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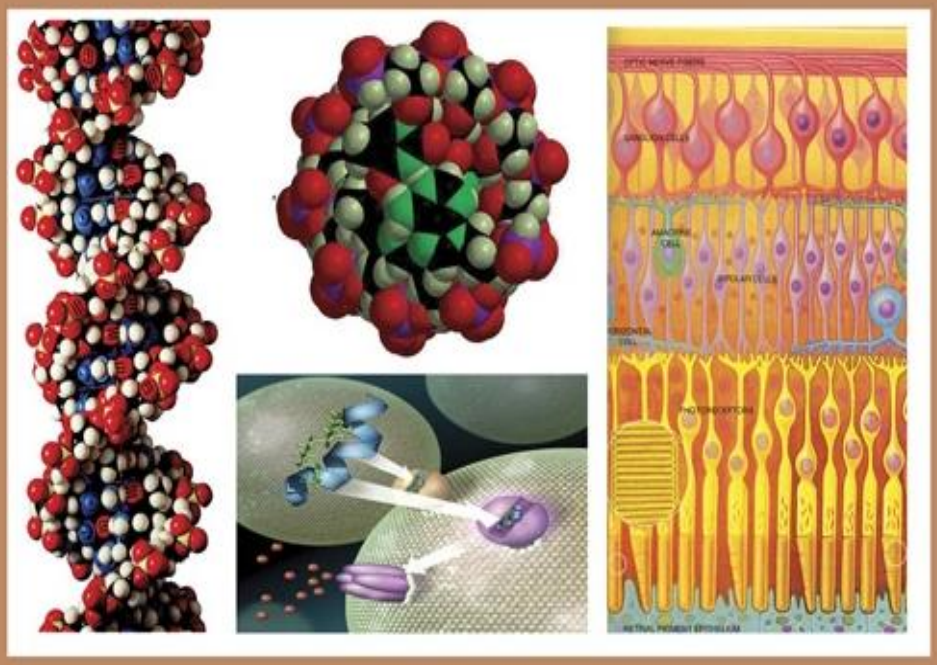

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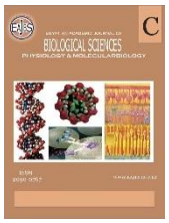

High and Low ki67 Expressions in Locally Advanced Breast Cancer after Neoadjuvant Chemotherapy Among Women in North-western Algeria

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ABSTRACT

Women with locally advanced breast cancer who have achieved a pathological complete response (pCR) after neoadjuvant chemotherapy (NCT) have significantly better survival than those not obtaining a pCR. Identifying certain prognostic factors for patients who had not reached pCR is important because fractions of this population might benefit from other new adjuvant treatments. High Ki67 expression, a nuclear marker of breast carcinoma cell proliferation, in remnant disease after NCT has been described as a poor prognostic factor.

This study aimed to assess post-neoadjuvant chemotherapy Ki67 index expression and estrogen receptor (ER) status on residual tumour; moreover, we attempted to elucidate the possible correlations between disease-free-survival (DFS) and overall survival (OS) as a function of these two parameters in a retrospective group of 184 women with locally advanced breast cancer stage IIB-IIIC, treated with NCT who had not obtained pCR and underwent surgery. We also analyzed the relationship between the expression levels of Ki67 (≥15%, <15%) and the clinical response, the histological types, the histopathological grades of the tumours as well as the lymph node involvement status in these patients from Hospital University Cancer Centre of Sidi-Bel-Abbes (west of Algeria). The median patients' age was 47years (27-81). Post-chemotherapy Ki67 index expression correlated directly with clinical response. The mean Ki67 expression value after NCT was significantly higher in patients with negative clinical responses than in those who developed objective responses (p=0.013). Univariate analysis of post-chemotherapy Ki67 expression levels as function of pathological tumour characteristics showed a significant difference for histopathological type (p = 0.025) and lymph node involvement status (p = 0.04). Patients' median follow-up was 23.5 months. Positive post-chemotherapy ER was associated with significantly higher 5-year DFS (p=0.006). Survival analysis conducted as function of Ki67 thresholds, confirmed a significantly shorter DFS and OS in patients with Ki67 expression ≥15%, following NCT compared with patients with low (<15%) Ki67 expression (p = 0.033 and p = 0.002, respectively). Based on patients' outcomes, the OS and DFS rates were improved in patients with lower Ki67 levels. The 5-year DFS was significantly worse in tumour with negative post-treatment estrogen receptors. A prognostic model could be formulated based on both the Ki67 index and ER expression parameters after NCT; it may improve the prediction of patient outcomes.

INTRODUCTION

In Algeria, due to a lack of awareness among women about breast cancer, cases are lately diagnosed and for the most part, treated immediately by radical surgery followed by adjuvant systemic treatments such as chemotherapy. Therefore, the costs and high morbidity risks associated with treatments for locally advanced breast cancers are an important public health problem (National Committee responsible for monitoring the fight against cancer in Algeria, National Cancer Plan 2015-2019).

Neoadjuvant chemotherapy (NCT) has been used to increase eligibility for breast-conserving surgery it was also used to assess biological markers that can predict response to subsequent treatment and clinical outcomes (Russo J. *et al.,* 2006; Jones R.L. *et al.,* 2010; Kaufmann M. *et al.,* 2007; Tanei T. *et al.,* 2011). Women who have achieved a pathological complete response (pCR) after NCT have significantly better survival than those without pCR (Colleoni M *et al.,* 2009; Guarneri V, 2006).

Among these markers, we will mention the proliferation factor Ki67 which is an intranuclear protein, expressed throughout the cell cycle, from the G1 phase to the M phase. The detection by immuno-histochemistry of infiltrating carcinoma cells expressing a high proliferation index Ki67 in breast tumour, is closely associated with the clinical outcomes of patients who did not have a pathological complete response (Jones R.L. *et al.,* 2010). Contrary to this, a low Ki67 index is observed in patients with a more favourable prognosis. Estrogen receptor (ER) status is considered a prognostic factor in breast cancer. Although negative tumours estrogen receptors are much more sensitive to chemotherapy, the prognosis for this group of patients is poor (Colleoni M. *et al.,* 2000).

Studies on the response to neoadjuvant chemotherapy in breast cancer have been conducted in populations of Western women with tumours with a high and low level of Ki67 expression according to prognostic factors and clinical response. (Kaufmann M. *et al.,* 2007; Dowsett M. *et al.,* 2005; Lee J. *et al.,* 2008). In addition, other studies had shown that patients with a Ki67> 14% in tumour cells have a higher risk of local recurrence or metastasis (Mohammed AA, 2019; Mahdi AS *et al.,* 2018). However, its significance in terms of survival in remaining tumour cells after neoadjuvant chemotherapy (NCT) has rarely been examined in Algeria.

This study aimed to assess the predictive value of Ki67 expression and ER status post-chemotherapy; moreover, we attempted to elucidate the possible correlations between disease-free survival and overall survival as a function of these two parameters in a retrospective group of 184 patients who had not reached pCR. We also analyzed the relationship between the expression levels of Ki67 and the clinical response, the histological types, the histopathological grades of the tumours as well as the lymph node invasion status in these patients from western Algeria.

MATERIALS AND METHODS

Patients And Treatments:

Patients (n = 184) were registered between January 2012 and June 2018 in a clinical database, collected from the Hospital University Cancer Centre of Sidi-Bel-Abbes (west of Algeria). All women with locally advanced breast cancer stage IIB-IIIC, following the recommendations of the International Union against Cancer (UICC) (Sobin and Wittekind, 1997) and who failed to achieve pCR, were enrolled in the study.

The patients received a median of 6 cycles (3-9) at 21-day intervals based on:

• Anthracyclin-basedregimens (51 patients, 60.7%): FEC 100 protocol (fluorouracil [5-FU] 500 mg/m2 Day 1, Farmorubicin [Epirubicin] 100 mg/m2 Day 1 and Endoxan [cyclophosphamide] 500 mg/m2 Day 1);

• Anthracyclin and taxane association (33 patients, 39.3%): TAC protocol (docetaxel [Taxotere] 75 mg/m2 Day 1, doxorubicin [Adriamycin] 50 mg/m2 Day 1 and cyclophosphamide 500 mg/m2 Day 1).

Our database included clinical

(examination of the breast and lymph node areas), radiological (mammography and bilateral breast ultrasound) and histological examinations by cutaneous micro biopsy of the primary tumour. Patients were operated on after 6 cycles of treatment. Adjuvant systemic treatment was administered to patients according to histopronostic factors and indicators of endocrine responsiveness of the tumour. An adjuvant endocrine therapy based on tamoxifen or aromatase inhibitor was administered to postmenopausal patients for 5 years. In premenopausal women, endocrine therapy was based on tamoxifen for 24 months, followed by 36 months of the aromatase inhibitor. Patients overexpressing Her-2 received trastuzumab as adjuvant therapy for a total of 12 months of treatment. Radiation was administered for cases of patients with positive nodes. Clinical responses were evaluated according to RECIST v1.1 Criteria (Therasse P. *et al.,* 2000). We stratified it into clinical negative response (NR) group and clinical objective response (OR) group.

Patient follow-up included clinical examination, complete blood chemistry and Ca15–3 markers every 3–6 months for up to 5 years; mammography was carried out every 12 months, chest radiogram and liver ultrasound were carried out every 6 months during 5 years and bone scintigraphy was performed one year after the reference examination or in the presence of clinical symptoms. Data were collected retrospectively and analyzed anonymously.

Breast Tumour Tissues*:*

According to various studies (Tacca *et al.,* 2007; Kasami *et al.,* 2008; Petrarca *et al.,* 2011; Spanheimer *et al.,* 2013; Miglietta *et al,* 2013), neoadjuvant chemotherapy may induce some changes in the histopathological and clinical characteristics of the tumour. Therefore, tumour tissues were evaluated after surgery. pCR was defined as the absence of invasive tumour cells in the breast and in axillary lymph nodes. The following biological markers were evaluated on operating parts after surgery: histological type, tumour SBR grade, node involvement status, Ki67 proliferation index and ER (estrogen receptor) status.

Breast tumour tissues were divided into Ki67 high and Ki67 low levels of proliferation tumours using a median cut-off value of ≥15% of the positive staining cells. This cut was chosen because it is located range reported in published studies (de Azambuja E et al., 2007). The histological grade for the tumour was done according to the modified Scarff-Bloom-Richardson Scoring System (Bahaddin M.M., 2020).

ER was defined as positive for ≥10% tumour cells with nuclear staining. To measure estrogen receptor (ER), the Roche Diagnostics antibodies ER 790-2223 prediluted (~ 1µg/mL) (Roche Diagnostics Gmbh, standhoderstrasse 116, D-68305, Mannheim, Germany) was used for the detection of hormonal receptor status, using a VentanaNeXes automat (Ventana medicals systems, Inc. 1910E. Innovation Park Drive Tucson, Arizona 85755, USA). The revelation was performed with the New DAB 760-091 detection kit from Ventana Medicals Systems. The monoclonal antibody (mAb) K2 was used for the Ki67 antigen (Ventana). The proliferation index evaluated by the Ki67 was studied on the blocks with the largest tumour area and not exclusively on the most prolific areas. He was appreciated "Visually" by the percentage of nuclei marque's (Frierson *et al.,* 1995).

Statistical Analysis:

Ki67 staining was analysed both as a continuous variable and after categorisation into 2 groups (≥15%, <15%). Pearson's Chi-square test and Student's t-test were preliminarily performed to compare categorical and continuous variables, respectively, and to evaluate potential differences in the distribution of the clinicopathological parameters among groups.

The OS was determined as the time from the date of diagnosis until the date of death (from any cause) or the date of the latest news. The DFS was calculated as the time between the date of diagnosis and the

date of first relapse (local, contralateral and distant event).

The OS and DFS curves were estimated using the Kaplan-Meier method (Kaplan E.L., Meier P., 1958). The survival analysis was conducted for 5 years. Statistical significance of associations between individual variables and DFS and OS was calculated by the log-rank test in univariate comparison for survival (Buchholz TA et al., 2003). Data are expressed as 95% confidence intervals (CI). A p-value of < 0.05 was considered significant for all analysis. All data analysis were performed on the IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

RESULTS

Patient characteristics are detailed in table 1. Among the 184 patients with locally advanced breast cancer, 105 of them have a Ki67 index> = 15% and 79 have a Ki67 index <15%. The median Ki67 index was 15% (range 1–90).

The median follow-up among all patients was 23.5 months (range 1 - 144).

Table 1: Patients, clinical and histopathological characteristics

Evaluable patients	184
Median Ki67, % (range)	15 (1–90)
Median age at diagnosis, years (range)	47 (27–81)
Menopausal status	
Premenopausal	99
Postmenopausal	85
Clinical stage	
IIB	30
IIIA	34
IIIB	116
IIIC	4
Histological type	
Ductal	151
Lobulal	33
ER status	
Negative	74
Positive	110
Tumour SBR grade	
I-II	113
III	71
Neoadjuvant chemotherapy	
Anthracycline based	15
Taxane + anthracycline	168
taxane	1
Surgery	
Mastectomy	134
Lumpectomy/quadrantectomy	50
Lymph node status at the surgery	
Positive	102
Negative	82

ER: estrogen receptors

Tumour Ki67 Expression and Clinical Response:

The comparative analysis of the clinical response after CTN treatment as a function of Ki67 rate shows that tumours that responded negatively (NR) to CTN treatment compared to those with clinical objective response (OR), express a higher median Ki67 (22% vs 15%). The minimum and maximum Ki67 ends in tumours that responded

negatively were higher than the Ki67 ends of tumours that have clinically responded positively (Fig1).

The comparative values of Ki67 expression in patients with clinical negative response and those with clinical objective response demonstrate a statistically significant distribution (p = 0.013).

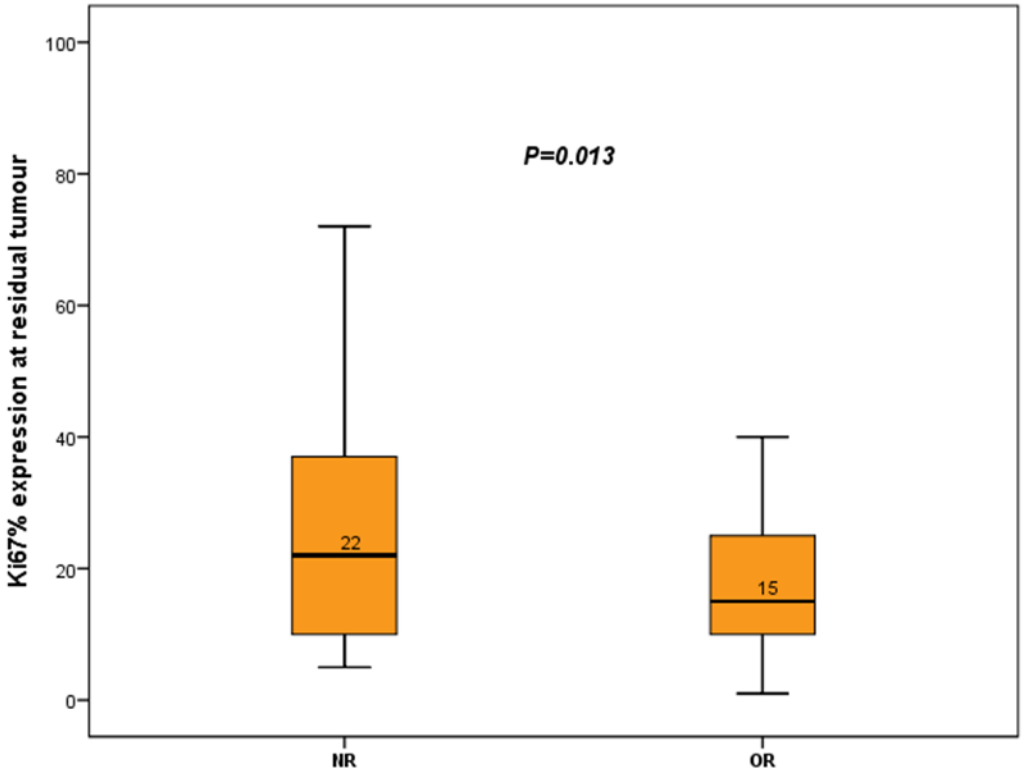

Fig. 1: Box and whisker plots of the distribution of Ki67% expression at the residual tumour, according to the clinical response obtained after neoadjuvant chemotherapy. NR: negative response/progression; OR: objective response.

Ki67 Expression Levels as A Function of Age and Pathological Tumour Characteristics*:*

The mean age compared between the group of patients with a low level of Ki67 expression (Ki67 <15%) and those in the group with a high level of Ki67 expression (Ki67> = 15%) was without a statistical difference (48.84 years ± 1.19 vs 48.15 years ± 1.16, p= 0.687). In comparison between the expression levels of ki67 and the histopathological types of the tumours, those with a ki67 index less than 15% tend to have a histopathological specific-type (13.3% vs. 5.7%), while tumours with a high level of Ki67 expression have an infiltrating ductal carcinomas type (88.6% vs 73.4%).

We found no significant difference between the Ki67 expression groups as a function of SBR tumour grade (I, II and III). However, the comparison of the two groups of Ki67 expression levels shows that tumours with a ki67> = 15% tend to have a high rate of SBR III grade (41% vs 34.4%) and a low rate of SBR I grade (4.8% vs 8.9%).

The status of pathological lymph node involvement was significantly different when compared to the two Ki67 expression groups (p = 0.04). There was a high rate of tumours with a positive node involvement status (pN +) having a ki67> = 15% (61.9% vs 46.8%), while a high rate of tumours that presented a negative node involvement status (pN-) had a ki67 <15% (53.2 vs 38.1%) (Table 2).

Table 2: Correlation between age and pathological tumour characteristics according to Ki67 expression levels

Variables	**Ki67<15% (n=79)**	**Ki67 >=15% (n=105)**	***P* value**
Age (mean ±SD)	48,84 ± 1,19	48,15 ± 1,16	0,687
Tumour histopathology Specific-Type CCI	 21 (13,3%) 58 (73,4%)	 12 (5,7%) 93 (88,6%)	0,025
SBR tumour grade I II III	 7 (8,9%) 44 (55,7%) 28 (34,4%)	 5 (4,8%) 57 (54,3%) 43 (41%)	0,465
Lymph node involvement **p**N - **p**N+	 42 (53,2%) 37 (46,8%)	 40 (38,1%) 65 (61,9%)	0,042

SD: Standard deviation; pN: pathological lymph node

Survival Analysis According to The Status of Post-Treatment Ki67 Index and Estrogen Receptor Expression:

The 5-year overall survival (OS) rate of all patients was 87.5%; 23 patients died; however, the median survival time has not yet been reached. For disease-free survival (DFS), it was 68%, 59 patients had a relapse and the median DFS time was of 52 months (95%CI, 32.327-71.673).

The expression levels of Ki67 had a significant effect on disease-free survival (p = 0.033) with a 5-year DFS rate of 73.4% in patients with a Ki67 <15% versus 63.8% in Ki67> = 15% group. This last, had a median DFS of 51 months [95% CI; 34.099 - 67.901] (Fig. 2a).

Patients with higher Ki67 (>=15%) following neoadjuvant chemotherapy experienced a significantly shorter 5-year OS rate compared with those with low Ki67 (<15%), indeed, 5-year OS was 81% versus 96% (p = 0.002), respectively (Fig. 2b). The survival curves were above-median.

Another factor with a significant inverse relationship with DFS was the post-treatment ER status: breast tumours that were ER-negative versus the ER-positive group showed 58 versus 74.5% of DFS (p=0.006), respectively (Fig.3). We did not find a significant association of estrogen receptors with overall survival (OS). However, patients with negative ER had a median overall survival of 30 months (95% CI: [7.494 - 52.506].

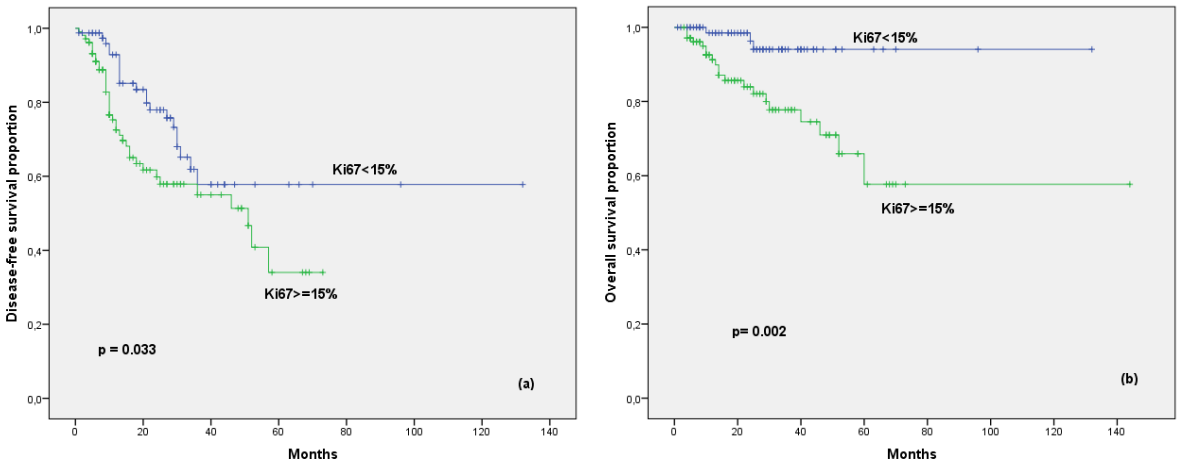

Fig. 2: Kaplan-Meier curve displaying DFS (a) and OS (b) by Ki67 expression levels assessed after NCT

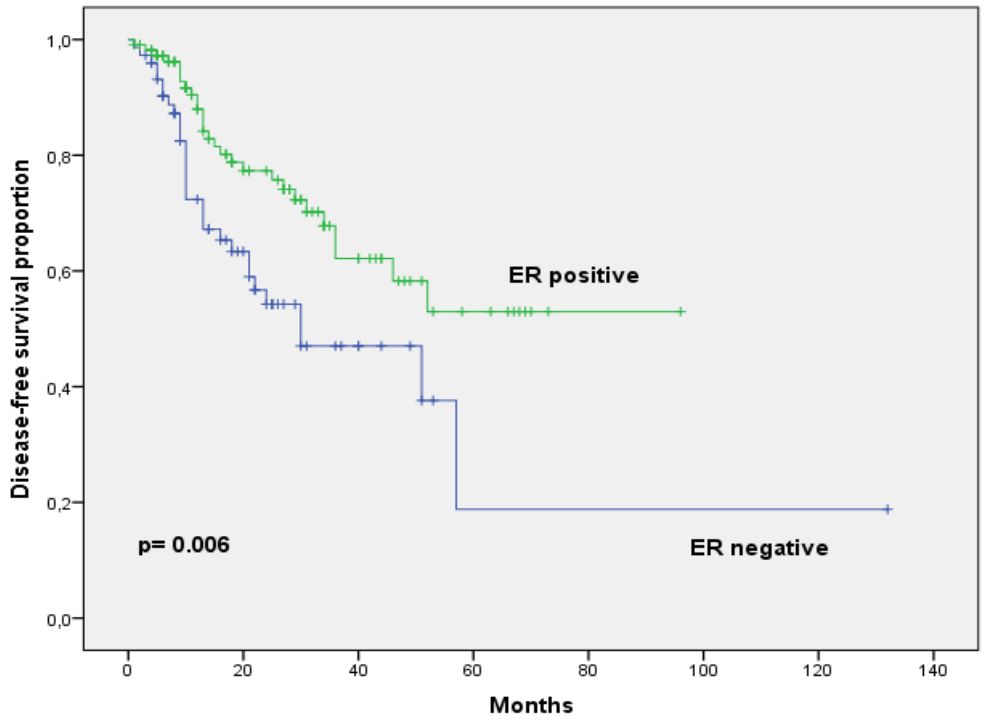

Fig. 3: Disease-free survival by ER expression after neoadjuvant chemotherapy. ER: estrogen receptors.

DISCUSSION

The prognostic factors studied and validated in locally advanced breast cancer are very numerous. Only those that have undergone prospective validation and relevant statistical analysis can be taken into consideration. The identification of prognostic factors would make it possible to characterize patients with worse or better survival and to evaluate their responses to treatment. (Amat S. *et al.*, 2005; Petrarca C.R. *et al.*, 2011; Guarneri V. *et al.*, 2006).

Breast cancers expressing high levels of Ki67, a marker of cell proliferation, are associated with poor results. Indeed, according to 2 meta-analyses, there is a significant association between elevated Ki67 expression and an increased risk of breast cancer relapse and death. (De Azambuja E. *et al.*, 2007; Stuart-Harris R. *et al.*, 2008). According to multivariate analysis in a series of 48 patients with locally advanced breast

cancer treated in a phase II trial, post-therapy, Ki67 is the only significant independent factor associated with OS (Lee J. *et al.,* 2008; Guarneri V. *et al.,* 2009; Jones RL *et al.,* 2009).

We selected a cut-off value of Ki67 ≥ 15% to identify breast cancers with high proliferative kinetic expression. Therein, the Ki67 threshold has been a subject of controversy because some studies have used 10 or 20% cut-off points (Viale G. *et al.,* 2008).

The association between Ki67 and the response to chemotherapy is well studied. Administration of chemotherapy in the neoadjuvant setting achieves a clinical response in 60 to 90% of patients (Kaufmann M. *et al.,* 2007; Penault-Llorca F. *et al.,* 2003). In our study, the correlation of post-chemotherapy Ki67 tumour expression with the clinical response was statistically significant (*p*=0.013). It was a predictive factor of clinical response. We used box plots to compare the rate of post-chemotherapy Ki67 tumour expression between the different clinical response groups. The minimum and the maximum value of Ki67 rate were represented. They were higher in the clinical negative response group compared with the clinical objective response group. The lower median rate of Ki67 was for the clinical objective response group, and the highest median Ki67 rate was for the negative one (15 vs 22, respectively). Our results agree with those of Bottini *et al.* (2001) in which Ki67 expression significantly decreased after chemotherapy; the reduction correlated with tumour response in both univariate (P < 0.005) and multivariate analysis (P = 0.02) (Bottini A. *et al.,* 2001). Unlike our results, many authors agree that Ki67 tumour expression predicts a better response to chemotherapy, with higher Ki67 scores being associated with a better response to chemotherapy (Bahaddin, M.M. 2020), (Chang J. *et al.,* 2000), (Archer C.D. *et al.,* 2003).

The comparative aspect between patients with low (ki67 < 15%) and high (ki67 >= 15%) ki67 expression thresholds according to the histopathological characteristics of the tumour in post-chemotherapy was carried out.

Age was without significant difference according to Ki67 thresholds, as well as tumour SBR grade this agrees with the results of Tanei (2011) and Elzawahry (2013) (Tanei T. *et al.,* 2011 ; Elzawahry H M, *et al.,* 2013). We note that histological grade is widely used as a prognostic factor of survival. The Scarff-Bloom-Richardson (SBR) classification thus makes it possible to isolate a group of patients with a high grade who present an increased relative risk of relapse for the SBR III group (Rosen P.P. *et al.,* 1993). The Ki67 is most often correlated with the SBR tumour grade (Qin Liang *et al.,* 2020; Bahaddin M. M., 2020), however, it must be admitted that in a small specimen of tumours there is a discrepancy between these different factors, in particular for certain histological tumours SBR grade II and a Ki67 index greater than 20%. (Le Doussal V. *et al.,* 1989).

Analysis of the histopathological characteristics of the tumour, namely histopathological type and lymph node infiltration were significantly associated with tumour Ki67 levels. Indeed, Ki67 proliferation index was significantly higher in patients with histological infiltrating ductal carcinomas while patients with histological specific type expressed low ki67 (p=0.02). These results agree with those of Carbognin *et al.* (2016) and those of Bustreo *et al.* (2016) which investigated 1688 female patients with primary breast cancers.

Ki67-high tumours were significantly associated with lymph node positivity. The lymph node involvement status (pN+ or pN-) was significantly different when compared between the two Ki67 expression levels (p = 0.04). A high percentage of patients with N+ status had ki67 >=15%, while patients with N- nodal status had ki67 <15%. Lymph node involvement is the most important prognostic factor. Our results were in agreement with those of Inwald *et al.* (2013), who reported in a large cohort that Ki67 level is an important

prognostic factor for breast cancer (Inwald *et al.,* 2013). Its high level was significantly associated with lymph node positivity (Kilickap *et al.,* 2014). Moreover, combining Ki67 with a number of metastatic lymph nodes was highly predictive of Disease-specific survival and Disease-free interval, at both uni- and multivariate analyses (Bustreo S. *et al.,* 2016).

In univariate survival analysis, positive post-treatment ER status was associated with significantly higher 5-year DFS compared to negative ER status of breast tumours (p=0.006). This result is consistent with several studies that present ER status as the only independent predictor of DFS in Multivariate Analysis (Penault-Llorca F. *et al.,* 2003; Daidone M.G. *et al.,* 1999; Jeruss J.S. *et al.,* 2008). The assessment of estrogen receptors of 1198 patients with breast cancer in a current study made by Cocciolone *et al.* (2017) has shown the Impact of positive estrogen receptors on DFS and OS in 20 years follow-up (Cocciolone *et al.,* 2017).

The results of our retrospective study confirm a longer DFS and OS in patients who present proliferation of the Ki67 index <15% after neoadjuvant chemotherapy.

A threshold of Ki67 index of more than 10–14% is often considered a factor of poor prognosis (Yerushalmi R. *et al.,* 2010). Our analysis of survival as a function of Ki67 expression levels had shown the prognostic role of ki67 in survival, where a strong significant difference was revealed between the expression thresholds of ki67 (Ki67<15% vs Ki67>=15 %) in overall survival (p=0.002) and for disease-free survival (p=0.03). the overall survival and disease-free survival rates were improved in patients with lower Ki67 levels, this parameter is a prognostic factor predicting disease-free and overall survival in breast cancer patients (Kilickap *et al.,* 2014; Guarneri V. *et al.,* 2009). Our results are confirmed by a large meta-analysis carried out on 12155 patients, showing a significant association between the expression of ki67 and overall and recurrence-free survival (de Azambuja E. *et al.,* 2007). Furthermore, and according to results of a large population-based cohort of a cancer registry, Inwald E.C. *et al.* (2013), covered 4692 patients in which, they confirmed a statistically significant correlation between the rate of Ki67 positive cells and overall and recurrence-free survival in uni and multivariate analysis. On the other hand, other authors have not found an independent relationship between post-neoadjuvant chemotherapy Ki67 and survival (Colleoni M. *et al.,* 2004; Schneeweiss A. *et al.,* 2004).

CONCLUSION

Our outcomes suggested a significant association between the high Ki67 tumour proliferation index and other prognostic factors including clinical negative response, infiltrating ductal carcinomas, and positive lymph node involvement in local breast cancer patients. Furthermore, the overall survival and disease-free survival rates were improved in patients with lower Ki67 levels. The 5-year DFS was significantly worse in negative post-treatment estrogen receptors.

This study, although conducted retrospectively in a small cohort of patients, shows that the post-therapy Ki67 proliferation index and post-treatment ER status are important biomarkers that were prognostic of DFS following neoadjuvant chemotherapy in locally advanced breast cancer patients. We found that post-treatment assessments of the Ki67 index and ER status may have a promising role in predicting the outcome following neoadjuvant chemotherapy.

Further investigation is important to elucidate possible correlations between disease-free survival, overall survival and the predictive value of post-chemotherapy Ki67 and ER expression; in patients who failed to achieve pCR. More than this, a prognostic model could be formulated based on these two parameters.

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ARABIC SUMMARY

تعبيرات Ki67 العالية والمنخفضة في سرطان الثدي المتقدم الموضعي بعد العلاج الكيميائي الأولي عند النساء في شمال غرب الجزائر

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تتمتع النساء المصابات بسرطان الثدي المتقدم الموضعي اللائي حققن استجابة مرضية كاملة (pCR) بعد العلاج الكيميائي الاولي (NCT) ببقاء أفضل بكثير من أولئك اللواتي لم يحصلوا على (pCR)من المهم تحديد عوامل التنبؤ للمرضى اللواتي لم يصلوا إلى (pCR)لأن أصناف من هؤلاء المرضى قد تستفدن من العلاج المساعد الجديد . تم وصف تعبير (Ki67) العالي في الأمراض المتبقية بعد (NCT) كعامل تنبؤ ضعيف.

هدف هذه الدراسة تقييم تعبير مؤشر ما بعد العلاج الكيميائي (Ki67) وحالة مستقبلات هرمون الإستروجين (ER) ؛ علاوة على ذلك ، حاولنا توضيح الارتباطات المحتملة بين البقاء على قيد الحياة الخالي من الأمراض(DFS) والبقاء الكلي (OS) حسب هادين العاملين في مجموعة مكونة من 184 امرأة مصابة بمرحلة سرطان الثدي المتقدم الموضعي (IIB-IIIC) و معالجة ب (NCT) اللواتي لم يحصلن على (pCR) وخضعن لعملية جراحية. قمنا أيضًا بتحليل العلاقة بين مستويات Ki67(<15%, >=15%) والاستجابة السريرية، والأنواع النسيجية، والدرجات النسيجية المرضية للأورام وكذلك حالة إصابة العقد الليمفاوية لدى هاؤلاء المصابات من المركز الاءستشفائ الجامعي للسرطان. بسيدي بلعباس (غرب الجزائر). كان متوسط عمر المرضى 47 عامًا (27-81 عاما). يرتبط تعبير مؤشر (Ki67) بعد العلاج الكيميائي مباشرة بالاستجابة السريرية. كان متوسط قيمة تعبير (Ki67) بعد (NCT) أعلى بشكل ملحوظ في المرضى الذين يعانون من استجابة سريرية سلبية مقارنة بأولئك الذين طوروا استجابة موضوعية (p=0.013). أظهر التحليل أحادي المتغير لمستويات التعبير ل Ki67بعد العلاج الكيميائي كدلالة لخصائص الورم المرضي اختلافًا كبيرًا في النوع المرضي للنسيج (p= 0.025) وحالة إصابة العقدة الليمفاوية (p= 0.04). بلغ متوسط متابعة المرضى 23.5 شهرًا. ارتبط (ER) الإيجابي بعد العلاج الكيميائي بشكل ملحوظ مع (DFS)أعلى لمدة 5 سنوات(p=0.006).أكد تحليل البقاء على قيد الحياة الذي تم إجراؤه حسب مستوياتKi67 وجود (DFS) و(OS) أقصر بشكل ملحوظ في المرضى الذين لديهم تعبير Ki67أكبر من أو يساوي من15 بالمئة ، بعد مقارنة بالمرضى اللواتي يعانون من انخفاض في تعبير Ki67(أقل من 15 بالمئة) (p= 0.033 ,p= 0.002 على التوالي) .

بناءً على نتائج المرضى، كانت معدلات (OS) و (DFS) لدى المرضى اللواتي يعانون من انخفاض مستوى (Ki67) في تحسن. كان DFS لمدة 5 سنوات أسوأ بشكل ملحوظ في الورم مع مستقبلات هرمون الاستروجين السلبية بعد العلاج الكيميائ. يمكن أن يعتمد النموذج النذير على كل من معلمات مؤشر(Ki67) و تعبير(ER) بعد العلاج الكيميائي الاولي؛ مما قد يحسن التنبؤ بنتائج المرضى.

الكلمات المفتاحية: سرطان الثدي المتقدم الموضعي، (Ki67)،العلاج الكيميائي الاولي ، عوامل التنبؤ ، البقاء على قيد الحياة