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Breast cancer subtypes criteria versus clinicopathological data

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ABSTRACT

Breast cancer in women is the second most frequent cancer incidence, the breast cancer cases with varied histopathological and biological aspects reflect different attitudes that result in various therapy responses and should be given different therapeutic strategies.This study aimed to differentiate the breast cancer due to the histopathological and molecular criteria, the first is inflammatory breast cancer (IBC) or non-IBC, and the second is hormonal positive breast cancer (HP BC) or triple negative breast cancer (TN BC), and the third is lymphovascular invasion positive (LVI-p) or lymphovascular invasion negative (LVI-n).Overall 78 female diagnosed with breast carcinoma were enrolled in this study. Using pathological, histological and molecular criteria to differentiate the breast cancer groups in tissue samples, and then we were statistically displayed some histopathological and molecular features for each group. The results indicated that most common age in breast cancer patient is 50, the tumor size in IBC, TN BC and LVI-p is significantly higher than non-IBC, HP BC and LVI-n respectively, the most common tumorgrade is grade II, the nodal status in IBC and TN BC is significantly higher than non-IBC and HP BC respectively, 95% of IBC and 87 % of non-IBC patients are diagnosed as invasive ductal carcinoma, and 5% of IBC and 8 % of non-IBC patients are diagnosed as invasive lobular carcinoma.

In conclusion statistical analysis of breast cancer clinicopathological data might help in improving of cancer treatment strategies.

Key words: inflammatory breast cancer (IBC), hormonal positive breast cancer (HP BC), triple negative breast cancer (TN BC), lymphovascular invasion positive (LVI-p), lymphovascular invasion negative (LVI-n).

INTRODUCTION

Breast cancer is the second most frequent cancer among women and the fifth highest common leading cause of cancer mortality rate worldwide and especially in Egypt (WHO 2018).Breast cancer is not only a disease, which includes of numerous biologically various structures with different pathological features and clinical consequences [(1-7)], accreted demonstrations have recommended that breast cancer cases with varied histopathological and biological aspects may need different therapeutic strategies [(8)].Therefore, stratification of clinically-related breast cancer subtypes is of particularrelevance for treatment decision [(9)].

Histologically, breast cancer is usually classified either carcinoma in situ when precancerous cells within a appointed tissue like, the mammary duct without invasion of the surrounding tissue, or invasive carcinoma due to the invasion of cancerous cells to the surrounding tissues.In both cases, breast cancer mostly is derived from the epithelium lining the mammary ducts or lobules [(10)].Most of the breast malignancies are adenocarcinomas, which represent more than 95% of breast cancer cases [(10)].

The histological diversity and cytological patterns help in breast cancer subtyping, where the breast cancers having malignant ductal proliferation along with stromal invasion

are called invasive ductal carcinomas (IDC), which constitutes about 55% of breast cancer incidence upon diagnosis [(10)].The second major mammary carcinoma other than IDC is the invasive lobular carcinoma (ILC), that has spread beyond the lobule to other parts of the breast tissue or other parts of the body, ILC constitutes about 5% to 15% of invasive breast carcinomas [(11)].

On the other hand, if the carcinoma cells did not spread into surrounding milk ducts of the breast tissues, it called ductal carcinoma in situ (DCIS), and it is calledlobular carcinoma in situ (LCIS) when non-spreading of the carcinoma cells surrounding of the breast gland lobules occur the other breast tissues [(10)]. DCIS constitutes about 20-25 % of all diagnosed breast cancer cases [(12)], and LCIS accounts about 1-2% of all breast cancers [(13)].There are many other uncommon breast cancer subtypes with differenthistological features [(10)].

Furthermore, immunohistochemistry (IHC) markers including the status of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) are classically applied for mammary tumor subtyping [(14)]. ER positive breast cancerrepresents 75% of all breast cancer patients, and configure 65% and 80%, respectively, patients under and above 50 years [(15)], PR positive tumors include 65% to 75% breast cancer cases [(16)], HER2 is overexpressed in about 20 to 30% of breast cancer patients [(17)].

A combination of various IHC markers including ER, PR and HER2, with or without additional markers, has been used to define breast tumor subtypes, where the statuses of ER, PR and HER2 have been considered as the most important features [(18)]. If ER or PR does not expressed with lacking HER2 overexpression or amplification, it is triple negative (TN) breast cancer, which accounts for 15% to 20% of all breast cancer cases [(19)].

In this study we will focus on inflammatory breast cancer (IBC) the most aggressive form of breast cancer- with unique clinical and pathological characteristics. Despite being comparatively rare, it is more prominent among young ages [(20)], and its incidence rates appear to be increasing over the last 20 years period before 2005 [(21)]. Clinically, IBC is defined by distinct features,; including rapid onset, erythema, edema of the breast, and a “Peaud'orange” appearance of the skin, high metastatic potential with formation of dermal and lymphatic emboli and extensive axillary lymph node involvement [(22-24)].

IBC constitutes 1% to 2% of all breast cancers in the United States [(25)]. However, it is higher in black Americans compared with whites[(21, 25)]. Also of note, the prevalence of IBC in North African countries ,such as Egypt, Tunisia, and Morocco represents about 10% to 15% of breast cancer [(26, 27)].IBC has no a certain histological subtype of mammary carcinomas, however most of IBC cases are ductal carcinoma with a high histological nuclear grade, where, about 90% of all IBC cases are with IDC and about 5% are withILC [(28)]. There are about 17- 30% of IBC cases are TN and 18-44% are HER2 positive [(29)]. Different studies have shown that TN IBC has a worse prognosis than those with positive for ER, PR, and/or HER2 [(30)].

This study aimed to differentiate the breast cancer due to the histopathological and molecular criteria, the first is inflammatory breast cancer (IBC) or non-IBC, and the second is hormonal positive breast cancer (HP BC) or triple negative breast cancer (TN BC), and the third is lymphovascular invasion positive (LVI-p) or lymphovascular invasion negative (LVI-n).

MATERIALS AND METHODS

Patients and Samples:

Adult women in this study referred to outpatients clinics of Ain-Shams University hospitals from January 2015 till January 2017,, whodiagnosed as breast cancer by clinical ultrasound examination, mammography and tru-cut biopsy, were enrolled where the carcinoma tissues were obtained during modified radical mastectomy (MRM)[(31)].

Ethical and approval statements:

The Egyptian ethics committee (EEC) approval was obtained by application to the institutional review board (IRB) of Ain Shams University (No.IRB0006379).All enrolled breast cancer patients signed informed consent that agrees with anonymous data publication.

Pathological data criteria:

Overall 78 female breast cancer patients were divided into 38 IBC versus 40 non-IBC group, 31 TN BC versus 47 Hormonal positive (HP) BC group and 31 lymphovascular invasion positive (LVI-p) versus lymphovascular invasion negative(LVI-n) group. Pathological diagnosis was done for each patient, including tumor size, tumor grade, disease stage, the lymph node (LN) status, presence or absence of lymphovascular invasion and dermal lymphatic emboli. According to the modified Bloom Richardson-Elston histological system, tumors were divided into I,II,III grades as well as breast cancer is staged into four main stages from I to IV based on TNM classification of malignant tumors where T describes (the tumor size) , N (normal) describes the LN status, and M (mass) describes the distance of metastasis [(32)]. Also, level of expression of estrogen/progesterone hormone receptors (ER/PR) and human epidermal growth factor receptor (HER2) were assessed by immune-histochemistry (IHC).

Hematoxylin and eosin stain (H&E) method:

Mammary tissues was dissected and fixed in 10% natural buffers formal for 48h, then fixed tissues trimmed into appropriate size and shape and place in embedding cassettes, the fixed tissues dehydrated in graded levels of ethanol, cleared in xylene, and embedded in paraffin wax for sectioning, the embedded tissue blocks sectioned to 3-5µm,floated on a water bath, picked up onto glass slides, placed in slide racks and stained with hematoxylin and eosin for histopathological evaluation according toCardiff *et al.* protocol[(33)].

Statistical Analysis

Data were expressed as mean (±) standard deviation (SD). The three types of average (mean, median and mode) were calculated. Statistical difference between groups was assessed by Student's t-test and Chi square test. *P* values < 0.05 were considered to be statistically significant using SPSS 22.0 software**.**

RESULTS

Patients' clinical and pathological characteristics:

The three types of average for patient age are shown in (Fig. 1A), where the mean, median and mode were the same, about 50 years old in IBC versus non-IBCgroup, HP BC versus TN BCgroup and LVI-p versus LVI-n, except in the age mode of LVI-ngroup, which was 40 years old with no significance variation in all group.

The second pathological criteria was the tumor size (T) (Fig. 1B), where the mean, median and mode were about 4cm in non-IBC group, whereas in IBC group, the T mean was 6cm, the T median was 5cm and the T mode was 4cm with significantly variation($P \leq 0.05$). The T mean was about 5cm in HP BC versus TN BCgroup and in LVI-n versus LVI-pgroup, whereas the T median and mode were about 4cm in HP BC versus TN BC group and in LVI-n versus LVI-pgroup withno significance variation.

The third pathological criteria was the tumor grade (G) (Fig. 1C), where the G median and mode were grade II (G2) in non-IBC versus IBC group and in HP BC versus TN BCgroup with significantly difference ($P \leq 0.05$) and in LVI-n versus LVI-p group withno significance difference, whereas the G mean was more than G2 in non-IBC versus IBC group

and in HP BC versus TN BCgroup with significantly variation ($P \leq 0.05$) and in LVI-n versus LVI-p group withno significance variation.

The fourth pathological criteria was thelymph nodes status (N)(Figure 1D), where the N mean was 2 in non-IBC versus 8 in IBC group, however the N median and mode were 0 in non-IBC versus 4 in IBC group with significantly variation ($P \leq 0.05$), whereas the N mean was 5 in TN BC versus 4 in HP BC, and the N median and mode were 4 in TN BC versus 2 and 0 in HP BC group respectively, while the N mean and median were about 7 and 4 in LVI-n versus LVI-p group respectively, and the N mode was 0 in LVI-n versus 4 in LVI-p group.

The hormone receptor and human epidermal growth factor receptor (HER2) status were helped in classification the breast cancer cases in this study, where, estrogen receptor (ER) status was positive in 50% of IBC patients and 60% of non-IBC patients, and progesterone receptor (PR) status was positive in 52.6% in both IBC and non-IBC cases, whereas, HER2 status was positive in only 23.7% of IBC patients and 20% of non-IBC patients.

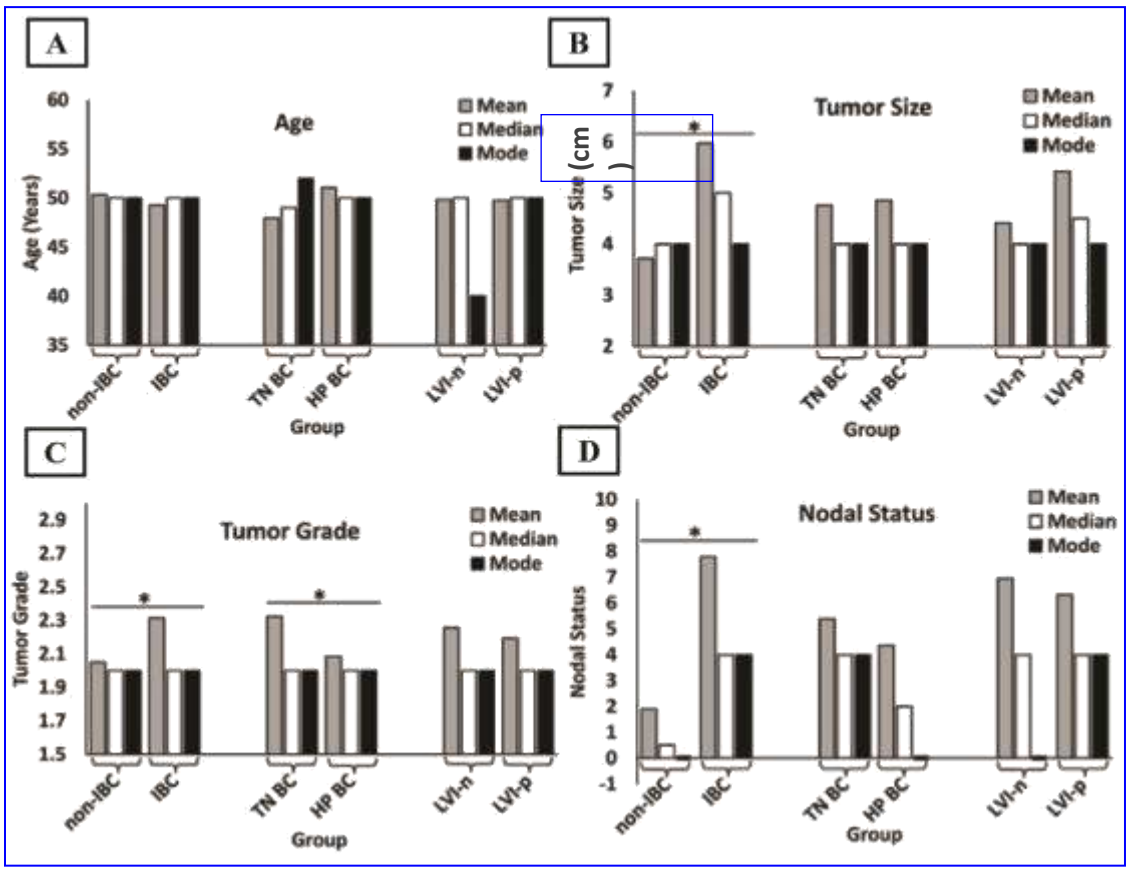

Fig. (1): The difference between the three types of average (mean, median and mode) for the clinical and pathological data of breast cancer patients in the six groups as the following, non-IBC versus IBC, TN BC versus HP BC and LVI-n versus LVI-p. (A)Bar graphs represent the variation in the averages of the patient ages. (B)Bar graphs represent the variation in the averages of the tumor size. (C)Bar graphs represent the variation in the averages of the tumor grade. (D)Bar graphs represent the variation in the averages of the lymph node status.*, represents $P \leq 0.05$ as determined by Student's t-test; IBC, inflammatory breast cancer **TN BC**,triple negative

Breast cancer subtypes criteria versus clinicopathological data

The histological analysis of the mammary carcinoma:

All adult women who participated in this study werepreviously diagnosed as breast cancer patients in clinics of Ain Shams University hospitals as the following: 38 IBC and 40 non-IBC patients, our histologic analysis showed that95% of IBC patient tissue samples were diagnosed as invasive ductal carcinoma (IDC) and the other 5% were diagnosed as invasive lobular carcinoma (ILC). On the other hand, 87% of non-IBC patient tissue samples were diagnosed as IDC, and 8% are diagnosed as ILC, and the last 5% are diagnosed as ductal carcinoma in situ (DCIS) (Fig. 2).

HP non-IBC tissue sections showed breast carcinoma with DCIS (Fig. 2a) with low-power field to illustrate DCIS that is limited to the inside of the breast ducts, and those ducts are surrounded by desmoplastic stroma, fat cells and luminal calcification. Whereas, the high-power field in (Figure 2b) to determine the carcinoma cells in the mammary duct like multiple nucleoli cells, some nuclear pyknotic cells and cytoplasmic vacuolar degeneration.

The other histological figures of HP non-IBC tissue sections showed breast carcinoma with ILC (Figure 2c) with low-power field to display sheets of malignant cells in mammary lobules which, are surrounded by desmoplastic stroma and vascular calcification, the high-power field in (Figure 2d) illustrates carcinoma cells with enlarged nuclei and many multiple nucleoli.

On the other side, the HP IBC tissue sections in (Fig. 2e) showed breast carcinoma with IDC in low-power field to illustrate the carcinoma cells invaded through the basement membrane of a breast ducts, which are surrounded by desmoplastic stroma and large vacuolar degeneration, as well in the highly magnified field (Fig. 2f), the breast carcinoma cells appear cytoplasmic vacuolar degeneration and many multiple nucleoli.

While, the other histological figures of HP IBC tissue sections in (Fig. 2g) with ILC in low-power field to show malignant cells in mammary lobules surrounded by vacuolar degeneration and stromal calcification, furthermore, the highly magnified field (Fig. 2h) is displayed carcinoma cells with many cytoplasmic vacuolar degeneration, many multiple nucleoli (MN), enlarged nucleoli and pyknotic nucleoli.

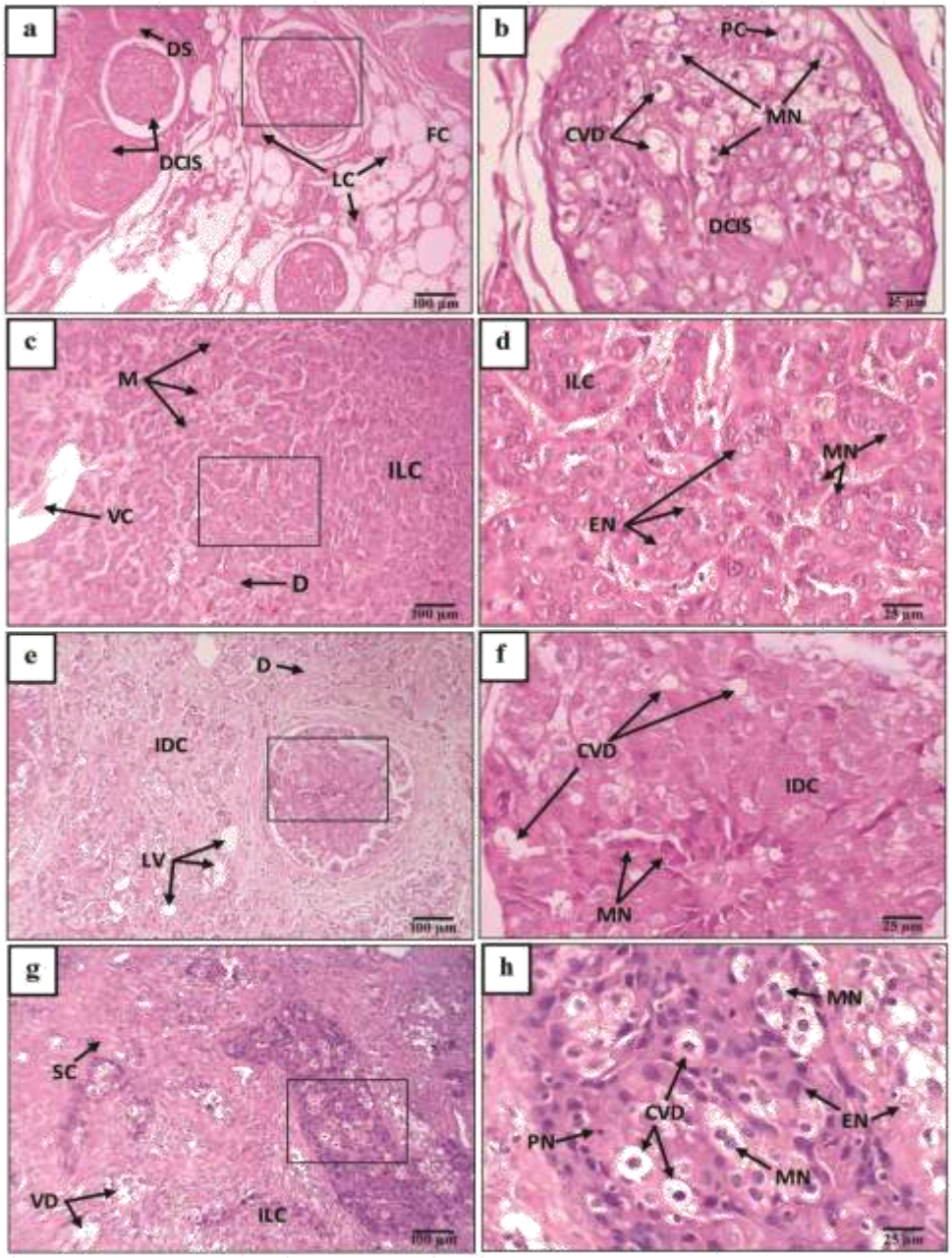

Fig. (2): Photomicrographs showing some histological subtypesof non-IBC versus non-IBC patients (H&E stain)**.** (a)non-IBC section showing with ductal carcinoma in situ (DCIS) surrounded by desmoplastic stroma (DS), fat cells (FC) and luminal calcification (LC), the square will be highly magnified in the next figure, (Scale bar 100µm). (b)HP non-IBC section with DCIS, showing carcinoma cells with many cytoplasmic vacuolar degeneration (CVD) and some multiple nucleoli cells (MN) and, some pyknotic cells (PC), (Scale bar 25µm). (c)HP non-IBC section showing, invasive lobular carcinoma (ILC) sheets of malignant cells (MC) surrounded by DS, vascular calcification (VC), the square will be highly magnified in the next figure, (Scale bar 100µm). (d)HP non-IBC section with ILC, showing carcinoma cells with enlarged nuclei (EN) with many MN, (Scale bar 25µm). (e)HP IBC section showing, invasive ductal carcinoma (IDC) surrounded by DS, large vacuolar degeneration (LVD), the square will be highly magnified in the next figure, (Scale bar 100µm). (f)HP IBC section with IDC, showing carcinoma cells with CVD and many MN, (Scale bar 25µm). (g)HP IBC section showing, ILC surrounded by vacuolar degeneration (VD), stromal calcification (SC), the square will be highly magnified in the next figure (Scale bar 100µm). (h)HP IBC section with ILC showing carcinoma cells with many CVD, many MN, EN and pyknotic nucleoli (PN), (Scale bar 25µm). **HP**, hormonal positive; **IBC**, inflammatory breast cancer; **H&E**, haematoxylin and eosin.

DISCUSSION

The present clino-pathological data analysis showed the difference among the three types of average values, where the mean value is a mathematical average, the median value is the middle value after the ascending order of selected patient data, and the mode value is the most common result among selected patient data[34].Our results showed that the average age and middle age for the selected patients and the most common age for breast cancer patients was 50 years old, and this result might agree with Sripan *et al*, investigation, where breast cancer incidence might be increased in women aged over 40 years but not those under 40 years[35].

This study showed that the average tumor size was 1.5 fold in IBC versus non-IBC patients, and it was the same in TN BC versus HP BC patients, and it was 1.25 fold LVI-p versus LVI-n breast cancer patients, on the other hand the middle value of tumor size for selected patients was 1.25 fold in IBC versus non-IBC patients, and it was the same in TN BC versus HP BC patients and in LVI-p versus LVI-n breast cancer patients, with regard tothe most common of tumor size for breast cancer patients was 4cm in all groups, this result agree with Lee *et al*, investigations in breast cancer patients[36].

The present results showed that the average tumor grade, middle tumor grade and most common of tumor grade were grade II (G2) in all groups, and these results agree with Lee *et al.* [36], who reported that most common tumor grade was the intermediate grade of breast cancer.

The current results showed that the average nodal status number was 4 fold in IBC versus non-IBC, and 1.25 fold in TN BC versus HP BC patients and 1.17 fold in LVI-n versus LVI-p breast cancer patients, on the other hand, the middle value of nodal status was 4 fold in IBC versus non-IBC, 1-fold in TN BC versus HP BC patients and the same in LVI-n versus LVI-p breast cancer patients, with regard to the most common of nodal status was zero in non-IBC, HP BC, LVI-n breast cancer patients, and it was four in IBC, TN BC and LVI-p groups, and due to et al investigations the presence of lymphovascular invasion was significantly concomitant with metastatic axillary lymph nodes, which plays a crucial role in the therapeutic protocol of breast cancer patients[37].

IBC is diagnosed with a characteristic clinical features, but it is not considered as a specific histological subtype of breast cancer [38, 39]. Where, in the most IBC cases, the tumor is usually characterized as ductal type with the emboli consisted of pleomorphic tumor cells with high nuclear grade [28, 39].

In 2017, the American cancer society estimated 252,710 new cases of invasive breast cancer and 63,410 cases of in situ breast carcinoma will be diagnosed among women. It should be noted that, the most common form of invasive breast cancer is invasive ductal carcinoma (IDC) [10, 40], and this agree with our results in IBC and non-IBC patients, and specifically in IBC patients, the ductal carcinoma cases are the most common versus lobular carcinoma, and this agree with the recent studies of Mamouch, Berrada [29] of diagnostic pathological criteria in the population of North Africa and African-American women.

There are few studies which have previously reported the characteristics of lobular histology in IBC, our study counts the ratio in those histological cases for the Egyptian breast cancer patients in both IBC and non-IBC, and it represents about 5% of IBC and 8% of non-IBC as invasive lobular carcinoma (ILC) of all our studied cases. These agree with Raghav, French [28] investigations of IBC patients in USA. Whereas, numerous researches show patients with ILC have better long-term outcomes than patients with IDC [41, 42], this histologic distinction between IDC and ILC is also considered a response predictive to therapy, where ILC is characterized by fewer pathologic response rates to chemotherapy [42].

Bertucci, Finetti [39] investigations showed that distinctive genes between IBC and non-IBC are associated with cellular processes concerned to cell motility, signal transduction,

adhesion and angiogenesis. Therefore, further studies into the molecular profile of IBC is needed to identify the tumor biology and to determine the potential role of those biological markers in IBC pathogenesis [(43)].

Conclusion

Statistical analysis of breast cancer clinicopathologic data might help in improving of cancer treatment strategies.

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معاير أنواع سرطان الثدى مقارنة بالبيانات الإكلينيكيةالمرضية

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المستخلص

يعتبر سرطان الثدى ثاني أكثرحالات الإصابة بالسرطان شيوعًا بين النساء، الا انه توجد اختلافات بين حالات سرطان الثدى من الجوانب البيولوجية والتشريحية المرضية النسيجية، مما يؤدى الى استجابات علاجية مختلفة، تحتاج الى تغييرات فى الاستراتيجيات العلاجية.تهدف هذه الدراسة الى التمييز بين حالات مرضى سرطان الثدى بناءا على المعايير البيولوجية الجزيئية و الجوانب التشريحية المرضية النسيجية، من حيث سرطان الثدى الالتهابى (IBC) أو غير الالتهابى (Non-IBC)، ومن حيث سرطان الثدي الإيجابي لمستقبلات الهرمون (HP BC) أو سرطان الثدي ثلاثي السلبية (TN BC)، وأخيرا من حيث انتشار سرطان الثدى الى الأنسجة اللمفاوية الوعائية (LVI-p) او عدم انتشاره (LVI-n).

يضم هذا البحث 78 حالة من النساء اللاتى تم تشخيصهم مسبقا بانهم مرضي سرطان ثدى بناءاً على المعاييرالمرضية والنسيجية والاستجابات البيولوجية الجزيئية للتمييز بين حالات سرطان الثدي في العينات النسيجية ، ثم تم عمل عرض إحصائي لبعض الصفات التشريحية والجزيئية لكل مجموعة. أوضحت النتائج ان متوسط العمرالأكثرشيوعًا في حالات مرضى سرطان الثدي هو 50 عامًا،أما بالنسبة الى حجم الورم في حالات IBC و TN BCوLVI-p فهوه أعلى بشكل ملحوظ عنه فى حالات Non-IBC وHP BCوLVI-n، في حين ان مستوى الورم الأكثرشيوعًاهوالمرحلة الثانية G2 فى جميع حالات مرضى سرطان الثدى،اما بالنسبة الى مستوى وصول انتشار الورم الى العقد اللمفاوية فهو أعلى بشكل ملحوظ في حالات IBC و TN BCعنه فى حالات Non-IBC و HP BCعلى نفس الترتيب، ويتم تشخيص 95 ٪ من حالات IBC و 87 ٪ من حالات Non-IBC على أنهاحالات سرطان القنوات المنتشر (IDC)،و 5 ٪ من حالات IBC و 8 ٪ من حالات Non-IBC يتم تشخيصها على أنها حالات سرطان فصيصي منتشر (ILC).

ووفقا لما اظهرته هذه الدراسة فان التحليل الإحصائي للمعاييرالبيولوجية المرضية والنسيجية لحالات مرضى سرطان الثدي قد يساعد في تحسين استراتيجيات العلاج الخاص بكل حاله من حالات سرطان الثدى.