ESMO Open
Cancer Horizons

Check for updates

Neoadjuvant radiotherapy in the approach of locally advanced breast cancer

Cláudia Sousa ,[1] Mafalda Cruz,[1] Ana Neto,[1] Kayla Pereira,[1] Marta Peixoto,[2] Joana Bastos,[3] Mónica Henriques,[1] Domingos Roda,[1] Rui Marques,[1] Cristina Miranda,[1] Gilberto Melo,[1] Gabriela Sousa,[2] Paulo Figueiredo,[4] Paula Alves[1]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/esmoopen-2019-000640).

To cite: Sousa C, Cruz M, Neto A, *et al*. Neoadjuvant radiotherapy in the approach of locally advanced breast cancer. *ESMO Open* 2020;**5**:e000640. doi:10.1136/esmoopen-2019-000640

Received 15 November 2019
Revised 22 January 2020
Accepted 23 January 2020

[1]Radiotherapy, Instituto Português de Oncologia de Coimbra Francisco Gentil, E.P.E, Coimbra, Portugal
[2]Medical Oncology, Instituto Português de Oncologia de Coimbra Francisco Gentil, E.P.E, Coimbra, Portugal
[3]Regional Oncology Registry of the Centre, Instituto Português de Oncologia de Coimbra Francisco Gentil, E.P.E, Coimbra, Portugal
[4]Anatomical Pathology, Instituto Português de Oncologia de Coimbra Francisco Gentil, E.P.E, Coimbra, Portugal

Correspondence to
MD Cláudia Sousa;
claudiacarreirosousa@gmail.com

ABSTRACT

Background Approximately 4% of European patients are diagnosed with locally advanced breast cancer (LABC), a clinical condition commonly associated with poorer prognosis. Systemic therapy is the recommended initial treatment and when inoperability criteria prevails, radiotherapy (RT) should be used for tumour downstaging. This study intends to evaluate the impact of neoadjuvant radiotherapy (NART) in the treatment of inoperable LABC.

Methods A retrospective study of female patients, submitted to the NART between January 2014 and December 2018 at our institution. The evaluation of pathological response (pR) was made based on Pinder criteria. Primary endpoint: pR. Secondary endpoints: overall survival (OS) and progression-free survival (PFS). OS and PFS were calculated using the Kaplan-Meier method. Differences between groups were compared using Student's t-test, ANOVA (Analysis of variance) and χ^2 test. The statistical analyses were performed using Stata (V.13).

Results A total of 76 patients were included, 18% with breast complete response. The 5 years OS was 54% and PFS was 61%. Subgroup analysis showed that pR >90% is correlated with a better OS (p=0.004). Basal-like intrinsic subtype is correlated with worse OS and PFS (p<0.05). No relation was found between response and age, intrinsic subtype, treatment performed and clinical T stage.

Conclusion Our study confirms that NART is an effective downsizing treatment in inoperable LABC, allowing for a surgical resection regardless of the systemic treatment performed. Response to NART is independent of the intrinsic subtype and pR >90% is correlated with a better OS. Prospective studies to explore predictive response biomarkers are necessary in order to improve patient selection and optimisation of the treatment.

INTRODUCTION

Radiotherapy (RT) plays an important role in the multidisciplinary treatment of breast cancer. Adjuvant RT is associated with better disease control, with a significant reduction in locoregional and distant relapse rates. It is also related to the increase of overall survival (OS) after conservative surgery and mastectomy.[1–3] Approximately 8.5% of American and 4% of European patients are diagnosed with breast cancer at a locally advanced stage.[3] This clinical condition is

Key questions

What is already known about this subject?

- Approximately 8.5% of American and 4% of European patients are diagnosed with breast cancer at a locally advanced stage (LABC). This clinical condition is commonly associated with an increased risk of locoregional recurrence, distant metastasis, reduced quality of life and overall survival.
- The standard treatment of LABC is almost always multimodal and involves systemic therapy with chemotherapy and/or hormone therapy, surgery and radiotherapy (RT).
- For inoperable breast cancer following neoadjuvant (NA) systemic therapy, RT may be applicable.
- There are no well-established guidelines for NART.

What does this study add?

- This study confirms that NART is an effective downsizing treatment in inoperable LABC, allowing surgical resection regardless of systemic treatment performed.
- Response to NART is independent of the intrinsic subtype, differentiation grade, age and time interval to surgery.
- Differences between intrinsic subtypes and achieved responses are statistically correlated with progression-free survival (PFS) and overall survival (OS).
- There was no correlation between intrinsic subtypes and response, but the luminal B HER2+ and basal-like have worse prognosis, with a 5 years PFS of 56% and 0% and a 5 years OS of 26% and 18%, respectively.
- Patients with a pathological response superior to 90% have a better 3 years and 5 years OS (83% and 68% vs 48% and 35%, p=0.004) and tend to have a better 3 and 5 years PFS (76% and 71% vs 53% and 47%, p=0.059).

How might this impact on clinical practice?

- Our data advocates for the role of RT in the multidisciplinary treatment of inoperable LABC. Prospective studies to explore predictive response biomarkers are necessary in order to improve patient selection and optimisation of the treatment.

commonly associated with increased risk of locoregional recurrence, distant metastasis, reduced quality of life and OS. The standard treatment of locally advanced breast cancer (LABC) is almost always multimodal and involves systemic therapy with chemotherapy (CT) and/or hormone therapy (HT), surgery and RT.[4 5] Systemic therapy is usually the first approach, however, more than a third of patients may not respond as expected.[6 7] When inoperability criteria prevails, RT should be used for tumour downstaging. Currently, neoadjuvant (NA) RT may be applicable for inoperable breast cancer to allow an effective and sometimes more conservative surgery.[6 8] Besides, there is the benefit of eradicating occult micrometastatic disease. This process may facilitate personalised therapy and allow the identification of more prognostic factors such as predictors of response.[9] Given the scarce literature, there are no well-established guidelines for RT following NA CT and/or HT (NACT/NAHT). The benefits of RT prior to surgical treatment are not conclusive and predictive biomarkers of response are unknown. With this study, we intend to evaluate the impact of NART in the treatment of the LABC.

MATERIAL AND METHODS

Study design, eligibility, treatment

We conducted a retrospective study of female patients with inoperable LABC submitted to NART between January 2014 and December 2018 at our institution. Radiation therapy was delivered using a mega-voltage linear accelerator with 6–15 MV photons, by three-dimensional conformal technique. Decisions regarding fractionation and target volumes were individualised and the RT regimens varied between 26 Gy/4 fr/2.5 weeks+30 Gy/10 fr/2 weeks, 50 Gy/25 fr/5 weeks and 60 Gy/30 fr/6 weeks on the breast volume, supraclavicular and axillary lymph node regions. Tumour response was assessed by microscopic examination of the excised primary lesion and lymph nodes. Patients who did not undergo surgical procedure were excluded.

Pathology assessment

Demographic information was collected and clinical information included the date of diagnosis, disease stage (according TNM system, seventh edition), Ki-67, grade, hormone receptors and HER2 status, NA systemic treatment performed, RT dose, fractionation, treatment volumes and technique, temporal interval of the treatments, date of surgery, margin status, pathological response (pR), date of progression and site and date of death and last follow-up. Histological characteristics were assessed by pathologists from biopsies taken at diagnosis. Hormonal receptors and HER2 status were evaluated by immunohistochemistry, with HER2-positivity defined as a score 3+ or a score 2+ followed by gene amplification by in situ hybridisation. pR was assessed by microscopic examination of the excised tumour and lymph nodes. In the primary tumour, breast pR was established based on Pinder criteria and the patient population was divided into three groups: 1—complete response (pCR), 2—pR >90% and 3—pR ≤90%. In this study, we focused on the pCR defined as the absence of invasive carcinoma regardless of the presence of in-situ carcinoma in the breast. Nodal response was assessed after comparison of the initial clinical nodal stage and the final pathological nodal stage. Surgical margins were defined as negative (R0) when no invasive or in-situ carcinoma was evident on the inked section or as positive (R1) when present. Locoregional and distant progression was considered.

Endpoints definitions

The primary endpoint was to evaluate breast and lymph node pR. The secondary endpoints were to calculate the OS and progression-free survival (PFS).

Statistical analysis

OS was defined as the time from the date of diagnosis to death or censored at the most recent follow-up. PFS was defined as the time from the end of RT to the first diagnosis of locoregional or distant progression. For patients with no progression, PFS was calculated as the time from the end of RT to death or last follow-up. Patients with missing values were excluded. Continuous variables were expressed as mean and median. Categorical variables were presented as percentages. OS and PFS were calculated using the Kaplan-Meier method. Differences between groups were assessed using Student's t-test, ANOVA and χ^2 test. The statistical analyses were performed using Stata (V.13).

RESULTS

Patient population, tumour and treatment characteristics

During delivery of the treatments, tumour response was routinely assessed by clinical examination, but due to the unavailability of a standardised radiological evaluation before and after the NA therapy, we considered the only way to objectively evaluate the response was with pathological examination of the excised tumour and lymph nodes.

A total of 76 female patients were included in this study. The mean age was 63 (32–88) years. Patients and disease characteristics are described in table 1.

Most patients (95%) had invasive carcinoma, eight with inflammatory carcinoma at presentation. The distribution according intrinsic subtypes is relatively balanced, except HER2+ subtype, which represents only 9% (n=7). At diagnosis, clinical stages IIIA and IIIB were the most frequent, accounting for 41% and 36%, respectively. 56 (74%) patients had nodal involvement at diagnosis. NACT was performed in 43 (57%) patients, 41 (95%) with anthracyclines and taxanes regimens (AC or EC q3w followed by docetaxel q3w or weekly paclitaxel) and 2 (5%) with weekly paclitaxel due to cardiac contraindication to anthracyclines-containing regimens. Eight (44%) from a total of 18 (24%) patients with HER2 positive tumours, received trastuzumab, completing 1 year

Table 1 Characteristics of the total study population (n=76)

Characteristics	N (76)		%
Age (years)			
Mean	63		
Range	32–88		
Gender			
Female	76		100
Histological subtype			
Invasive	72		95
In situ	4		5
Intrinsic subtype			
Luminal A *like*	15		20
Luminal B *like*	24		32
Luminal B *like* HER2+	11		14
HER2+	7		9
Basal *like*	19		25
Grade			
G1	25		33
G2	31		41
G3	20		26
TNM stage			
IIB	11		14
IIIA	31		41
IIIB	27		36
IIIC	7		9
Neoadjuvant treatment performed			
Chemotherapy and radiotherapy	43		57
Hormone therapy and radiotherapy	19		25
Radiotherapy	14		18
Systemic therapy regimens			
Anthracyclines and taxanes	74		97
Taxanes	2		3
HER2-targeted therapy	9		12
Aromatase inhibitors	19		25
Fractionation schemes			
50 Gy/25 fr/5 weeks on the breast volume and regional lymph nodes	36		47
60 Gy/30 fr/6 weeks on the breast volume and 50 Gy/25 fr/5 weeks on the regional lymph nodes	29		38
26 Gy/4 fr/2.5 weeks on the breast volume and 30 Gy/10 fr/2 weeks to regional lymph nodes	11		15
Surgical margins			
R0	76		100
Breast pathological response			
Complete response	14		18
Partial response >90%	31		41
Partial response ≤90%	31		41
Breast pathological response by intrinsic subtype	**pCR**	**pR >90%**	**pR ≤90%**
Luminal A *like*	2	7	6
Luminal B *like*	6	9	9
Luminal B *like* HER2+	2	6	3
HER2+	2	2	3
Basal *like*	2	6	11
Breast pathological response by neoadjuvant treatment performed			
Chemotherapy and radiotherapy	8	21	14
Hormone therapy and radiotherapy	2	8	9
Radiotherapy	4	2	8
Nodal pathological response			
Clinical nodal stage	**ypN+**	**ypN0**	**ypT0ypN0**
cN1	18	21	9
cN2	10	2	1
cN3	3	2	1

pR >90%, pathological response superior to 90%; pR ≤90%, pathological response equal ou inferior to 90%; cN, clinical nodal stage; fr, fraction; Gy, Grey; pCR, pathological complete response; ypN, pathological nodal stage after neoadjuvant treatment; ypT, pathological tumour stage after neoadjuvant treatment.

of HER2 blockade. Four patients did not have clinical conditions for trastuzumab. In six patients there was no information regarding trastuzumab because the systemic therapy was made in another hospital. NAHT was given to 19 (25%) patients with aromatase inhibitors.

The median time between the end of chemotherapy/beginning of hormone therapy and the start of RT was 5 (3–56) and 27 (1–69) weeks, respectively. All patients received external beam RT to the breast volume, supraclavicular and axillary lymph node regions. Decisions regarding dose and fractionation varied between 26 Gy/4 fr/2.5 weeks, 50 Gy/25 fr/5 weeks and 60 Gy/30 fr/6 weeks on the breast volume, 30 Gy/10 fr/2 weeks and 50 Gy/25 fr/5 weeks on the lymph node regions. No CT was given concomitant to RT.

Patients who completed the NART but did not undergo surgery or had missing values were excluded. Out of 11 excluded patients, 7 did not proceed with surgical treatment, partly due to age and comorbidities, and 4 were excluded due to lack of information.

Pathological response

A multidisciplinary evaluation was performed by the end of the NART, and was decided based on a clinical impression if the patient had conditions to proceed to surgical treatment. The median time to surgery after RT was 7 (1–78) weeks. All patients included were submitted to mastectomy, and pathological analysis confirmed that none had a positive margin. 14 (18%) had pCR, 31 (41%) had partial response >90% and 31 (41%) had partial response ≤90%. pR by NA treatment performed and by intrinsic subtype are described in table 1.

Of the 56 (74%) of patients with an initial clinical nodal involvement at diagnosis, 25 (45%) of patients were classified as ypN0 after locoregional treatment and 11 (44%) were classified as ypT0, corresponding to breast and nodal pCR. This result was mostly represented by the cN1 subgroup (70% of these patients), in which nodal pCR was seen in 54% and breast pCR in 23%. In total, breast and lymph node pCR was confirmed in 14,5% of the patients. Of the eight patients with inflammatory carcinoma, six received both CT and RT and two received only RT. In this subgroup, only one pCR was obtained and there was no evidence of nodal downstaging. There were no statistically significant differences between the pR and the intrinsic subtypes (p=0.092), grade of differentiation, age (p=0.184), stage (p=0.665), treatment performed (p=0.242) and time interval between RT conclusion and surgery.

Progression-free survival

After treatment, 25 (33%) of patients progressed and 56% of these had basal-like intrinsic subtype, which corresponds to 74% of this entire intrinsic group. Four (16%) had luminal B like HER2+, three (12%) had luminal A like, two (8%) had luminal B like and the other two (8%) had HER2+. The median time of progression was 45 weeks. Of the three patients that had locoregional cutaneous recurrence, two of them had a basal-like and one with luminal A like subtype. The most frequent sites for distant metastasis were lung (n=9, 36%) and brain (n=6, 24%), and mostly presented as single organ metastasis. Hepatic involvement (n=5, 20%) in all cases was diagnosed in pluri-metastatic context.

Regarding the pR, 11 (44%) of the patients who progressed had pR >90% and 14 (56%) had pR ≤90%. There was no statistically significant relation between the TNM stage (p=0.098) and the treatment performed (p=0.510). On the other hand, there were statistically significant differences between intrinsic subtypes (p=0.000) and patients with pR >90% tend to have a better PFS at 3 years and 5 years (p=0.059).

Globally, with a median 24.2 months of follow-up, a 3 years and 5 years PFS was 66% and 61%, respectively. Subgroup analysis showed an inferior PFS to luminal B like HER2+ and basal-like subtypes. PFS by intrinsic subtype and pR are described in online supplementary figure 1.

Overall survival

At the time of this review, 25 patients have died, 7 of which without evidence of disease progression. The 1 year, 3 years and 5 years OS was 95%, 68% and 54%, respectively. There were statistically significant differences between intrinsic subtypes (p=0.000) and pR (p=0.004). The patients with a longer OS had luminal A like intrinsic subtype and a pR >90%.

There was no statistically significant relation between age, TNM stage and treatment performed.

Global OS and OS by subgroups are described in online supplementary figures 2 and 3.

DISCUSSION

In the past, the treatment of LABC was comprised a combination of RT and surgery. This brought satisfactory results in locoregional control, however, insufficiency in distant disease control was acknowledged to be responsible for poorer results (5-year OS 24% and DFS 12%).[10 11] Even though outcomes for these patients have improved with a multimodality strategy, the treatment of LABC remains a clinical challenge.[12] NACT is known to reduce the risk of distant recurrence and also allows an early evaluation of the effectiveness of systemic therapy. pCR in patients treated with NACT was prognostically significant. After NACT, patients with pCR, compared with those with residual invasive disease had significant improvements in both OS (HR 0.48, 95% CI 0.33 to 0.69) and DFS (HR 0.48, 95% CI 0.37 to 0.63). These differences are more expressive in patients with more aggressive breast cancer subtypes (triple negative and HER2-positive breast cancer).[13–16] Failure in response to systemic therapy is associated with a worse prognosis for this subgroup of patients, however, our data confirmed the importance of RT in the multidisciplinary treatment of these patients. Jasmina Mladenovic *et al* published results of 134 patients with LABC submitted to NART, with a total dose of 45 Gy in 15 fr over 6 weeks to the breast and regional lymph nodes. Radical mastectomy was performed 6 weeks after finishing NART. Adjuvant systemic therapy was administered as per protocol. pCR in the breast was observed in 15% of the patients, 7.5% of which with lymph node pCR as well. Relapses were confirmed in 61.9% and 95% of these were distant metastasis. The 5-year DFS and OS were 39.2% and 55.1%, respectively. This study showed that patients achieving clinical complete responses had longer OS (p=0.038) and the trend is towards longer DFS in patients achieving pCR with NART.[17] Elie Calitchi *et al* published results of 74 patients with LABC submitted to NART, with 45 Gy in 25 fr over 5 weeks to the breast and regional lymph nodes, tumourectomy and adjuvant RT boost to the tumour bed with 20 Gy by interstitial brachytherapy. pCR in the breast was observed in 11% of the patients. Relapses were confirmed in 47%, 77% of these being distant metastasis. The 5-year DFS and OS were superior to 70%.[18] In our study, systemic therapy was prescribed to 82% of the patients and the ones without favourable conditions were treated with RT alone. It should be noted that 57% were refractory to NACT, being ineligible for surgical treatment before RT. All of these patients were able to undergo surgical procedures after NART. Contrary to the evidence regarding NACT,[14] the pR achieved was cross-sectional to all grades of differentiation, intrinsic subtypes, stages and treatments performed without statistically significant differences. Breast pCR was observed in 18% of the patients and 59% had more than 90% of tumour regression. Total pCR, in breast and

lymph node, was confirmed in 15% of the patients. With a median follow-up of 20.8 months, 3-year and 5-year PFS was 66% and 61%, respectively.

Intrinsic subtypes showed significant differences with evidence of an inferior PFS in basal-like and luminal B like HER2+ subtypes. Regardless of the adjuvant systemic therapy, none of these patients had a favourable clinical response to the NA systemic therapy, performed in 68% and 67%, respectively and only 8 of 18 HER2+ tumours received target therapy. Patients with >90% of pR tend to have better PFS (p=0.059).

The 3 years and 5years OS was 68% and 54%, with evidence of significant differences between intrinsic subtypes (p=0.000) and pR (p=0.004).

Interesting studies have been published with promising results about concomitant CT and RT NA. With different toxicity profile, given the chosen regimens, these studies show a satisfactory tolerance with breast pCR of 29.1%–42.1%, 5-year DFS of 60.6%–81% and 5-year OS of 71.6%–84.2% with concomitant treatment.[19–22]

With this study we cannot affirm that NART is as relevant as NACT in the treatment of LABC, but we can consider RT as valid therapy in this context, with a favourable impact on locoregional control, PFS and OS. Given the limitation of options after insufficient response to systemic therapy, RT may contribute without being selective. Prospective studies should be developed to evaluate tumours and patient characteristics in order to identify predictive response factors and promote accuracy in patient selection.

Future directions will explore the role of RT promoting conservative surgery, immediate reconstructive surgery and its potential with definitive intent in disease with good response to systemic therapy and dismissal of surgery.

This is a retrospective cohort of a small number of patients in a single institution. No severe toxicities and interruptions in the treatment occurred. Despite similar results in other studies, a longer follow-up of this cohort could allow for the consolidation of the impact of NART in inoperable LABC.

CONCLUSION

The present study confirms that NART is an effective downsizing treatment in inoperable LABC, allowing for a surgical resection regardless of the systemic treatment performed. Our findings also confirm that response to NART is independent of the intrinsic subtype. pR >90% is correlated with a better OS. These findings corroborate the literature, with the basal-like intrinsic subtype and luminal B HER2+ correlating with a worse prognosis. Prospective studies should be developed to evaluate predictive response factors and to promote accuracy in patient selection.

Acknowledgements Many thanks to Leonor Pinto, MD for her helpful first-hand insight for the planning of the study, to André Rui Graça, PhD for his comments and suggestions and my colleagues at IPOCFG for their continued support and contribution.

Contributors Study design: CS. Data collection: CS, MC and AN. Statistical analysis: JB and CS. Drafting of the manuscript: CS. Critical revision of the manuscript for important intellectual content: CS, MC, AN, KP, MP, JB, MH, DR, RM, CM, GM, GS, PF, PA.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as supplementary information. This is an Open Access article distributed by Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivate works on different terms, provided the original work is properly cited and the use is non-commercial. ORCID 0000-0002-7235-6327.

ORCID iD

Cláudia Sousa http://orcid.org/0000-0002-7235-6327

REFERENCES

1 Clarke M, Collins R, Darby S, *et al*. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;366:2087–106.
2 Darby S, McGale P, Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378:1707–16.
3 McGale P, Taylor C, EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014;383:2127–35.
4 Mathew J, Asgeirsson KS, Cheung KL, *et al*. Neoadjuvant chemotherapy for locally advanced breast cancer: a review of the literature and future directions. *Eur J Surg Oncol* 2009;35:113–22.
5 Tryfonidis K, Senkus E, Cardoso MJ, *et al*. Management of locally advanced breast cancer-perspectives and future directions. *Nat Rev Clin Oncol* 2015;12:147–62.
6 Cardoso F, Senkus E, Costa A, *et al*. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. *Ann Oncol* 2018;29:1634–57.
7 Tanić M, Krivokuća A, Čavić M, *et al*. Molecular signature of response to preoperative radiotherapy in locally advanced breast cancer. *Radiat Oncol* 2018;13:1–10.
8 Souchon R, Dunst J, Hartmann KA. Radiotherapie im Konzept der primären („neoadjuvanten") systemischen Behandlung des Mammakarzinoms. *Strahlenther Onkol* 2006;182:202–9.
9 Liedtke C, Mazouni C, Hess KR, *et al*. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *J Clin Oncol* 2008;26:1275–81.
10 Chu AM, Cope O, Doucette J, *et al*. Non-Metastatic locally advanced cancer of the breast treated with radiation. *Int J Radiat Oncol Biol Phys* 1984;10:2299–304.
11 Montague ED, Eleanor D. Radiation management of advanced breast cancer. *Int J Radiat Oncol Biol Phys* 1978;4:305–7.
12 Untch M, Konecny GE, Paepke S, *et al*. Current and future role of neoadjuvant therapy for breast cancer. *Breast* 2014;23:526–37.
13 von Minckwitz G, Untch M, Blohmer J-U, *et al*. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol* 2012;30:1796–804.
14 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.

15 Symmans WF, Wei C, Gould R, *et al*. Long-Term prognostic risk after neoadjuvant chemotherapy associated with residual cancer burden and breast cancer subtype. *JCO* 2017;35:1049–60.
16 Mieog JSD, van der Hage JA, van de Velde CJH. Preoperative chemotherapy for women with operable breast cancer. *Cochrane Database Syst Rev* 2007:CD005002.
17 Mladenovic J, Susnjar S, Tanic M, *et al*. Tumor response and patient outcome after preoperative radiotherapy in locally advanced non-inflammatory breast cancer patients. *J Buon* 2017;22:325–33.
18 Calitchi E, Kirova YM, Otmezguine Y, *et al*. Long-Term results of neoadjuvant radiation therapy for breast cancer. *Int J Cancer* 2001;96:253–9.
19 Adams S, Chakravarthy AB, Donach M, *et al*. Preoperative concurrent paclitaxel-radiation in locally advanced breast cancer: pathologic response correlates with five-year overall survival. *Breast Cancer Res Treat* 2010;124:723–32.
20 Shanta V, Krishnamurthi S. Preoperative multimodal therapy for locally advanced non-inflammatory breast cancer. *Clin Oncol* 1991;3:137–40.
21 Semiglazov VF, Topuzov EE, Bavli JL, *et al*. Primary (neoadjuvant) chemotherapy and radiotherapy compared with primary radiotherapy alone in stage IIb-IIIa breast cancer. *Ann Oncol* 1994;5:591–5.
22 Alvarado-Miranda A, Arrieta O, Gamboa-Vignolle C, *et al*. Concurrent chemo-radiotherapy following neoadjuvant chemotherapy in locally advanced breast cancer. *Radiat Oncol* 2009;4:24.