EGYPTIAN ACADEMIC JOURNAL OF
BIOLOGICAL SCIENCES
PHYSIOLOGY & MOLECULARBIOLOGY

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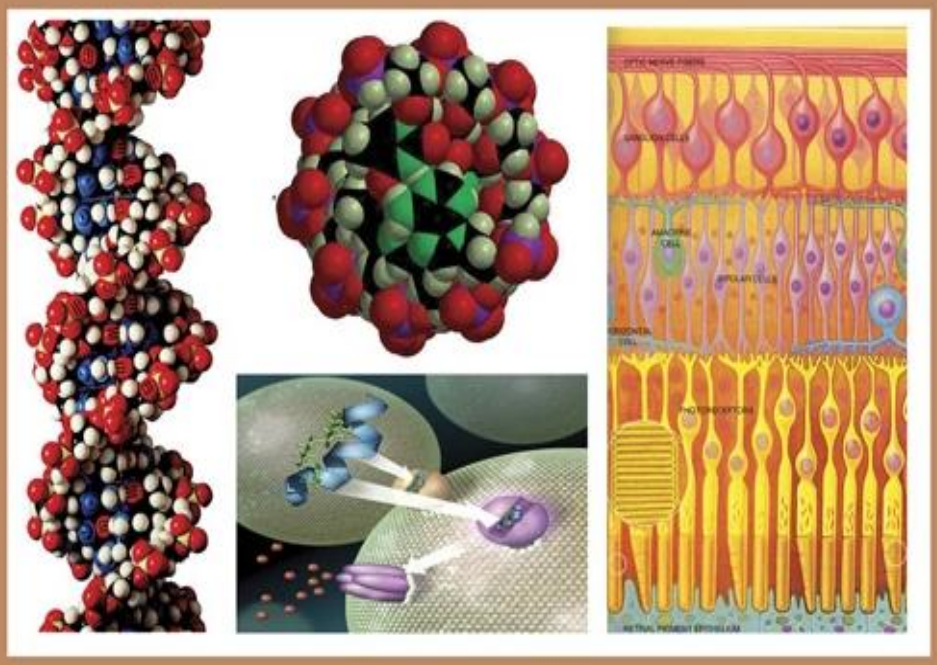

ISSN
2090-0767

WWW.EAJBS.EG.NET

Vol. 15 No. 1 (2023)

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Citation: *Egypt.Acad.J.Biolog.Sci. (C.Physiology and Molecular biology) Vol. 15(1) pp73-83 (2023)*
DOI: 10.21608/EAJBSC.2023.282289

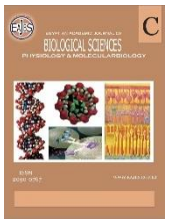
Egypt. Acad. J. Biolog. Sci., 15(1):73-83 (2023)

Egyptian Academic Journal of Biological Sciences

C. Physiology & Molecular Biology

ISSN 2090-0767

www.eajbsc.journals.ekb.eg



Prognostic Factors, Survival and Benefit of Neoadjuvant Chemotherapy in Operable Breast Cancer in Women from Northwest Algeria

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ARTICLE INFO

Article History

Received:25/11/2022

Accepted:23/1/2023

Available:28/1/2023

Keywords:

Operable breast cancer, prognostic factors, neoadjuvant chemotherapy, survival.

ABSTRACT

Prognostic factors are a clinical decision-making tool in choosing the most appropriate treatment for each patient. Women with operable breast cancer who have been treated with and without neoadjuvant chemotherapy (NCT) have significantly different outcomes. Finding a distinction between the outcomes of these two therapeutic situations is important because fractions of this population might benefit from other new adjuvant treatments.

The aim of this retrospective study was to identify certain prognostic factors by comparing the outcomes of patients that were treated with NCT (NCT subgroup) and without NCT (Non-NCT subgroup) in 470 women with operable breast cancer. Moreover, we attempted to elucidate the possible association between overall survival (OS) and disease-free survival (DFS) as a function of prognostic factors. Patients had a median age of 49 years (range 28-97). The clinical and pathological aspects compared between the two subgroups with and without NCT gave a highly significant difference ($p < 0.008$). Indeed, patients of NCT subgroup had significantly fewer invaded lymph nodes (2.40 ± 0.32 *vs* 3.82 ± 0.25, $p = 0.0003$) and their positive lymph node status was lower than patients of Non-NCT subgroup (58.3% *vs* 71.3%, $p = 0.003$). Comparison of the two subgroups of patients (NCT versus Non-NCT) gives a significant difference in the positive Ki67 expression status where NCT subgroup has a low rate of positive Ki67 status compared to Non-NCT subgroup (60.7% *vs* 84%, $p = 0.002$). After a median follow-up of 32 months (range 5-138 months), the univaried analysis in the NCT subgroup showed that hormone receptors (HR) were a significant prognostic factor of 5-year OS and 5-year DFS with a respective *p*-value equal to 0.03 and 0.005. Patients with HR+ had a median OS of 72 months [95% CI: 63.50 -80.50]. The Her2 factor had a significant effect only on OS ($p=0.035$). Node invasion was strongly associated with survival (OS and DFS) ($p < 0.01$).We found that Post-treatment assessments of the HR, lymph node involvement and Her2 status may have a promising role in predicting the outcome and must be strongly considered after neoadjuvant chemotherapy, in order to choose an adjuvant treatment for each individual patient.

INTRODUCTION

Chemotherapy uses a number of molecules to treat breast cancer in order to kill or stop the growth of cancer cells. There are several reasons why neo-adjuvant chemotherapy (NCT) should be considered in the initial management of operable breast cancer. This regimen allows for a reduction in tumour size, which will increase the possibility of conservative surgical treatment for those forms requiring mastectomy (Chen *et al.*, 2018)

In Algeria, breast cancer represents more than 40% of all female cancers with more than 12000 new cases estimated per year. It is cancer that has been increasing significantly over the last twenty years (Grangaud, 2020). Currently, breast cancer is the first cause of mortality in Algerian women. Mortality is estimated at around 3500 cases per year (Chaouche, 2018). Operable forms are predominant. They represent more than 75% of breast cancer cases.

The prognosis of breast cancer is related to its immunohistochemical profile and stage at diagnosis (Goldhirsch *et al.*, 2013). Prescribing neoadjuvant chemotherapy (NCT) requires the identification of prognostic and predictive factors for response and survival, which are used as a guide to possible personalised treatments. (Amat *et al.*, 2005). It also allows early identification of chemoresistant tumours with a high risk of relapse (Mauri *et al.*, 2005; van der Hage *et al.*, 2007).

The aim of this study is to know whether subgroups of patients benefit more or less from chemotherapy in the neoadjuvant setting. Comparing patients treated by neoadjuant chemotherapy (NCT) with those non-treated by neoadjuant chemotherapy (Non-NCT), in operable breast cancer has been retrospectively analysed in 470 women with operable breast cancer, from western Algeria. We analysed the relationship between the modality of chemotherapy treatment and the clinicopathological characteristics of the tumour, hormone receptor, Her2 status, Ki67 expression and survival.

MATERIALS AND METHODS

1. Patients and Treatment Modalities:

Between January 2012 and March 2017, 470 patients with operable breast cancer were collected from the Hospital University Centre of Sidi-Bel-Abbes (west of Algeria). Among these women, a subgroup of 355 had received no treatment by neoadjuvant chemotherapy (Non-NCT subgroup) and 115 were treated with neoadjuvant chemotherapy (NCT subgroup), following the recommendations of the International Union against Cancer (UICC) (Sobin and Wittekind, 1997). Our database included clinical (examination of the breast and lymph node areas), radiological (mammography and bilateral breast ultrasound) and histological examinations.

Patients of NCT subgroup were treated by 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).

Patients were operated on after 6 cycles of treatment for the NCT subgroup. The Non-NCT subgroup had a systematic surgery.

Adjuvant systemic treatment was administered to all 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).

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.

2. Evaluation of Prognostic Factors:

We studied the parameters evaluated for NCT subgroup after NCT (post-chemotherapy markers) and for the non-NCT subgroup after surgery, as prognostic factors. These parameters were recorded from pathological analysis reports (Hospital University Centre of Sidi-Bel-Abbes) of patients, evaluated from surgical tumour specimens:

• The evaluation of SBR grade according to the Elston-Ellis method (Elston and Ellis, 1991).

• The hormonal receptor (HR) status was determined by immunohistochemistry (IHC) to measure estrogen receptors (ER) and progesterone receptors (PR). The Roche Diagnostics antibodies ER 790-2223 and PR 790-4324 prediluted (~ 1µg/mL) (Roche Diagnostics Gmbh, standhoder Strasse 116, D-68305, Mannheim, Germany) were used for the detection of hormonal receptor status, using a Ventana NeXes 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 Her-2 protein expression was assessed by immunohistochemistry analysis using the 4B5(Ventana) 790-2991 rabbit monoclonal antibody prediluted (6 µg/mL). Only tumours Her-2 3+ are considered positive for overexpression. Her-2 2+ tumours are regarded as positive only after demonstration of ErbB2 gene amplification by fluorescence in situ hybridization (FISH) analysis in which it was used a Dako cut 17, Her-2 (Her-2 / CEP 17) K5731 probe kit (Dako Denmark A/S, produktiensvej 42. DK-2600 Glostrup, Denmark).

• The lymph node involvement was evaluated from surgical axillary lymph node dissection.

• And 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).

3. Statistical Analysis:

Chemotherapy treatment setting was analysed as categorisation into 2 subgroups (NCT, Non-NCT). Distributions of continuous and categorical histo-clinical and other immunohistochemical variables were compared between patient subgroups using the Chi2 test, Student’s t-test and Fisher's exact test.

The OS was calculated from the date of diagnosis until the date of death (from any cause) or the date of the latest news. The DFS was defined as the time between the date of diagnosis and the date of the first relapse (local, contralateral and distant event). The OS and DFS were calculated by Kaplan-Meier method (Kaplan and Meier, 1958). The survival analysis was conducted for 5 years. Survival was analysed as a function of prognostic factors post-neoadjuvant chemotherapy. The statistical log-rank test was used in univariate comparison for survival. Data are expressed as 95% confidence intervals (CI). A p-value of < 0.05 was considered significant for all analyses. All data analyses were performed on the IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

RESULTS

Neoadjuvant Chemotherapy Approach and Prognostic Factors:

The clinicopathological aspects in

Table 1 compared the two subgroups (CTN versus Non-CTN) gave a highly significant difference (p< 0.008). Patients with Non-CTN treatment had a higher mean age than those treated with CTN (52.07 ± 0.64 vs 48.73 ± 0.96), without statistical significance. Patients of CTN subgroup were significantly related to larger clinical tumour size compared to the Non-CTN subgroup (11.13 ± 1.65 vs. 5.07 ± 0.28; p < 0.001), respectively.

Table 1 : Clinicopathological tumour characteristics according to Chemotherapy treatment.

Variables	NCT (n=115) (%)	Non-NCT (n=355) (%)	*p* value
Age (mean±SD)	48.73 ± 0.96	52.07 ± 0.64	0.008
Clinical size of tumours (mean ±SD)	11.13 ± 1.65	5.07 ± 0.28	<0.001
Stage			
I	0 (0%)	11 (3.1%)	0.001
II	41 (35.7%)	181 (51%)	
III	74 (64.3%)	163 (45.9%)	
SBR tumours grade			
I	16 (13.9%)	11 (3.1%)	<0.001
II	53 (46.1%)	209 (58.9%)	
III	46 (40%)	135 (38%)	
Lymph node invasion status			
N-	48 (41.7%)	102 (28.7%)	0.003
N+	67 (58.3%)	253 (71.3%	
Number of N+ (mean±SD)	2.40 ± 0.32	3.82 ± 0.25	0.003

The NCT subgroup population had a significantly higher rate of clinical stage III tumours compared to the Non-NCT population (64.3% vs 45.9%; p= 0.001). The patients in NCT subgroup had lower rates of tumour grade SBR II than those in the Non-NCT subgroup (46.1% vs 58.9%; p<0.001). Furthermore, the SBR grade I is more representative in the NCT population than the Non-NCT subgroup (13.9% vs 3.1%).

The number and status of involved nodes were significantly different when compared between patients in the NCT and the Non-NCT subgroups. Patients treated with NCT had fewer mean number of involved nodes (2.40 ± 0.32 vs. 3.82 ± 0.25; p=0.0003) and low rate of positive node status (58.3% vs. 71.3%; p=0.003), respectively, compared to the non-NCT subgroup.

In Table 2, patients treated with NCT had the highest rate of negative estrogen receptor (49.6% vs. 31%; p= 0.001) and negative progesterone receptor (59.1% vs. 33.8%), with a significant difference compared to patients in the Non-NCT subgroup (p < 0.001). There was no significant difference between the two subgroups according to Her2 status (p= 0.061).

Table 2 : Hormonal receptors, Her2 and Ki67 status according to chemotherapy treatment**.**

Variables	NCT (n=115) (%)	Non-NCT (n=355) (%)	*p* value
ER (-)	57 (49.6%)	110 (31%)	0.001
ER (+)	58 (50.4%)	242 (68.2%)	
PR(-)	68 (59.1%)	120 (33.8%)	<0.001
PR(+)	47 (40.9%)	232 (65.4%)	
Her2 (-)	78 (67.8%)	119 (56.1%)	0.061
Her2 (+)	37 (32.2%)	153 (43.1%)	
Ki67 (-)	11 (39.3%)	31 (15.6%)	0.002
Ki67 (+)	17 (60.7%)	168 (84.4%)	

ER: Estrogen Receptors, PR: Progesterone Receptors

The comparison of the two subgroups of patients according to positive Ki67 index showed a significant difference, where patients of NCT subgroup had a low rate of positive Ki67 index compared to patients of Non-NCT subgroup (60.7% vs 84.4%; p= 0.002).

Survival Analysis as A Function of Prognosis Factors in Patients of NCT Subgroup:

The median follow-up of patients treated by NCT (n=115) was 32 months (range 5-138 months), and at 5 years, the overall survival (OS) and disease-free survival (DFS) rates were respectively 70.6% and 67.9%. At 72 months, the OS rate was 50% [95% CI, 61.9 -82.1] and at 58 months, the DFS rate was 51% [95% CI, 37 - 65]. OS and DFS were analysed according to hormone receptor, Her2 status and pathological lymph node involvement after neoadjuvant chemotherapy.

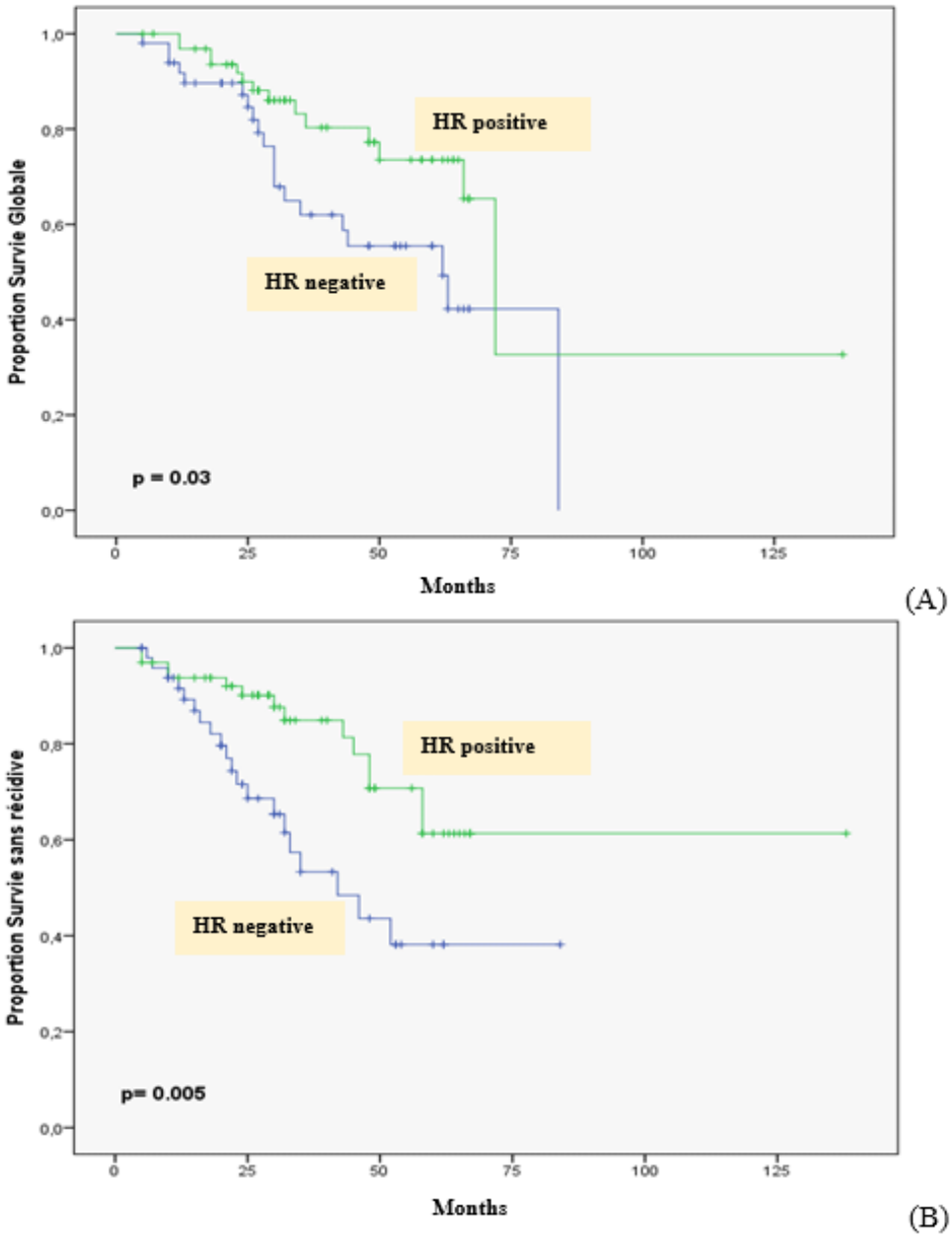

Fig. 1: Kaplan-Meier curve displaying OS (A) and DFS (B) by hormone receptor status assessed after NCT.

As shown in Figure 1, hormone receptors were a strong prognostic factor for overall survival and disease-free survival with a p-value of 0.03 and 0.005 respectively. Patients with positive Hormonal Receptors (HR) had a better 5-year OS (78.5% vs. 60%) rate compared to those with HR-. Patients with HR- had a median overall survival of 62 months [95% CI: 35.47 - 88.53], and a median DFS of 42 months [95% CI: 24.81 - 59.19]. Patients with HR+ had a median overall survival of 72 months [95% CI: 63.50 - 80.50].

Her2 status had a significant effect on OS (p = 0.035) with a 5-year OS rate of 83.3% in patients with a positive Her2 status versus a rate of 64.6% in patients with a negative Her2 status. However, no statistical significance was found for 5-year DFS (p = 0.171). A median OS of 66 months [CI95%:59.074 - 72.926] and of 52 months [CI95%:40.145 - 63.855] for DFS was noted in patients with Her2 negative status (Fig. 2).

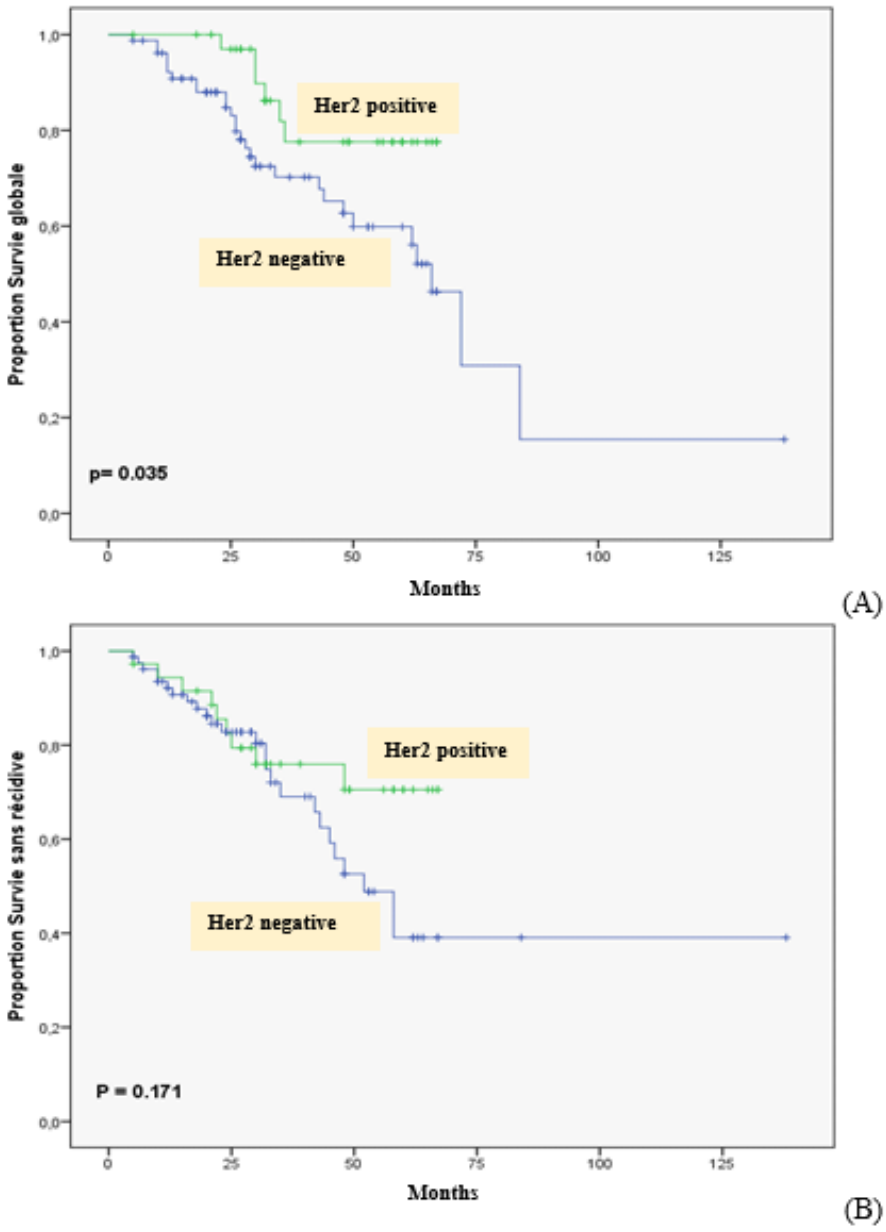

Fig. 2: Kaplan-Meier curve displaying OS (A) and DFS (B) by Her2 status assessed after NCT.

The 5-year overall survival rate in patients with negative lymph node involvement compared to those with positive lymph node involvement was significantly better (80% vs. 64.3%, p= 0.009, respectively). It was also better in 5-year DFS (70.6% vs. 66%, p= 0.018) (Fig. 3). A median OS of 62 months [95% CI: 37,402 - 86,598] and a median DFS of 46 months [95% CI: 40,385 - 51,615] was noted in patients with positive lymph node involvement.

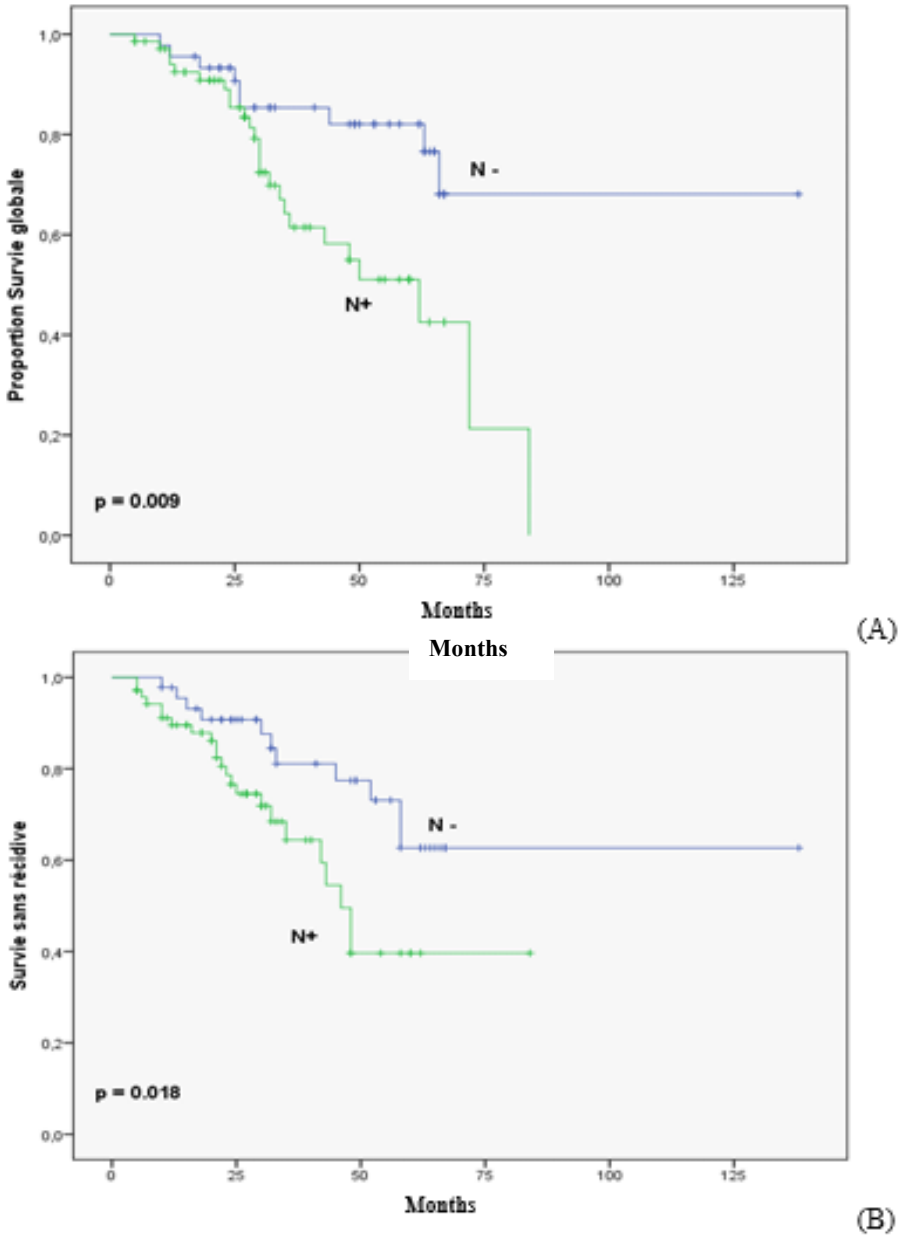

Fig. 3: Kaplan-Meier curve displaying OS (A) and DFS (B) by lymph node involvement status assessed after NCT.

DISCUSSION

The identification of prognostic factors, in operable breast cancer, would make possible the characterization of patients with worse or better survival and to evaluate their responses to treatment by neoadjuvant chemotherapy. (Amat S *et al.*, 2005 ; Petrarca *et al.*, 2011 ; Guarneri *et al.*, 2006).

Analysis of the clinicopathological

aspects of the tumours compared between the NCT and Non-NCT subgroups revealed a significant trend of younger patients in the NCT subgroup than in the Non-NCT subgroup (p = 0.008). These results are consistent with those of Carlie *et al.* (2010). Furthermore, the work of Mcpherson *et al.* (2000) shows that between the ages of 20 and 50, the risk of operable breast cancer increases very quickly, and then more slowly after menopause (around the age of 50) to stabilise after the age of 80 years.

In the NCT subgroup of patients, the mean tumour size and the rate of clinical stage III were significantly higher than in the Non-NCT subgroup (p<0.001). These results are justified experimentally and clinically by different studies (Morère *et al.,* 2008; Carlie *et al.,* 2010). The Scarff-Bloom-Richardson (SBR) classification thus isolates a group of high-grade patients who have an increased relative risk of relapse for the SBR III group (Rosen *et al.,* 1993). SBR grade I was significantly more representative in the NCT subgroup than in the Non-NCT subgroup (p <0.001). These results are consistent with those reported by Chollet (2005) where post-neoadjuvant chemotherapy SBR grade is significantly related to response to NCT treatment. The patients in NCT subgroup had lower rates of tumour grade SBR II than those in Non-NCT subgroup (p<0.001). These results are in accordance with the study of (Hajji *et al.,* 2020) who found a raté of 31.9% in SBR grade III cases.

The number of involved nodes as well as the node involvement status were significantly different when compared between patients in the NCT subgroup and the Non-NCT subgroup. Patients treated with NCT had fewer invaded nodes (p=0.03) and their positive node status was significantly lower than patients in the Non-NCT subgroup (p=0.003) (Benchiha, 2016).

In our study, we correlated hormone receptors, Her2 and Ki67 status with the two subgroups (NCT versus Non-NCT). Patients treated with NCT had the highest rate of negative hormonal receptors, compared to patients of Non-NCT subgroup, with a significant difference (p<0.001). These findings are very close to those reported in the study of Tardieu *et al.* (2018).

The comparison between the NCT subgroup of patients and the Non-NCT subgroup according to Ki67 tumour expression revealed a significant difference as a function of positive Ki67 index, where patients treated with NCT had respectively low positive Ki67 rates compared to Non-NCT subgroup of patients (60.7% vs 84.4%; p= 0.002) (Miglietta *et al.,* 2013).

A second objective of our work was to investigate the 115 patients in the NCT subgroup in order to conduct a study of overall survival (OS) and disease-free survival (DFS) according to prognostic factors. The median follow-up of patients was 32 months. OS and DFS were analysed according to hormone receptor, Her2 status and pathological lymph node involvement after neoadjuvant chemotherapy.

In the univariate analysis, patients with hormone receptor-positive tumours had a significant benefit in terms of overall survival and disease-free survival (p<0.031), which is similar to the results reported by Amat *et al.* (2005). The Her2 status had a significant effect on OS but no significant effect on DFS (p=0.171) (Benchiha *et al.,* 2015). Overall survival and disease-free survival in Algerian women with operable breast cancer are shorter than those found in studies conducted in European (Amat et al., (2005); Miglietta *et al.,* 2013) and American populations (Howard-McNatt *et al.,* 2013). These differences are at the origin of the lack of awareness of the early diagnosis of breast cancer and the delays in diagnosis. In fact, in Algeria, women are not aware of cancer screening through self-care and the health system does not promote systematic screening and timely treatment of cases. However, the overall survival and disease-free survival rates in our sample are better than those reported in the Brazilian population, probably due to the non-adjuvant treatment with Trastuzumab of Her-2 overexpressing patients as described by Petrarca *et al.* (2011).

The lymph node invasion factor showed a significant relationship with survival ($p<0.019$). These results are in agreement with those demonstrated by Amat *et al.* (2005) and Guarneri *et al.* (2009). As already revealed by several authors, the survival study according to the number of positive nodes was highly significant with a decrease in survival associated with an increase in the number of invaded nodes (Botti C *et al.*, 1995; Bonadonna *et al.*, 1998; Pierga *et al.*, 2000; Curé *et al.*, 2002).

CONCLUSION

Comparative analysis in patients with operable breast cancer treated with and without neoadjuvant chemotherapy showed significant differences in some prognostic factors. Indeed, patients in the NCT subgroup had better rates of positive hormone receptors of negative lymph node involvement, and of negative proliferation index than those in the Non-NCT subgroup.

Our outcomes suggested a significant association between the patients in the NCT subgroup and the prognostic factors already mentioned in operable breast cancer patients. For this purpose, a univariate survival analysis was conducted only on patients treated with NTC according to prognostic factors. Hormone receptor, Her2 and lymph node involvement status were all significantly associated with overall survival. The same was observed for disease-free survival except for Her2 factor.

This study, although conducted retrospectively in a small cohort of patients, shows that the post-therapy hormonal receptors, node involvement and post-treatment Her2 status are important biomarkers that were prognostic of OS and DFS following neoadjuvant chemotherapy in operable breast cancer patients. We found that post-treatment assessments of the HR, node involvement and Her2 status may have a promising role in predicting the outcome following neoadjuvant chemotherapy, in order to choose an adjuvant treatment for each individual patient.

The implementation of a Cox model, in the future, would give us more significant results that could demonstrate the combined effect of prognostic factors and therefore appreciate the relative risks of each factor on survival.

ACKNOWLEDGEMENT

We thank all the Medical Oncology staff, of Hospital University Centre of Sidi-Bel-Abbes (Algeria) that facilitated our work throughout the study.

REFERENCES

Amat S., Abrial C., Penault-Llorca F., Delva R., Bougnoux P., Leduc B. *et al.*, 2005. High prognostic significance of residual disease after neoadjuvant chemotherapy: a retrospective study in 710 patients with operable breast cancer. *Breast Cancer Research and Treatment*, 94: 255–63.

Benchiha N.N., Moulessehoul S., Yekrou D., Houti L., 2015. Prognostic Factors in Response to Neoadjuvant Chemotherapy in Operable Breast Cancer in Western Algeria. *European Journal of Scientific Research*, 128: 4, pp. 325-334.

Benchiha N.N., 2016. Carcinogenèse mammaire et chimiothérapie néo-adjuvante chez des patientes de l'ouest algérien. *Thèse de doctorat en science*, 110 p.

Bonadonna G., Valagussa P., Brambilla C., Ferrari L., Moliterni A., Terenziani M. *et al.*, 1998. Primary chemotherapy in operable breast cancer: eight-year experience at the Milan Cancer Institute. *Journal of Clinical Oncology*, 16: 93–100.

Botti C., Vici P., Lopez M., Scinto A.F., Cognetti F., Cavaliere R., 1995. Prognostic value of lymph node metastases after neoadjuvant chemotherapy for large-sized operable carcinoma of the breast. *journal of the American College of Surgeons*, 181: 202–08.

Carlie R. Kennedy, B.S., * Feng Gao, Ph.D., † and Julie A. Margenthaler, M.D., 2010. Neoadjuvant Versus Adjuvant Chemotherapy for Triple Negative Breast Cancer. *Journal of Surgical*

Research, 163: 52–57.

Chaouche B. H. E. Y. et Nabila S.,2018. « Contribution de l'immunohistochimie et de la biologie moléculaire au diagnostic anatomo-pathologique des cancers du sein », Thesis.

Chen R. *et al.*, 2018. « Assessment of the predictive role of pretreatment Ki-67 and Ki-67 changes in breast cancer patients receiving neoadjuvant chemotherapy according to the molecular classification: a retrospective study of 1010 patients », *Breast Cancer Research and Treatment*, vol. 170, no1, p. 35-43. doi: 10.1007/s10549-018-4730-1.

Chollet P. Moluçon C., Vanlemmens L., 2005. Pathologic complete response with neoadjuvant chemotherapy (Trastuzumab and Docetaxel) in HER2 positive locally advanced breast cancer patients. *Breast Cancer Research and Treatment*, vol 82.A 253.

Curé H., Amat S., Penault-Llorca F., le Bouëdec G., Ferrière J.P., Mouret-Reynier M.A., *et al.* 2002. Prognostic value of residual node involvement in operable breast cancer after induction chemotherapy. *Breast Cancer Research and Treatment*,76: 37–45.

Elston C.W., Ellis I.O., 1991. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology*; 19: 403–10.

Frierson HF. Jr.., Wolber RA., Berean K.W., Franquemont D.W., Gaffey M.J., Boyd J.C., Wilbur D.C., 1995. Interobserver reproducibility of the Nottingham modification of the Bloom and Richardson histologic grading scheme for infiltrating ductal carcinoma. *American Journal of Clinical Pathology*;103(2):195–8.

Goldhirsch A. *et al.*,2013. « Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013 », Ann. Oncol. Off. *European Society for Medical Oncology*, vol. 24, no 9, p. 2206-2223, doi: 10.1093/annonc/mdt303.

Grangaud Jp., 2020. L'évaluation : moteur du processus de planification sanitaire "Plan National Cancer 2015-2019" », *Algerian Journal of Health Sciences* , vol. 2, no 3, p. 53-61.

Guarneri V., Broglio K., Kau S.W., Cristofanilli M., Buzdar A.U., Valero V., *et al.* 2006. Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factors. *Journal of Clinical Oncology*, 24(7):1037–44.

Guarneri V., Piacentini F., Ficarra G., Frassoldati A., D'Amico R., Giovannelli S. *et al,* 2009. A prognostic model based on nodal status and Ki-67 predicts the risk of recurrence and death in breast cancer patients with residual disease after preoperative chemotherapy. *Annals of Oncology*; 20: 1193–8.

Hajji, A., Toumi, D., Daldoul, A., Njima, M., Mhabrech, H. E., & Faleh, R., 2020. Cancer du sein traités par chimiothérapie première: Facteurs prédictifs du traitement radical (étude rétrospective à propos de 72 cas). *The Pan African Medical Journal*, 36(174), Article 174. https:// doi. Org /10.11604/pamj.2020.36.174.24036

Kaplan EL., Meier P., 1958. Nonparametric estimation from incomplete observations. Clinical course of breast cancer. *Journal of the American Statistical Association,* 185: 1457–81.

Mauri D., Pavlidis N., et Ioannidis J. P. A., 2005. « Neoadjuvant Versus Adjuvant Systemic Treatment in Breast Cancer: A Meta-Analysis », *Journal of the National Cancer Institute*, vol. 97, no3, p. 188-194,

doi: 10.1093/jnci/dji021.

Mcpherson K., Steel C.M., Dixon K.M., 2000. « ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics». *British Medical Journal*, 9;321(7261):624-8. doi: 10.1136/bmj.321.7261.624.

Miglietta L., Morabito F., Provinciali N., Canobbio L., Meszaros P., Naso C. *et al.*, 2013. A prognostic model based on combining estrogen receptor expression and Ki-67 value after neoadjuvant chemotherapy predicts clinical outcome in locally advanced breast cancer: Extension and analysis of a previously reported cohort of patients. *European Journal of Surgical Oncology*; 39: 1046-52.

Morère Jean François, Penault-Liorca Frédérique,. Aapro Matti S, Salmon Rémy.; 2008. Le cancer du sein. Collection oncologie pratique, *Ed: Springer*, 312p.

Petrarca C.R., Brunetto A.T., Duval V., Brondani A., Carvalho G.P., Garicochea B., 2011. Survivin as a predictive biomarker of complete pathologic response to neoadjuvant chemotherapy in patients with stage II and stage III breast cancer. *Clinical Breast Cancer*; 11: 129-34.

Pierga J.Y., Mouret E., Dieras V., Laurence V., Beuzeboc P., Dorval *et al.*, 2000. Prognostic value of persistent node involvement after neoadjuvant chemotherapy in patients with operable breast cancer. *British Journal of Cancer*; 83: 1480–87.

Rosen P.P., Groshen S., Kinne D.W., *et al.*, 1993. Factors influencing prognosis in node-negative breast carcinoma: analysis of 767 T1N0M0/T2N0M0 patients with longterm follow-up. *Journal of Clinical Oncology*; 11(11): 2090–100.

Sobin, L.H. and, Wittekind C.H., 1997. "UICC. TNM Classification of Malignant Tumours" *Wiley-Liss publishing*, New York, p. 226.

Tardieu, A., Mesnard, C., Margueritte, F., Mollard, J., Lacorre, A., Aubard, Y., Deluche, E., & Gauthier, T., 2018. Récidive axillaire après prélèvement du ganglion sentinelle avant chimiothérapie néo-adjuvante dans le cancer du sein. *Gynécologie Obstétrique Fertilité & Sénologie*, 46(6), 509-513. https://doi.org/10.1016/j.gofs.2018.05.002

Therasse P., Arbuck S.G., Eisenhauer E.A., Wanders J., Kaplan R.S., Rubinstein L, *et al.*, 2000. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National cancer Institute of Canada. *Journal of the National Cancer Institute*; 92:205-216. doi:10.1093/jnci/92.3.205.

Van der Hage J. H., van de Velde C. J., Mieog S. J., et Charehbili A.,2007. « Preoperative chemotherapy for women with operable breast cancer », *Cochrane Database of Systematic Reviews*, no2, doi: 10.1002/14651858.CD005002.pub2.