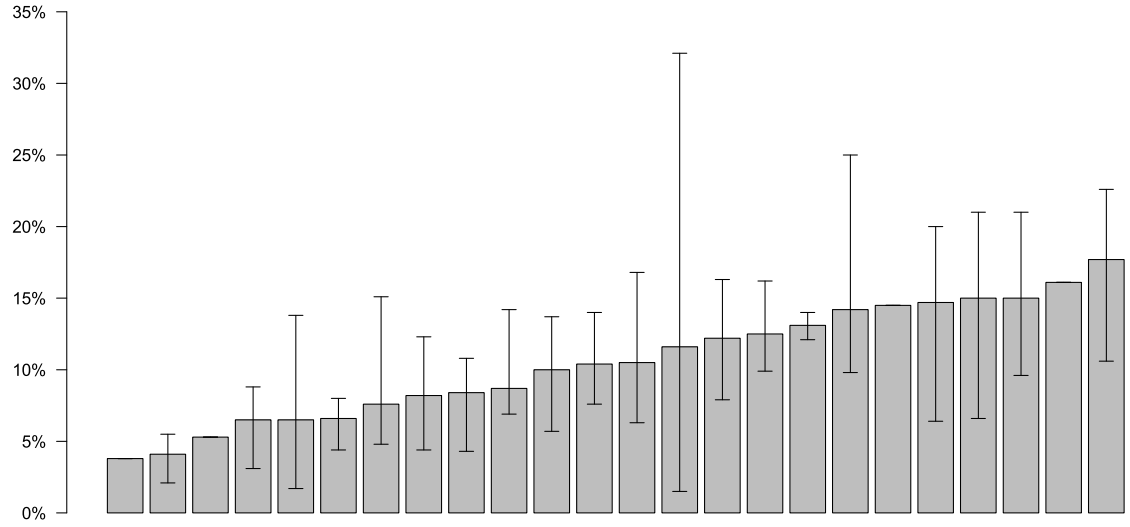

Fig. 4. Variability in indication to NACT over time among Breast Centers participating in Senonet.

draft, Methodology. **I. Palumbo:** Writing – review & editing, Writing – original draft, Methodology. **L. Fortunato:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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