Original Article

Eur J Breast Health 2020; 16(3): 213-218
DOI: 10.5152/ejbh.2020.5487

Evaluation of Pathologic Complete Response (pCR) to Neoadjuvant Chemotherapy in Iranian Breast Cancer Patients with Estrogen Receptor Positive and HER2 Negative and impact of predicting variables on pCR

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ABSTRACT

Objective: The pathologic complete response (pCR) in the breast and axillary lymph node after neoadjuvant chemotherapy (NAC) would improve outcomes and it is used as a surrogate marker for survival. Our objective was to evaluate the breast and nodal pCR in breast cancer patients with estrogen receptor-positive (ER) and HER2 negative subtypes. Meanwhile, we sought to examine the impact of predicting factors on the rate of pCR.

Materials and Methods: In this multicenter retrospective study, medical records data of 314 women with ER+/HER2- breast cancer subtype who received neoadjuvant chemotherapy was extracted from oncology centers' data between 2011 and 2018. Breast and axillary lymph node pCR were assessed. Meanwhile, receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value for proliferative index (Ki-67%) expression.

Results: Breast pCR was seen in 25.2% (n=79) of the 314 cancer patients and partial response was seen in 47.8% (n=150), too. Nodal pCR was reported in 30.9% (n=97) of the 249 node-positive patients. The overall pCR (both breast & node) was observed in 14.6 % (n=46) of the 272 patients in which the data of breast and nodal were available. We identified 22.5% as the best cut-off value for ki-67 expression in predicting complete response to NAC.

Conclusion: The pCR rate after NAC in ER+/HER2– subtypes of breast cancer is low. Therefore, the optimal therapy for these patients should be further investigated.

Keywords: Breast cancer, HER-2 protein, neoadjuvant therapy

Cite this articles as: Omranipour R, Jalili R, Yazdankhahkenary A, Assarian A, Mirzania M, Eslami B. Evaluation of Pathologic Complete Response (pCR) to Neoadjuvant Chemotherapy in Iranian Breast Cancer Patients with Estrogen Receptor Positive and HER2 Negative and impact of predicting variables on pCR. Eur J Breast Health 2020; 16(3): 213-218.

Introduction

Systemic therapy in a newly diagnosed patient with breast cancer is increasing as an integral part of the multi-disciplinary treatment considering primary tumor factors (1, 2). Neoadjuvant chemotherapy (NAC) as a valuable tool, can reduce the size of primary tumors and control loco-regional recurrence rates and eradicate the disease in the regional lymph nodes and convert node-positive disease to node-negative (3). Widespread uses of NAC will downstage the primary tumor in most women and increasing the feasibility of breast-conserving surgery (BCS) in previously mastectomy candidates and decreasing the extent of avoidance of axillary lymph node dissection (ALND) in nodal positive patients (4). In this regard, combination chemotherapy regimens are superior to single-agent chemotherapy (5) and regimens contain both anthracycline and taxane had the highest of complete response.

The pathologic complete response (pCR) in the breast and axillary lymph node after NAC would improve outcomes and it is used as a surrogate marker for survival for some groups (6, 7). Breast cancer subtypes are classified by molecular markers such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) and these subtypes are associated with different behavior and response to the chemotherapy (8, 9). Several studies have shown pCR rates with some variation up to 40% after NAC based on tumor biologic subtypes (7, 10-12). The pCR rate and a favorable outcome are highest for triple-negative (TN) tumors, followed by HER 2 positive tumors and least for hormone-positive (12).

Some limitations such as a non-standardized pCR definition, presence of non-invasive and invasive cancer, prognostic impact of breast cancer subtypes, and difference in NAC regimens have caused unexpected differences in reported pCR.

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Received: 20.01.2020
Accepted: 17.05.2020

Since the luminal subtypes of breast cancer (estrogen-receptor and/or progesterone-receptor positive and HER2 negative) were reported about 60% of cases in our country (13), the evaluation of the pathologic response to NAC in this group seems to be necessary.

The first goal of this study was to evaluate the breast and nodal pathologic response in breast cancer patients with ER positive and HER2 negative subtypes and the secondary objective was to examine the impact of predicting factors on the rate of pCR.

Materials and Methods

The present study was approved by the ethics committee of Tehran University of Medical Sciences and patients' consent was available in hospital medical file for research projects considering ethical issues.

This multicenter retrospective study was conducted in the oncology centers of Tehran capital city of Iran. Patients' information (age at the time of diagnosis, initial tumor size with ultrasonography before NAC, tumor type, stage, and nuclear grade, NAC regimen, Ki-67 proliferation marker, and type of surgery) was extracted from their medical records of patients between 2011 and 2018 by the main investigator. All patients with pathologically confirmed invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC) of the breast with stage I to III who received NAC were included in this study.

In order to decrease the false-negative rate of SLNB after NAC as a reliable technique to replace ALND, certain precautions have been applied as a standard protocol in all oncology centers. For all patients, dual tracer radio-labelled colloid and patent blue have been injected for SLN mapping and only patients with at least three reactive SLNs were considered as node negative. None of our patients had nodal localization with clips or tattooing at the time of needle biopsy.

Patients were eligible for inclusion if they were ER positive and HER2 negative based on their diagnostic core biopsy. Hormone positivity was defined as ≥ 1% of cells staining positive for ER or PR. HER2 receptor status was defined at immunohistochemistry (IHC) as negative with staining of 0 or 1+. HER2 amplification was assessed in equivocal (2+) by fluorescence in situ hybridization (FISH). Patients previously had an excisional biopsy for diagnosis or if they had any part of their surgery such as sentinel lymph node biopsy before NAC were excluded from the study. Ki-67 was calculated using scoring systems to estimate a proliferation index (PI); the number of positively stained tumor nuclei divided by the total number of nuclei in a specific region by pathologists. All tumors were unifocal and patients with multifocal and multicentric tumors were excluded from the study.

Key Points

- The rate of pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) in ER+/HER2- subtype of breast cancer is low.
- Younger age, progesterone receptor-negative, and increasing ki-67 (cutoff point: 22.5%) as predicting factors were associated with an increased rate of pCR after NAC.
- Further studies are needed to find the best treatment in ER+/HER2- subtype of breast cancer.

The majority of patients have received combination NAC with AC-T (Doxorubicin, Cyclophosphamide, and Taxane) regimen. After completion of NAC, all patients underwent breast and axillary surgery, and surgical specimens were evaluated by expert pathologists.

Overall pCR was defined as no evidence of residual invasive cancer both in breast and axilla according to the most widely used definition. We assessed pathologic response in the breast regardless of axillary response and in the axilla regardless of breast response, too. Partial response (PR) was considered if there was any response regardless of the amount of changes in breast or axilla. No response (NR) was recorded if there was not any changes and sign of regression in breast and axilla.

Statistical analyses

Statistical analyses were performed using IBM Statistical Package for the Social Sciences version 20.0 (IBM SPSS Corp.; Armonk, NY, USA). Continues variables were reported as mean ± standard deviation (SD) and categorical variables were identified as a number with percentages. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value for Ki-67 expression. The impact of factors such as age at the time of diagnosis (<50, ≥50 years), tumor size (<50, ≥50 mm), pathologic tumor (T) and nodal (N) score, nuclear grade, Ki-67 proliferation index (<22.5, ≥22.5), and progesterone receptor expression on pCR were determined using univariable analysis. Multivariate logistic regression analysis was performed using age category, stage T, ki-67% category, and PR expression based on the univariable analysis (p-value less than 0.05 entered to the model). Odds ratio (OR) and 95% confidence interval (CI) are presented. All tests were two-sided and a p-value less than 0.05 was considered statistically significant.

Results

A total of 314 patients with ER+/ HER2- receiving NAC were identified. The characteristics of study population are shown in Table 1. Median patients' age was 48 years old and median tumor size at baseline was 30 (7-88 mm) by ultrasonography. The majority of the cancers (97.1%) were ductal, and 9 (2.1%) were lobular.

The pathological response data are listed in Table 2. Breast pCR was seen in 25.2% (n=79) of the 314 cancer patients and partial response was seen in 47.8% (n=150), too. Nodal pCR was reported in 30.9% (n=97) of the 249 node-positive patients. Finally, the overall pCR (both breast & node) was observed in 14.6 % (n=46) of the 272 patients in which the data of breast and nodal were available. One hundred twenty-three (39.2%) patients were considered successfully treated with BCS after NAC. Our results showed NAC resulted in avoidance of ALND in 20.7% (n=65) of node-positive cases.

The area under the ROC curve (AUC) for ki-67 expression was 0.67 (p=0.001; 95% CI: 0.58- 0.75). We identified 22.5% as the best cut-off value for Ki-67 expression in predicting a complete response to NAC. This cut-off level was associated with an optimal sensitivity of 72% and specificity 59%.

Table 3 highlighted the association between predicting factors and overall pCR. The results show Ki-67 ≥22.5 and PR negative had more complete breast and nodal response. The adjusted OR of multivariate logistic regression analysis, illustrated a statistically significant positive association between younger age (<50 years), Ki-67 ≥22.5 and PR expression and overall pCR (Table 4).

Table 1. Characteristics of study population (n=314)

Characteristics	
Patient age, years	48.43±11.59*
<50	168 (53.5)
≥50	134 (42.7)
Missing data	12 (3.8)
Tumor type	
IDC	305 (97.1)
ILC	9 (2.9)
Clinical T at presentation	
T1	27 (8.6)
T2	160 (51)
T3	24 (7.6)
T4	54 (17.2)
Missing data	49 (15.6)
Nodal category at presentation	
N0	23 (7.3)
N1	161 (51.3)
N2	88 (28)
N3	0 (0)
Missing data	42 (13.4)
Tumor grade	
1	46 (14.6)
2	223 (71)
3	39 (12.4)
Missing data	6 (1.9)
Ki-67%	26.33±19.56*
Progesterone receptor	
Positive	288 (91.7)
Negative	26 (8.3)
Types of surgery	
BCS +SLNB	47 (15)
BCS +ALND	76 (24.2)
MST +SLNB	29 (9.2)
MST + ALND	162 (51.6)

*Mean±SD. Categorical variables were expressed as number with percentages in parenthesis. IDC: invasive-ductal carcinoma; ILC: invasive-lobular carcinoma; BCS: breast conserving surgery; SLND: sentinel lymph node dissection; ALND: axillary lymph node dissection; MST: mastectomy

Table 2. Pathologic response of breast and node

Pathologic Response	Number (%)
Breast (n=314)	
pCR	79 (25.2)
RR	150 (47.8)
NR	85 (27.1)
Nodal (n= 249)	
pCR	97 (30.9)
PR	35 (11.1)
NR	117 (37.3)
Overall breast & nodal	
pCR	46 (14.6)
PR	168 (53.5)
NR	58 (18.5)
Treated with BCS	123 (39.2)
Avoidance of ALND in node positive	65 (20.7)

pCR: Pathologic Complete Response; PR: partial response; NR: no response; BCS: Breast Conservative Surgery; ALND: Axillary Lymph Node Dissection

Discussion and Conclusion

In this multicenter retrospective study, data of 314 luminal breast cancer patients treated with neoadjuvant chemotherapy were evaluated for pathologic response rate. We found patients with ER positive and HER2 negative breast cancer had a 25.2% pCR rate in breast and 30.9% in axillary lymph nodes. The impact of NAC on pCR in both breast and axilla was 14.6%. Our results demonstrated that ALND can be avoided for 20.7% of patients with nodal metastases. The breast conservation rate of this study was 39.2%. Results of multivariate analysis showed that younger age, PR negative and increasing Ki-67 score were associated with an increased rate of pCR after NAC.

The pCR rate in both breast and axilla of the present study (14.6%) is higher than previously reported by the other studies. The pCR rate of the ACOSOG Z1071 multicenter clinical trial with 317 cases was 11.4% (3) and in I-SPY trial with 93 cases was 9% (14). Von Minckwitz et al. (10) study was reported the pCR rate of 8.9% in luminal A and 15.4% in luminal B/HER2- disease in the German population (n=1994 for these two categories). A pCR rate of 9% has been reported by Caudle and their colleagues from MD Anderson Cancer Center, in 309 patients with HR+ /HER2- subtype (15). However, some studies manifested the lower pCR rate in both breast and axilla as about 5% in Petruolo et al. study and 4.3% in Lips et al. study (16, 17). Petruolo study also showed the overall pCR is more common in ductal than lobular carcinoma (6% vs 1%) and lobular ones were less likely downstage than those with ductal carcinoma (16). Lips et al. have shown that lobular histology was not associated with chemotherapy response when the analysis is restricted to HR+/HER2- tumors, too (17). Despite our small sample size of lobular carcinoma (n=9), our result confirmed by their findings and only one of the lobular patients responded completely to NAC.

A large scale study that analyzed pooled data of 12 international trials with 11,955 patients reported the low pCR rate (7.5%) in HR+ / HER2 - (grade 1,2), 16.2% in HR+/ HER2- (grade 3) compared with another subtypes. They reported the association between pCR and the long-term outcome was weakest for this subtype of breast cancer (6). Our results showed the pCR in grades 1 and 2, and 3 were 16.3% (38/233), and 17.6% (6/34), respectively and the pCR differ-

Table 3. Predictive factors associated with pathologic complete response (pCR)

Variable	pCR	Partial response & No response	p
Age			0.001
<50	34 (80.95)	115 (52.5)	
≥50	8 (19.05)	104 (47.5)	
Tumor Type			0.64
IDC	45 (97.8)	218 (96.5)	
ILC	1 (2.2)	8 (3.5)	
Grade			0.84
1 & 2	38 (86.4)	195 (87.4)	
3	6 (13.6)	28 (12.6)	
Stage T			0.07
1 & 2	37 (82.2)	149 (68.7)	
3 & 4	8 (17.8)	68 (31.3)	
N Score			0.76
0 & 1	32 (69.6)	152 (67.3)	
2	14 (30.4)	74 (32.7)	
Ki-67%			0.006
<22.5	11(30.6)	111 (59)	
≥22.5	25 (69.4)	77 (41)	
PR			0.002
Positive	36 (78.3)	212 (93.8)	
Negative	10 (21.7)	14 (6.2)	
Tumor size (mm)			0.25
<50	36 (78.3)	158 (69.9)	
≥50	10 (21.7)	68 (30.1)	

pCR: Pathologic Complete Response; PR: Progesterone Receptor; IDC: invasive-ductal carcinoma; ILC: invasive-lobular carcinoma

Table 4. Logistic Regression analysis for factors associated with pCR

Variables	Adjusted OR	95%CI	p
Age category (<50 / ≥50)	3.07	1.17-8.08	0.02
Ki-67% (≥22.5 / <22.5)	2.66	1.15-6.16	0.02
PR (Negative/Positive)	3.52	1.24-9.94	0.02

PR: progesterone receptor; OR: odds ratio; CI: confidence interval. Considering univariable analysis age category, stage T, ki-67% category, and PR expression were entered to the model.

ences between grades were not statistically significant. Boughey et al. study revealed the overall pCR was significantly higher in patients with triple-negative (38.2%) and HER2 positive (45.4%) disease than in those with HR+/HER2- (11.4%) (3).

Based on this knowledge and low pathologic response rate in ER+/HER2- breast cancer patients, it should be investigated whether the initial treatment approach would be NAC or surgery.

On the other hand, achieving a pCR is not the only aim of treatment with NAC and some evidence showed the pCR is not valid as a surrogate endpoint for improved event-free survival (EFS) and overall survival (OS) (6). So other benefits such as increasing the eligibility for BCS and decreasing the rate of ALND should be considered. In the present investigation, 38.5% of the patients have treated with BCS. Our result was consistent with another study in this subtype of breast cancer, which reported about 38% of patients could have BCS regardless of patient preference (16). It should be mentioned; in the present investigation, we don't know how many patients selected mastectomy without considering physician's recommendation for BCS.

Many studies have found that tumors with more proliferating activity, benefit more from chemotherapy and Ki-67% can be used as a predictor factor for a higher rate of pCR (18). Hormone positive receptor breast cancer subtypes often have low Ki-67 expression, resulting in lower response to chemotherapy (19, 20). In accordance with the other studies (21, 22), our study confirmed the Ki-67 proliferation index is a predictor of pCR to NAC in ER+/HER2- patients. Therefore, Ki-67 score should be considered as a biomarker for predicting pCR after NAC. In order to assess the potential value of Ki-67 in predicting response to NAC in breast cancer patients and suggest a cut-off value, several studies have recommended different values from 12% to 25% (23-26). Some of them adopted cutoff value without any valid explanation or based on the median value. Our result was near to another study with Kim and colleagues that suggested a 25% level of Ki-67 is a reasonable value for predicting response to chemotherapy. We found 22.5% of Ki-67 expression as a cutoff value; can predict the pCR in HR+/HER2- breast cancer patients.

As well as, the impact of PR expression on the response of NAC was seen in our analysis which was consistent with other studies that reported significantly higher pCR in PR negative than PR positive (16, 17). Of course, the number of patients with progesterone receptor negative in our study is very low (n=26) and a wide confidence interval indicates that further studies with more sample size in this category are needed.

This study was the first evaluation of this context in Iranian women with breast cancer and it was our advantage. The other advantage was the high sample size. This study had some limitations. Since the study was extracted the data from medical records, missing data of some variables were high and as a major limitation, it may cause inaccurate results. The second limitation was due to the incomplete record of NAC regimen. Therefore, the evaluation of the effect of different regimens on pCR was not possible. Since our study was a retrospective study, we couldn't calculate the down-staging rate to BCS and it was third limitation of our study. One hundred forty- two patients with locally advance disease (T4 and N2) received NAC without considering the breast conserve is possible or not. The rest of patients were treated by NAC to decrease the tumor size. As we mentioned before, we don't know who were candidate for mastectomy before NAC and down staged to BCS after NAC and how many patients selected mastectomy without considering physician's recommendation for BCS due to fear of disease recurrence, and also we don't know how many patients were eligible for breast conserving at the time of diagnosis but they received NAC in order to achieve better cosmetic. Therefore, the frequency of patients who treated with BCS after NAC was reported.

In conclusion, considering the results of the present study and other investigations, the pathologic complete response rate after NAC in ER+/HER2- subtypes of breast cancer is low. Therefore, the optimal therapy for these patients should be further investigated. Meanwhile, Ki67 expression with cutoff point 22.5% could predict the pCR after NAC in ER+/HER2- as a biomarker. Although the decision to refrain from NAC in ER+/HER2– breast tumors should not be based on only one predictive marker, other variables such as age and progesterone receptor expression should be considered carefully.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1397.609).

Informed Consent: The institutional review board of has approved this study and patients' consent was available in hospital medical file for research projects considering ethical issues.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - R.O., R.J.; Design - R.O., R.J., B.E.; Supervision - R.O., B.E.; Resources - R.O., A.Y., A.A., M.M.; Data Collection and/or Processing - R.J., A.Y., A.A., M.M.; Analysis and/or Interpretation - B.E.; Literature Search - R.O., B.E.; Writing Manuscript - R.O., B.E.; Critical Review - R.J., A.Y., A.A., M.M.

Acknowledgements: The authors would like to thank Dr. Azadeh Joolaii, Dr. Parisa Azimnejadian, Dr. Farhad Shahi, and Dr. Feresteh Ensani for their assistance.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: This study (no # 38580) was financially supported by the Vice-Chancellor of Research affairs, Tehran University of Medical Sciences.

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