Review article

Histological grade and Breast Cancer – are we using it right?

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ABSTRACT:

Breast cancer is the most common malignancy among women all around the world. There is geographical variation in the relative rate from one country to the other, Breast cancer is the most common malignancy among women all around the world. there is geographical variation in the relative rate from one country to the other, nevertheless it remains at the top. Not only it is the top most cancer among females but it is also the leading killer and the oldest known disease among women.

Introduction

Breast cancer is the most common malignancy among women all around the world (1-3). However there is geographical variation in the relative rate from one country to the other, nevertheless it remains at the top. Not only it is the top most cancer among females but it is also the leading killer and the oldest known disease among women. The history of breast cancer is as old as of human being which can be evidenced by the oldest books on medicine, written in different ages like Nei Jing; written by Huang Di Chinese Emperor in 2698 BC [(4)]. The oldest description of the breast cancer was given by Edwin Smith, written on Papyrus leaves in Egypt in 1600 BC (5)who described it as the bulging lump, cool to touch, having no treatment. In the period of Greeks the Hippocrates linked breast cancer with cessation of menstrual cycle in today's terminology menopause(6) . Major milestone in the history of breast cancer is the discovery of the lymphatic system in 1650s by Jean Pecquet, Thomas Bartholin and OlofRudbeck and another is the association of hormonal factors with the development and progress of the cancer by George Beaston in 1896 when he demonstrated the remission of the cancer after oophorectomy (5). Subsequently the discovery of oestrogen receptors in 1962 by Jenson & Jacobson, and identification of genetic mutations have added in the understanding of the disease[(6)].

The realisation of the importance of the understanding of the breast cancer biology also dates back to the

centuries ago, when the medical scholars and treating physicians observed that patients of the same age group and similar clinical parameters of the tumours behave so differently that with even minimal treatment survive almost natural life span while others with maximum possible aggressive treatment die within a short period of time(7). This realisation made them study inside of the tumours. This understating improved step by step, first the scientists noticed that morphological differences in terms of the histological type and grade and further advanced to the more sophisticated molecular and genetic differences(8, 9). Recent advances in the understanding of the disease have greatly improved survival. This improved understating of the biology has resulted in the development of more targeted therapy such as use of hormonal therapy in oestrogen receptor (ER) positive patients and trastuzumab in patients having Human epidermal growth factor (HER2)-2 positive(10, 11). The understanding of the biology of the disease therefore remains the fundamental to the oncologists dealing with the disease.

Histologically breast cancer arises from the duct cells or the lobular cells, thus the basic histological types of breast cancer are named after these cells of origin(12). Further specialised types of cancers are also seen but usually perceived as variants of ductal carcinoma. These cancer types include no special type, mucinous, papillary carcinoma, tubular and tubular mixed, comedo carcinoma etc. Breast cancer has potential to disseminate away from the breast, resulting in the metastases spread to lymph nodes and systemic spread to bone, liver, lung and brain. In order to identify the cases at highest risk of distant metastases a number of histopathological, molecular and genetic factors have been studied resulting in basic prognostic index such as Nottingham Prognostic index or more sophisticated such as Oncotype Dx are in practice. Given the economic burden associated with high tec analysis it is important to identify some economic tool. Grade could be one of those.

Histological grade of breast cancer

Histological grade of the breast cancer is the degree of differentiation of the tumours cells define in the terms of mitotic count, nuclear pleomorphic and the tubular formation. It was given by the Scarff-Bloom-Richardson in 1957, which was then modified by the Eliston and Elis in 1991[1,2]. The Eliston Ellis modification of the histological grade of the breast cancer is also known as Nottingham histological grading system. The Eliston Ellis modification of the histological grade considers three components of the tumour cells including tubule formation, mitotic count and the nuclear pleomorphism in a specified field, cumulative score of these three components is then considered as the tumour grade[2]. Figure 1 summarises the grading system of the breast cancer. Grade I is the well differentiated tumour while grade III is the poorly differentiated tumour. Biologically they pose different characteristics, their growth rate is also different, where poorly differentiated tumours show high rate of growth, resulting in poor prognosis.

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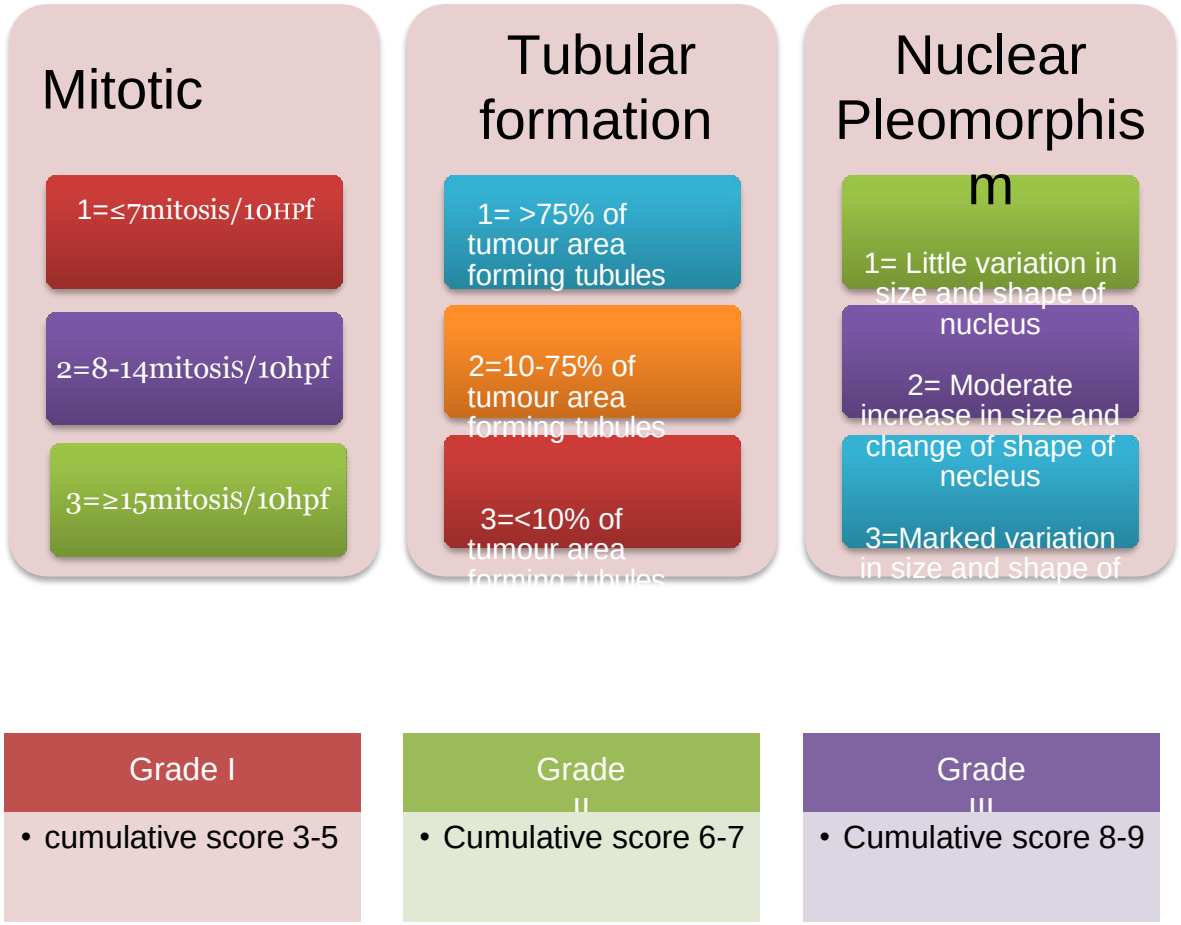

Figure.1. Histological grade of breast cancer

Correlation between the histological grade and the doubling time of tumour cells

The cell doubling time is the duration of the cell required to divide (ie mitosis). Figure 2 shows log of the doubling of cells in the cell division. The cell divides in log manner. One cell divides into two, two into four, four into eight, eight into sixteen and so on. The cells when divide at 20th time the theoretical number of cells would be around 1million and the clump of this number of cells make a mass of 1 mm[3]. When these cells divide 30 times they make a mass of 1 cm[3]. However in tumours all cells do not divide at one time. Some remain at resting stage for sometime before they enter into cell division again. Tumours with increased mitotic count and shorter interval between mitosis increase in size quickly.

When tumours have adequate blood supply the cells can divide at almost constant rate and also the supply of the activators of the cell growth such as oestrogen and progesterone e.g rapidly growing tumours have high mitotic count, shorter mitotic interval and reached to palpable stage quickly. The grade I tumours having <10% mitotic count show low growth rate because only 10% of cells dividing thus the increase in the size of the tumour takes longer duration as compared to the tumours having >75% of cells dividing. The study by Mehara et al analysed computer simulated doubling time to assess tumour growth rate. They used doubling time of the cells[4]. They measured tumour at day 1 and 200[4]. They concluded that the doubling time is not the sole predictor of the growth rate. Here again comes the theory that the tumour mass has heterogeneous pattern of cells. Some divide rapidly some at slow rate and at the same time some cells may be lost. Thus the increase in the size of tumour takes into account all these factors. However if 75% of cells are dividing and a constant rate of 10% are lost even then 65% of cells will increase in number with each cell division making the tumour mass grow rapidly as compared to the tumour where only 10% of cells are dividing and 5% of which are lost during that period.

Practical example is of the ER positive tumours (where majority show low grade tumours) in older women where great majority present with low grade and show very slow growth rate. Sometimes it may take years to increase in size. In contrast triple negative breast cancer in younger population where majority show high grade of tumours grow rapidly and show a poor prognosis. The rate of mitotic count and average doubling time of the tumours have potential to accurately predict the growth rate of the tumours (Figure 3.).

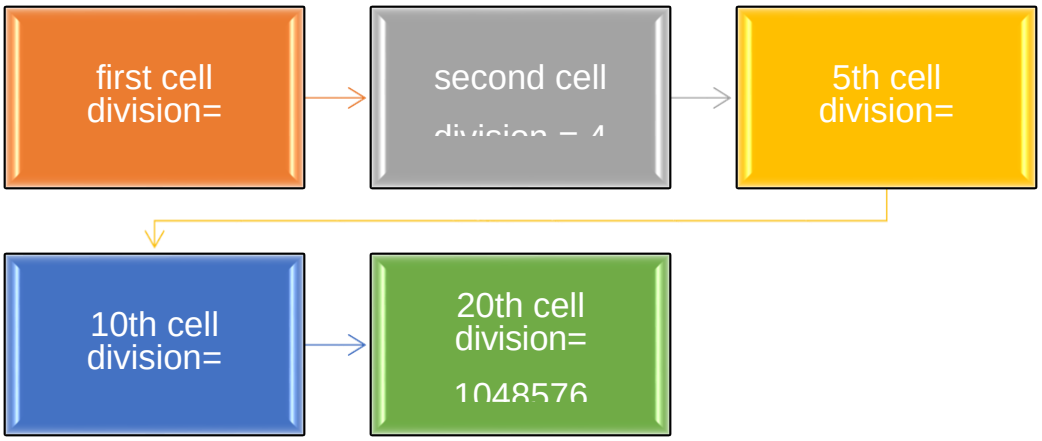

Figure 2. Log of the cell division pattern

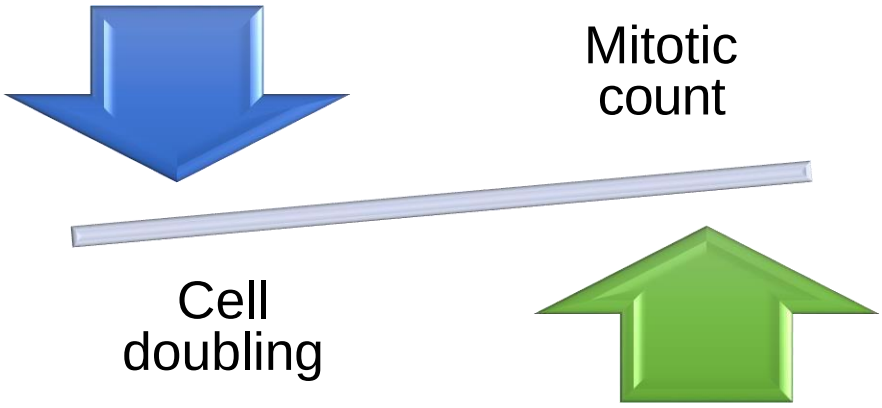

Figure 3. Relationship of the mitotic count with the cell doubling time in correlation with the tumour growth

Prognostic and predictive significance of grade in Breast cancer

Overall there is predominance of Grade II and the Grade I & III remain at the nearly similar pattern(13, 14). The studies have reported change in the pattern of grading distribution with age. In young patients there is predominance of the aggressive tumours with (ie. Grade III) while with advancing age there is change in the pattern and there is predominance of the less aggressive

phenotype (ie grade I & II). As a result of change in the demographic characteristics of the breast cancer in different continents, African and Asian national have predominance of younger age group resulting in majority of high grade tumours.

The SBR grading system was known for years but couldn't get acceptance as the prognostic factor in breast cancer due to lack of reproducibility and high level of subjectivity. However Eliston Ellis modification was tried on a large Nottingham/ Tenovus series (N=1831) with operable primary breast cancer in patients

<70 years of age(15, 16). This series was aimed to analyse prognostic factors in breast cancer. The Nottingham tenovus series analysis showed that tumour grade is the strong prognostic factor which differentiates between the patients enjoying better survival and those who develop progression of disease early. As a result histological grade was also included in the Nottingham Prognostic Index. A number of studies then followed and tested prognostic significance of the histological grade(17-19). The histological grade has even maintained it prognostic significance in the modern era of the genetic testing. In other words it wont be wrong if we say that the morphological pattern in terms of grade in a way represents molecular and genetic pattern of the tumours. However with advancements in the management and targeted therapies the survival has improved though categorical distribution among the grade ranks remained the same. There is also indirect relation of the grade with the prognosis in terms of direct relationship with poor prognostic factors such as the S-phase fraction and Ki-67 and inverse relation with good prognostic factors such as hormone receptor status(14, 20).

Histological grade represents cell differentiation and the rate of growth. Thus theoretically it can predict response to the therapeutic agents which act on dividing cells such as cell cycle specific chemotherapy ie methotrexate(21). Technically it is not appropriate to assess the predictive response of a therapy when tumour is being removed. Once tumour is removed there are a number of confounding factors which may affect the predictive value of the histological grade. Chemotherapy on the other hand is the systemic therapy indicated as neo-adjuvant (before surgery) in locally advanced breast cancer, Adjuvant (after surgery) in operable primary breast cancer or as primary therapy in advanced cancer. There are different groups of cancer chemotherapy drugs classified on the basis their pharmacological groups or their mechanisam of action. A summary of the drugs used in breast cancer is given in figure 4. On the basis of their phamocological groups they are divided as cell cycle specific and non specific drugs. The cells have mixed pattern of cells having some cells dividing and others are at resting state. Thus a mixture of both group is given. Cell cycle specific chemotherapy affects the cells dividing actively. These drugs act on the cells in the log manner such that 50% of the dividing cells will be killed by one cycle. These drugs include fluorouracil, Methotraxate, Paclitaxil and docitaxel. Thus these drugs would ideally be useful for high grade tumours. Cell cycle non specific chemotherapy affects resting cells. These drugs include cyclophosphamide, Epirubicin and Doxorubicin. Low grade tumours can get maximum benefit from this group of drugs.

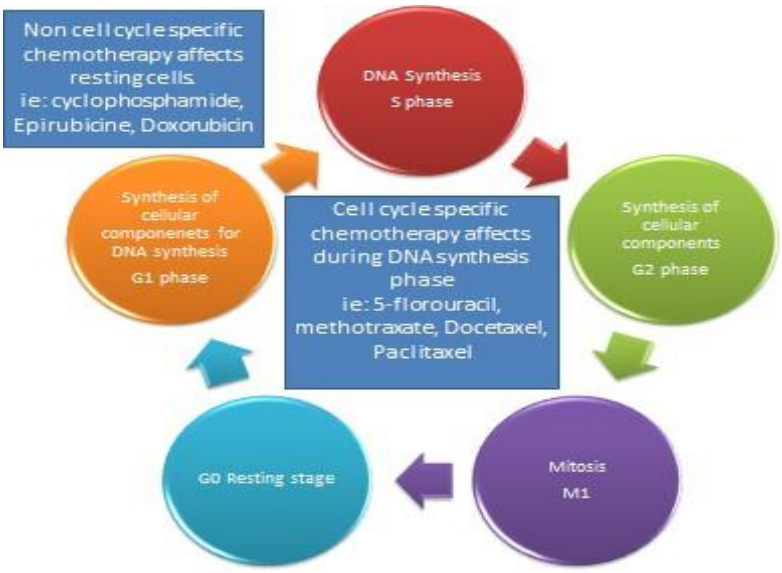

Figure. 4. Chemotherapeutic agent groups in relation to cell division

Conclusion

Histological grade of the breast cancer is not merely a morphological feature of the tumour but it portrays a whole spectrum of the molecular architecture of the tumour. Thus have potential to predict survival and role of different therapeutic agents. Further exploration of the factors governing histological grades need further exploration.

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