Advances in Bioresearch
Adv. Biores., Vol 10 (6) November 2019: 155-161
©2019 Society of Education, India
Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.10.6.155161

Advances in Bioresearch

ORIGINAL ARTICLE

Breast Cancer in West of Algeria: Clinic-morphological and biological characteristics of 370 infiltring ductal carcinomas diagnosed in Oran

Chahinaize ZAOUI[1,2*];Dounia ADNANE[3]; Soria BAROUAGUI[1,4];Miloud MEDJAMIA[3];Nejadi MERAIR[3];Adnane ABDELWAHEB[3]; Zohra BEKKOUCHE[1,5];Khadîdja TERKI[3]; F. HAIBA[3]; Tewfik SAHRAOUI[1,5].

1. Laboratory of Developmental Biology and Differentiation (LDBD). Faculty of Natural and life sciences, Department of Biology, University ORAN1 AHMED BENBELLA,BP 1524 EL MnaourOran Algeria.
2. Department of Pharmacy, Faculty of Medicine, UniversityORAN1 AHMED BENBELLA.
3. Department of Medicine, Faculty of Medicine, UniversityORAN1 AHMED BENBELLA.
4. Department of natural and life Sciences, faculty of Natural and life Sciences, IbnKhaldoune Tiaret University.
5. Department of Biology, Faculty of natural and life Sciences,ORAN1AHMED BENBELLA University. BP 1524 EL Mnaour, Oran Algeria.

Correspondent Author: Chahinaize ZAOUI, Email: zaouibiocell98@gmail.com zaoui_chahineiz@live.fr

ABSTRACT

In Western Algeria, breast cancer is the primary cancer diagnosed in women and the leading cause of cancer related deaths with predominant invasive ductal carcinomas. The aim of this study is to describe infiltring ductal carcinoma diagnosed that has been treated in Oran according to their clinic-morphological and biological characteristics. This descriptive study was carried out at the laboratory of developmental biology and differentiation in collaboration with the units of care of the breast cancer at Oran, through the period of January, 2012 to December 31, 2016. 370 cases were studied whose age average is 44±5.93 years. The tumors are classified as T2 (78.91%) and pT2 in 55.13% of cases, G3 (34.05%), SBR III (61.08%). The intraducal component is associated with 43% and atypical hyperplasia with 87.03% of cases. The vascular emboli are observed in 31.89%. The tumors are pN+ in 55.95% and 57.14 % with invading less than 3 nodes. Overexpression of oestrogen receptors is observed in 58.11%,the status of androgen receptors is negative (RA-) in 57% of cases with 71.42% of HER1-, 61.90% HER2-, 61.90 CK5 / 6 + and 90.47% Ki67 > 14%. Androgen receptor status is positive (RA +) in 43% with 81.25% HER1-, 62.50% HER2-, 68.75 CK5 / 6 + and 68.75% Ki67 > 14%that of oncoprotein HER2 in 38.10%. Marking of Ki67 is positive in 81% of tumors, that CK5/6 is 65.13%. The tumors are luminal in 58.01%,14.08% HER2 and 28.91% triple negative. The tumors studied significantly vary from each other and include factors of poor prognosis in most cases.

***Keywords**: Breast Cancer, Prognostic, HER2, Ki67, molecular Profile.*

Received 29.09.2019 Revised 21.10.2019 Accepted 11.11.2019

How to cite this article:
C Zaoui; D Adnane; S Barouagui; M Medjamia; N Merair; A Abdelwaheb; Zohra Bekkouche; K Terki; F. Haiba; T Sahraoui.. Breast Cancer in West of Algeria: Clinic-morphological and biological characteristics of 370 infiltring ductal carcinomas diagnosed in Oran. Adv. Biores., Vol 10 [6] November 2019. 155-161.

INTRODUCTION

The records of cancer cases in the last two decades shows a clear increase in the epidemic rate of breast cancer amongst women[1]the primary cancer diagnosed in women in Algeria. The Oran cancer registry indicates that breast cancer ranks first with an incidence of 39.4 per 100,000 and a predominance of histological type invasive ductal carcinoma (80%) [2].It is also at the head of mortality despite the progress of treatments and the appearance of targeted therapies [3].

The clinico-morphological and biological characteristics of cancers are predictive and/or prognostic factors. Their identification is very important for a better orientation of the screening program, an adaptation of the therapeutic choices and especially to launch new lines of research [4].

The aim of this work is to describe the infiltring ductal carcinomas diagnosed in Oran according to the clinico-morphological and biological characteristics.

MATERIAL AND METHODS

Patients:

The patients included in our study have breast cancer whose diagnosis is confirmed by two histopathologists. Only the cases of invasive ductal carcinoma (IDC), diagnosed and treated in Oran are studied.

Methods:

A descriptive study was carried out on the 370 women with invasive ductal carcinoma (IDC) diagnosed and treated in Oran. This work was carried out at the Laboratory of Biology of Development and Differentiation (LDBD) in collaboration with the various units for breast cancer care in Oran, from January 1st, 2012 to December 31st, 2016. The cases were selected on the basis of an anatomo-pathological diagnosis confirmed after reading slides by two different pathologists. Patients with neo-adjuvant treatment are excluded.

For our study, necessary information are gathered in technical data sheet, clinical-morphological and biological characteristics are reported for each patient who signed informed consent.

The complete clinical examination is necessary to identify the patient's personal and clinical characteristics, completed with mammography, breast ultrasound and micro-biopsy with extension assessment.

We relied on clinical examination and radiology data to identify seat and tumor size (T) given that anatomical tumor size (pT) was assessed on macroscopic examination and confirmed at baseline microscopic examination.

TNM staging was done according to the TNM classification (2005) [5]. In all cases, the diagnosis is clinico-radiological and anatomopathological (micro-biopsy) and then, on operative specimens (mastectomy and axillary dissection).

The histological classification used is that of WHO (2002-2003), whereas the morphological molecular classification is that of Peru and Sorli [6].

All specimens were fixed with 1:10 diluted formalin, buffered saline, then paraffin-embedded. Hematoxylin-eosin tint was performed on 5-micron histological sections of the tumor and axillary lymphnodes. The slides are read using a light-field optical microscope.

After identification of the infiltrating component, sections of 3 to 4 microns were made and spread on silanized glass' slides. For immunohistochemical study, DAKO products were used for the labeling of different antigens:

- Estrogen Receptors (RE): (clone 1D5 DAKO ref. PDM001-01).
- RP Progesterone Receptors: (PgR 636 DAKO REF: M3569).
- RA Androgen Receptors (clone AR441 ref M3562).
- HER1 Oncoprotein (clone H11 Ref 3563).
- HER2 Oncoprotein: (polyclonal Rabbit antihuman clone C-erbB2 DAKO ref A0485).
- Ki67: (cloneSP6 REF: RMAB004).
- Cytokeratin CK 5/6 (clone: D5/16B4).
- Diluents ref: S3022.

After reading labeled slides for HER2 score 2 (in immunohistochemistry), these tumors are treated with in situ hybridization (CISH, HER2 CISH pharmDx Kit, Code SK 109).

During this study, we conducted a detailed descriptive analysis of our series, several variables were studied:

- Clinical features: the age at diagnosis, these at and the tumor size (T)
- Tumor morphological characteristics: Anatomic size (pT), Histopronotic grade G, Histopronotic grade SBR, The presence of the associated in situ component, The presence of associated a typical hyperplasia and, Vascularemboli.
- Morphological characteristics relating to tumor stroma: necrosis of the stroma.
- Morphological characteristics relating to the axillary ganglia: the ganglionic status, the pN classification and the number of ganglions invaded according to the prognosis.
- Biological characteristics relating to the tumor: Hormone receptor status (RE, RP, RA), oncoprotein (HER1, HER2), Ki67 and cytokeratin 5/6; phenotypic molecular classification.

RESULTS

Clinical features:

The age of the patients at diagnosis is between 20 and 75 years, the most affected age group is from 40 to 50 years (45.94%) with an average of 44 ± 5.93 years. Patients under 35 years old account for 16.28% of cases compared to 83.72% of those over 35 year old.

Straight breast involvement predominates (78.91%) with 57.02% sitting at the level of the super-external quadrant.

The clinical size (Figure 1a) T 2 is found in 70.81% of cases followed by 28.92% of T3. Sizes are from 20mm to 60mm with an average of 38.71 ± 3.45mm for T2 and 59.72 ± 0.92mm for T3.

Morphological characteristics relating to the tumor:

The anatomical size (Figure 1b) pT2 is predominant (55.13%) with an average of 37.97 ± 12.42 mm. The pT1 is found in 28.92%, the pT3 in 14.86% of the cases against 01.08% of pT4. Tumors, measuring more than 25mm, account for 57.83% of cases compared to 42.17% below 25mm.

The histopronotic grade (Figure 2a) G3 (poorly differentiated carcinoma) is found in 34.05% of cases followed by G2 (moderately differentiated carcinoma) in 29.19% of cases, G4 (undifferentiated carcinoma) in 20.81% and 15.95% are G1.

The histopronotic grade (Figure 2b) SBRIII (SCARFF and BLOOM-RICHARDSON) predominates (61.08%). The SBRII is found in 24.05% and the SBRI in 14.86% of the cases.

The intraductal component associated in 10 to 20% of the tumor surface is found in 42.97% of cases, 21.08% in 1 to 10% of the tumor surface, 16.22% in 20 to 30% of the tumor surface, 11.08% in 0 to 1.

Atypical hyperplasia are associated with 87.03% of cases in 1-15% of the tumor area.

Vascularemboli (Figure 3a) are observed in 31.89% of the tumors studied.

Morphological characteristics relating to tumor stroma:

Tumor stromal necrosisis observed in 51.08% of cases.

Morphological characteristics relating to axillary lymphnodes:

The nodes invasion (pN+) (Figure 4a) is observed in 55.95% of cases against 44.05% pN0. The pN1 predominates (Figure 4b) with 38.11% followed by pN3 (12.16%), the pN2 represents 05.95%. For the number of nodes invaded (Figure 4c), in 57.02% of cases less than 3 nodes invaded followed by 35.68% of 3 to 10 nodes invaded and 07.30% more than 10 nodes invaded. Capsular rupture was observed in 3 cases pN +.

Biological characteristics relating to the tumor:

For hormone receptors, the profile of estrogen receptors is positive in 58.11% of cases, progesterone receptors (PR) are positive in 51.08%. The status of androgen receptors is negative (RA-) in 57% of cases with 71.42% of HER1-, 61.90% HER2-, 61.90 CK5 / 6 + and 90.47% Ki67 > 14%.

Androgen receptor status is positive (RA +) in 43% with 81.25% HER1-, 62.50% HER2-, 68.75 CK5 / 6 + and 68.75% Ki67 > 14%

The membrane staining of HER2 oncoprotein is of score 3 in 28% of cases, score 2 in 17% and negative (score 0 and 1) in 55%. After marking scores 2 by CISH, 10% of cases showed an amplification of the gene cerb-B2 doc tumors HER2 + represent 38.10% against 61.90% of cases.

Ki67 is over-expressed in 81.08% of cases.

Cytoplasmic staining of cytokeratin 5/6 is positive in 65.13% of cases.

The tumors are luminal A in 34.05% of cases, luminal B in 24.06%, HER2 in 14.08% of cases, 28.91% are triple negative of which 17.03% basal and 11.86% non-basal like.

DISCUSSION

In Algeria, breast cancer is a major public health problem with a real urgency of intervention and management. This cancer affects both sexes with a clear predominance of women.

Each year, 7500 cases of breast cancer with around 3500 deaths are registered and usually diagnosed at a late stage so the survival rate remains slow [3]. Invasive ductal carcinoma is the main histological entity (80%) [2].

Age is a prognostic factor. Two studies have shown that age below 35 years is correlated with a bad prognosis [7]. In Hery's N- patients' study, young age appears as a local early recurrence factor in the first five years, and then its influence fades [8]. In our series more than $4/5^{th}$ patients are over 35 years old.

The seat of the tumor does not have a very clear prognostic value. Some authors, however, have reported the worst evolution of central or internal tumors because of direct lymphatic connections with the internal breast chain. It appears that tumors located in the outer quadrants are more frequently accompanied by axillary metastases (72%) than those located in the central or inner quadrants (66% and 55% respectively) whose lymphatics are drained towards the ganglia of the internal breast chains. As a

result, the latter can be invaded without the armpit being affected [08]. In our series, more than half of the tumors are located in the outer quadrants.

The size of the tumor is related to the evolution [09]: the larger the tumor, the lower the Relapse-Free Survival (RFS). The rate of RFS is about 42% at 10 years when the size is between 50 and 70 mm, while it is about 65% for tumors less than 20 mm. The tumor dimension is a risk factor for loco-regional recurrence after mastectomy. The frequency of axillary metastases increases significantly with the size of the tumor, whether clinical or anatomical. Thus, it goes from 24% for T0 to 38% for T1, 60% for T2 and 71% for T3 [09]. Therefore tumor size is also a clinical prognostic factor for metastatic relapse found in the literature [10]; this factor is independent of others. A tumor size of 40 mm correlates with a potential metastatic risk of approximately 50% [11]. Conversely, a patient with a tumor less than 10 mm, without lymph-node involvement, has a very low metastatic potential: 91% of relapse-free survival at ten years [12]. In our series, almost 3/4 tumors are T2 and T3 and more than ½ anatomical sizes (pT) measure more than 25mm.

The degree of differentiation is based on the resemblance of the tumor tissue to the normal tissue. Thus, a ductal carcinoma is said to be well differentiated when tubulo-glandular formations, quite clear, persist. The more marked the glandular differentiation, the more favorable the prognosis [13]. The more undifferentiated the tumors, the more aggressive they are. Conversely, the more differentiated a tumor is, the more favorable is its evolution [14]. In our series, half of the tumors are less differentiated and undifferentiated.

There is a clear prognostic difference between SBRI grade tumors on the one hand and SBR II, SBR III grades on the other hand: about 10 to 15% gain over six-year survival for the SBRI grade [15]. In our series, 2/3 of the tumors are SBR III grade.

The abundance of intraductal carcinoma (DCIS) associated with invasive carcinoma is extremely variable. Some studies have shown that the presence of extensive DCIS correlates with a better prognosis and a lower frequency of lymph-node metastases. However, associated intraductal carcinoma is associated with an increased risk of local recurrence [16]. In our series, in 2/3 of tumors, DCIS is associated in 1 to 10% of the tumor surface. Atypical hyperplasia is considered a precursor lesion conferring a moderate risk of invasive carcinoma [14]. In our series, more than 4/5th of tumors are associated with atypical hyperplasia.

Vascular emboli or lymphatic invasion is predictive of local recurrence after conservative treatment and distant relapse [17]. In our study group, vascular emboli are observed in 1/3 of the tumors.

The presence of necrosis is frequently at the center of the tumor and is especially present in NST ductal carcinomas; it would not be an independent prognostic factor. Extensive and confluent necrosis is more frequently observed in high-grade cancers [18]. In our series, stromal necrosis is observed in ½ of the studied tumors.

The staging of axillary lymph-nodes offers important prognostic information [19]. Numerous studies have shown that patients with loco-regional metastases have a poorer prognosis than those without lymph-node involvement [20]. In our series, almost ½ of the axillary dissections are pN +. The invasion of the axillary lymph-nodes remains the most important criterion.

There is a parallelism between the number of ganglia invaded and the risk of relapse, but also between the survival and the number of metastatic nodes: beyond 10 ganglia invaded, survival at 5 years and low, less than 25% [21]. In our series, the number of ganglia invaded is less than 10 in more than 4/5th of the metastatic lymph-nodes.

The expression of the hormonal receptors is a prognostic factor which is all the more important since the patients have, moreover, other criteria of good prognosis. This N- population was studied in two original studies: NSABP [22] and McGuire [23] found a survival difference of about 10% for estrogen receptor positive status (ER +). In our series, more than half of the tumors studied over express estrogen receptors (ER +).

Among the oncogenes that seem to be emerging today, Her-2/neu, also called C-erb-2 or HER2, is probably the most interesting. HER2 is over expressed in 20 to 30% of tumors [24]. Over expression of the HER2 oncoprotein is a poor prognostic factor for N + patients [25]. In addition, there appears to be a correlation between elevated SBR levels and over expression of this oncogene [26-28]. Finally, over expression of HER2 could also be a predictor of treatment response [29]. In our series, almost 4/10th tumors over express HER2.

The Ki67 (or Mib1) detects a nuclear antigen present throughout the cell cycle except the quiescent phase (G0). A correlation was established between the level of Ki67 positive cells and the proliferation index measured by BrdU incorporation or mitotic counting. The average value of Ki67-positive cells in mammary tumors is 15%. This figure is correlated with grade, reaching the highest values in poorly differentiated tumors. In addition, tumors lacking hormone receptor soften have high Ki67 values. A

strong correlation between Ki67 expression and survival is also reported [30]. In our series, Ki67 status is positive in 4 / 5th of tumors.

In immunohistochemistry, there is a concordance between basal type carcinomas and the expression of high molecular weight cytokeratin CK5-6, CK14 and CK17, also known as basal cytokeratin, because of their expression in normal basal or myoepithelial cells of the milk ducts. The concordance is not perfect, however, and carcinomas express one or more of these markers [31]. In our series, the status of CK5-6 is positive in 2/3 of tumors.

The analysis of the expression profiles by breast cancer chips identified four major molecular categories, called luminescent, HER2, basal and normal-like. These categories are defined by a specific and reproducible transcriptomic signature, and are associated with different clinical evolutions [6]. In our series, 58.01% tumors are luminal, 14.08% HER2 and 28.91% triple negative.

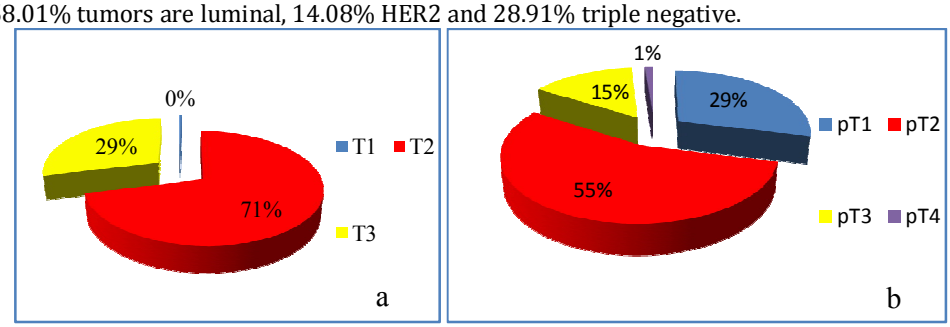

Figure 1: Tumor distribution by size (a: Clinical size, b: Anatomic size)

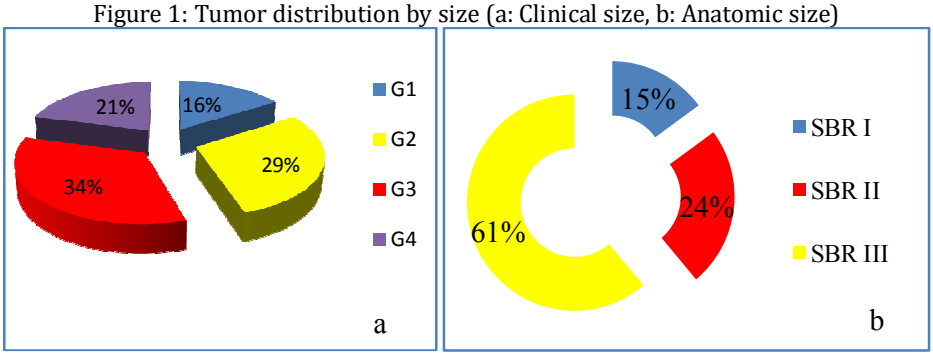

Figure 2: Tumor distribution by histopronostic grade (a: grading G, b: SBR)

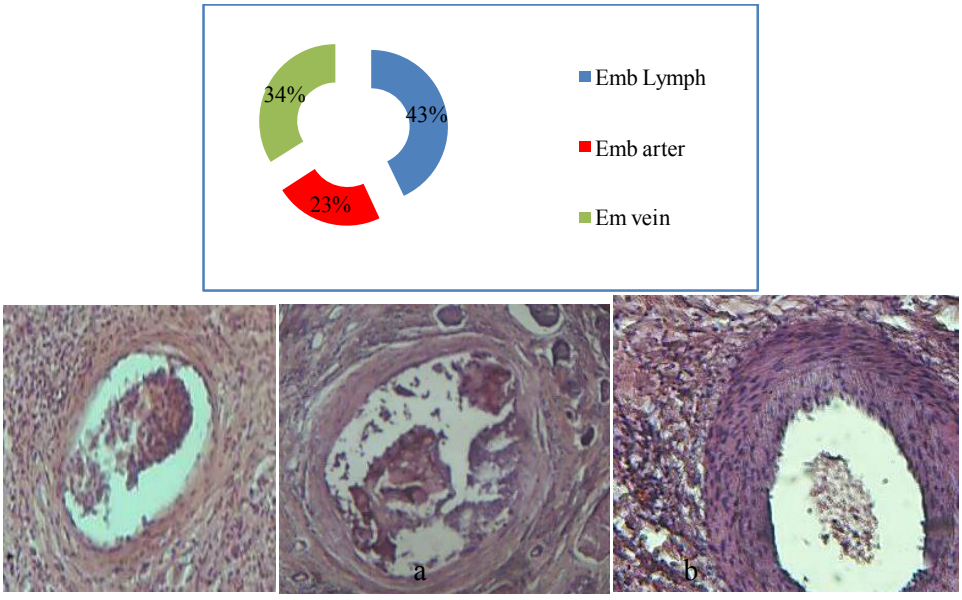

Figure 3: Tumor distribution according to the type of vascular embolus (a: Lymphatic embolus (EmbLym), b: Venousemboli (Embvein), c: Arterialemboli (Emb art).

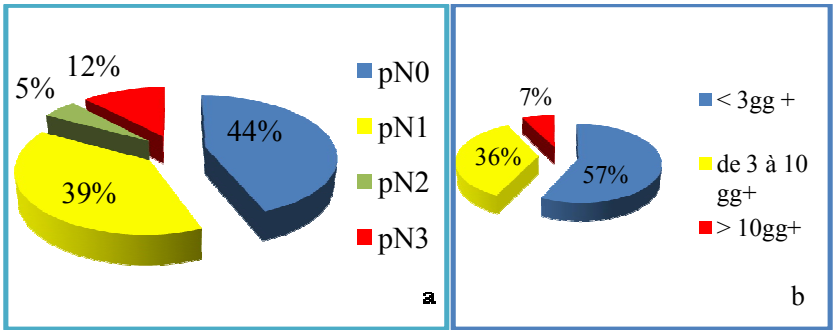

Figure 4: Distribution of tumors according to the lymphnode status (a: According to the pTNM classification, b: according to the number of lymphnodes affected

DECLARATION OF INTERESTS

The authors declare that they have no conflicts of interest in relation to this article.

ACKNOWLEDGMENT

The authors also wish to acknowledge valuable contribution from ZAOUI Mohammed Mostefa and KOKKONI Panayiotis.

REFERENCES

1. Bendib S.E. (2011). 9th Intensive Seminar in Oncology Mustaga Hotel, Mostaganem 10/13.
2. Ammour A, Fouatih Z. A, Mokhtari L. (2014). Oran Cancer Registry, 16 years of registration. Journal of Epidemiology and Public Health Volume 62, Supplement 5, Page S213
3. Mahnane A, Hamdi Cherif M. (2012). Epidemiology of breast cancer in Algeria. Setif Cancer Registry. Algerian Society of Medical Oncology (SAOM).
4. Aksim M, Karkouri M, Bennani N, Mekouar H, Sebbar L, Jabri L, Zamiat S.(2012). "Breast cancer: study of histopronostic factors (about 239 cases".
5. TNM classification of Malignant Tumors, Breast tumors, LH, Sobin, Armed Force Institute of Pathology(2003). http: //www.mrw. Interscience. Wiley.com/tnmc/articles/tnm29/France.htlm
6. Peru CM, Sorlie T, Eisen MB, et al Molecular portraits of human breast tumor, Nature 2000; 406: 747-52.
7. De La Rochefordière A., Asselain B., Campana F. et al. (1993). Age prognostic factor in premenopausal breast carcinoma. Lancet; 341: 1039-43
8. Héry M., Tessier E., RamaiolaA., Et al. (1998). Is the age less than or equal to 40 years a contraindication to conservative treatment? Study of 141 cases without axillary involvement (N-). Cancerradiother. 2 (5): 484.
9. Contesso G., Bertin S., Mathieu M.C. (1991). Pathological anatomy of breast cancer. Encycl Med Chir; 865 (B10): 1-17.
10. Carter CL, Allen C, Henson DE. (1986). Relation of tumor size, lymph node status and survival in 24270 breast cancer cases. Cancer;63:181-7
11. Koscielny S., Tubiana M., Lé M.G.et al. (1884). Breast cancer: relationship between the size of primary tumor and the probability of metastatic dissemination. Br J Cancer;49:709-15.
12. Rosen P.P., Groshen S., Kinne D.W., Norton L. (1993). Factors influencing prognosis in node-negative breast carcinoma : analysis of 767 T1N0M0/T2N0M0patients with long-term follow-up J ClinOncol, :11 (11) : 2090-100.
13. General oncology, Anatomy Pathology, Ed. OPU edition n ° 1638-September 1984 A. YAKER.
14. Memento de pathologie, Ed. (2004). Vernazbres-Grego- 1st edition (P225-236).
15. Contesso G., Mouriesse H., Fridman S. et al. (1987). The importance of histological grade in long-term prognosis of breast cancer : a study of 1010 patients, uniformly treated at the institute Gustave-Roussy.JClinOncol: 5(9): 1378-86.
16. Jacquemier J, Kurtz JM, Amalric R, Brandone H, Ayme Y, Spitallier JM, (1990). An assessment of extensive intraductal component as a risk for local recurrence after breast-conserving therapy. Br J Cancer;61:873-6.
17. Arnaout-Alkarain A, Kahn AJ, Narod SA, Sun PA, Marks AN. (2007). Significance of lymph vessel invasion identified by the endothelial lymphatic marker D2-40 in node negative breast cancer. Mod Pathol; 20:183-91.
18. Visscher DW, Wallis T, Jimenez RE. (2000). Centrally necrosing carcinoma: a distinctive histologic subtype of breast cancer with an aggressive clinical behavior. Mod Pathol; 13:49A.
19. Quiet CA, Ferguson DJ, Weichselbaum RR, Hellman S. Natural History of node-positive breast cancer: the curability of small cancers with a limited number of positive node. J ClinOncol 1996;14: 3105-11.
20. Galant C, Berlière M, Leconte I, Marbaix E. (2000). News in the histopronostic factors of breast cancer. Women's imagery 210 ; 20: 9-17.
21. Nemoto T, Vana J., Bedwani R. N. et al.(1980).Management and survival of female breast cancer: results of national survey by the American college of Surgeons. Cancer; 45: 2917-24.

22. Fisher B., Redmond C., Fisher E.R., Caplan R. (1988). Relative work of oestrogen or progesterone receptor and pathologic characteristics of differenciation as indicators of prognosis in node negative breast cancer patients; finding from the National Surgical Adjuvant breast and bowel Project protocol B-06. J ClinOncol; 6(7):1076-87.
23. McGuive W.L, Clark G.M. (1989). Pronostic factors for recurrence and survival in axillary node-negative breast cancer. JSteroidBiochem ; 34 (1-6):145-8.
24. Salmon D.J, et al. (1987). Humain breast cancer: Correlation of relapse and survival with amplification of the Her-2/neu oncogene. Science; 235:177-82.
25. Nieto Y. NawazS,Cagnoni P.J, et al. (1999). Overexpression of Her2/Neu (H2N), hut not P53 mutations is a poor prognostic factor of high-risk primary breast cancer (HRPBC) treated with high-dose chemotherapy (HDC) and autologous stem-cell transplant (ASCT). Proc Am SocClinOncol 1999; 18: abstr.290.
26. Siegel R.S, Kothary N, Johnson M. et al. (1999). Analysis of 512 breast cancer in which Her-2/Neu assessment was performed. Proc Am SocClinOncol; 18: abstr.290.
27. Scurr M., Cooke B., Lonergan D. et al. (1999). Asinglecentre prospective study of c-erbB-2 expression in early stage breast cancer. Its relationship with other prognostic variables.Proc Am SocClinOncol ; 18: abstr.382.
28. Gancberg D., Lespagnard L., Rouas G. et al. (1999). Routine evaluation of Her-2/Neu amplification and overexpression in breast cancer: correlation with grade, proliferation and E-cadherin expression.Proc Am SocClin Oncol; 18: abstr.2397.
29. Niskanen E., Franssila K., Blomqvist C. et coll. (1992). The prognostic role of histological grade and c-erbB-2 oncogene amplification in primary tumors of metastatic breast cancer. Proc Am SocClinOncol; 11(74): S82(abstr.427).
30. Aber JM, Riggs MW, Arber DA. Correlation among MiB-1 paraffin section proliferation index and recurrence in low stage breast cancer, Applimmunohistochem 1998;5:117-24.
31. Fulforg LG, Easton DF, Reis-Filho JS, Sofronis A, Gillet CE, Lakhani SR, et al. (2006). Specific morphological features predictive for the basal phenotype in 3 invasives ductal carcinoma of the breast. Histopathology; 49:22-34