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Mini-Review Article

Current Approaches to Diagnosis and Treatment of Breast Cancer and Future Directions

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Introduction

Breast cancer is the most common cancer in women worldwide (GLOBOCAN 2012) (1). It is estimated that over 2 million new breast cancer (BC) cases are diagnosed worldwide and over 600,000 women would die of the disease annually [1, 2].

The gold standard for the diagnosis of any concerning breast lesion involves a triple assessment protocol, including clinical examination, radiologic imaging and confirmatory tissue diagnosis. Clinical examination is important in assessing patients presenting with palpable abnormalities. It should include assessment of the axillary and clavicular lymph node (LN) basins. Screening mammography is the most common method of detecting BC [3-6]. Breast tomosynthesis, also called three-dimensional (3-D) mammography and digital breast tomosynthesis (DBT), is an advanced form of breast imaging, or mammography, that uses a low-dose x-ray system and computer reconstructions to create three-dimensional images of the breasts. Breast tomosynthesis aids in the early detection and diagnosis of breast disease. Ultrasound and MRI are additional imaging modalities that are also routinely used for diagnosis. In a large, randomized controlled trial comparing screened versus unscreened populations in Sweden, mammography was estimated to reduce BC mortality by approximately 30%. This is similar to the estimates in the United States based on 30 years of data [7]. The United States Preventive Services Task Force USPSTF now recommends that only women aged 50 to 74 years undergo a screening mammogram every 2 years [8,9].

Appropriate tissue diagnosis can be achieved via fine needle aspiration, core needle biopsy or by open biopsy or lumpectomy. Currently, fine needle aspiration is no longer recommended in many institutions, as it does not demonstrate tissue architecture and precludes pathologists from differentiating preinvasive from invasive disease. Nowadays core needle biopsy is the standard approach used for diagnosis [10,11].

Pathology

Breast cancer is a heterogeneous disease encompassing various entities with distinct morphologic features and clinical behaviors. This diversity is the result of distinct genetic, epigenetic, and transcriptomic alterations. In order to categorize this heterogeneity and standardize the language, BC classification systems have been developed. These classification schemes have evolved over many decades into a valuable tool that is used to aid in treatment and prognosis. Breast cancer can be broadly categorized into non-invasive (in-situ) and invasive (infiltrating) carcinomas [12-15]. Breast carcinoma in situ is further sub-classified as either ductal or lobular. Cell types, growth patterns and cytological features form the basis to distinguish between the two types. Ductal carcinoma in situ (DCIS) is considerably more common than lobular carcinoma in situ (LCIS) and encompasses a heterogeneous group of tumors.

DCIS has traditionally histologically been further sub-classified based on the architectural features of the tumor which has given rise to at least five well recognized subtypes including Comedo, Cribriform, Micropapillary, Papillary and Solid variants [12,13].

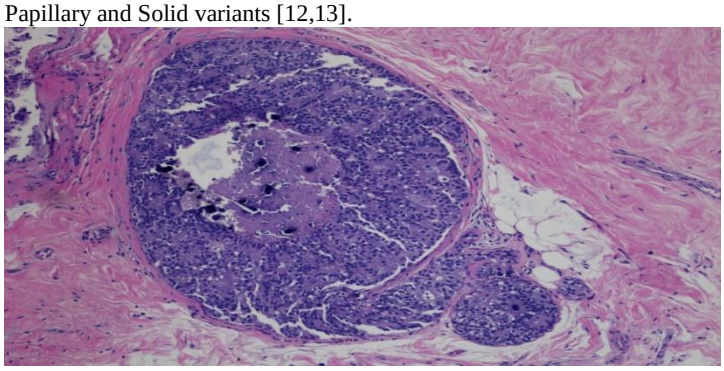
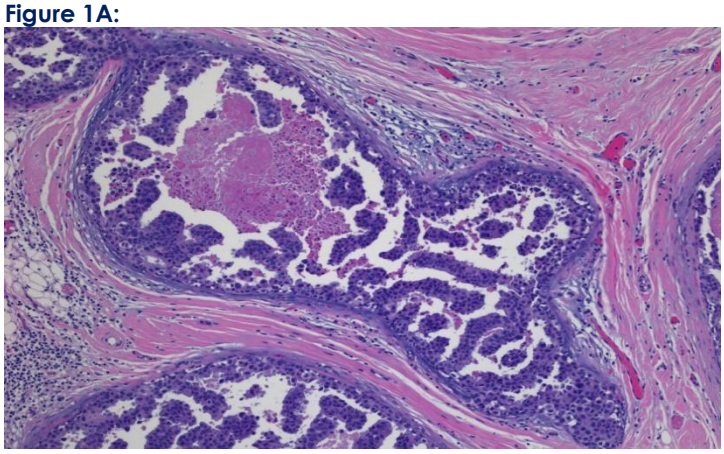


Figure 1A:



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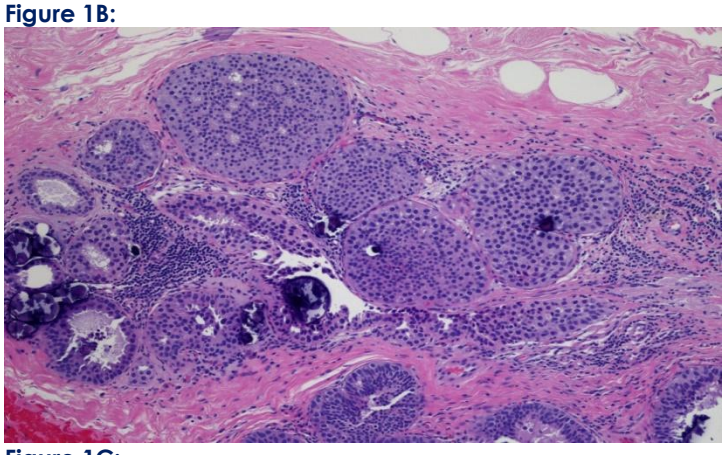

Figure 1C:

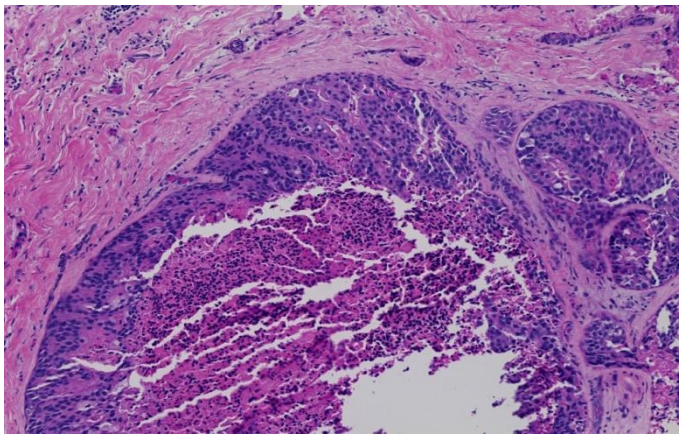

Figure 1D: Representative examples of ductal carcinoma in-situ.

Figure 1A shows a cribriform DCIS with calcification and central necrosis. B show a micropapillary pattern. Solid pattern is identified in C and high-grade DCIS with Comedo necrosis in D (Hematoxylin and eosin, magnification x10).

Similarly, invasive carcinomas are as complex and as heterogeneous as their DCIS counterparts. They are differentiated into various histological subtypes, some with well characterized histologic features while the majority remain to be of no special type [12-15]. The major invasive tumor types include infiltrating ductal, lobular, mucinous (colloid), tubular, cribriform, medullary, squamous and papillary carcinomas (Figures 2 and 3). Examples of rare types include apocrine, metaplastic, secretory, hypersecretory, glycogen-rich, lipid-rich, adenoid cystic and small cell neuroendocrine carcinomas. Of these, infiltrating ductal carcinoma (IDC) is, by far, the most common subtype accounting for 70–80% of all invasive lesions (Figure 2).

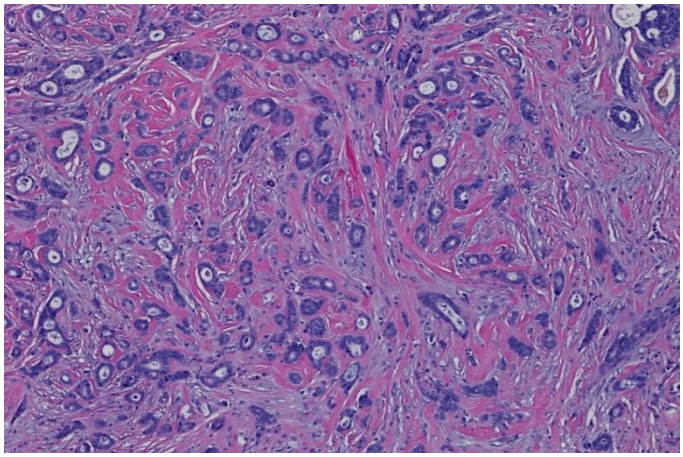

Figure 2A.

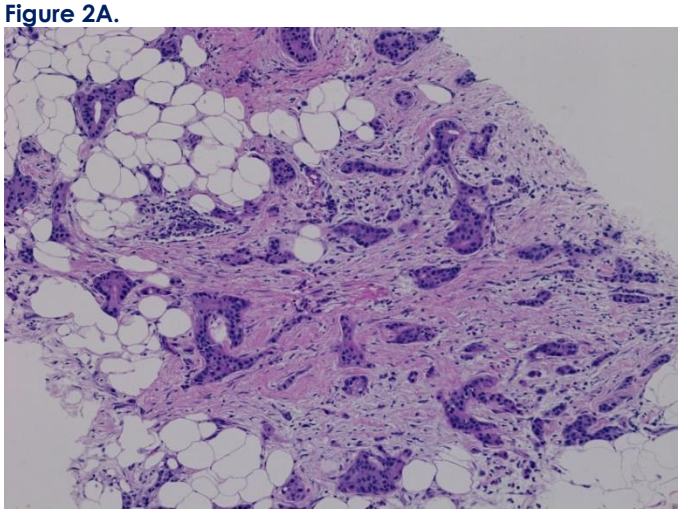

Figure 2B:

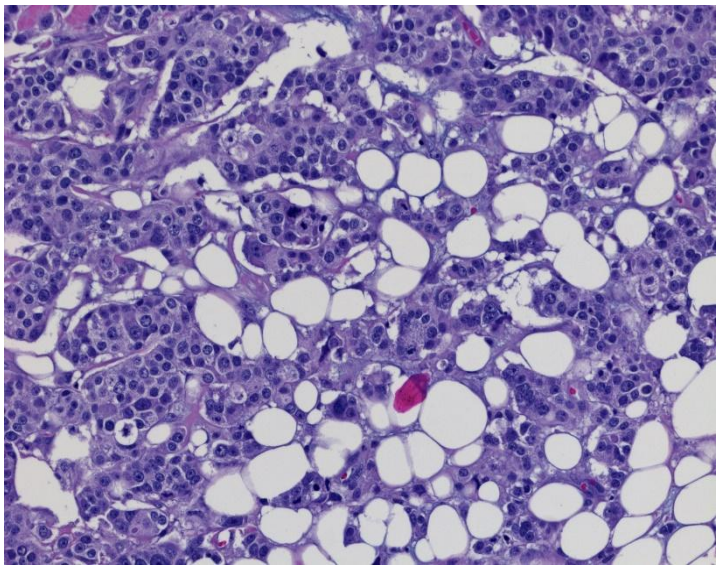

Figure 2c: Representative examples of invasive ductal carcinoma with different histologic grades.
A well differentiated ductal carcinoma in A, moderately differentiated carcinoma in B and poorly differentiated carcinoma in C (Hematoxylin and eosin, magnification A: 10x, B and C: 20x).

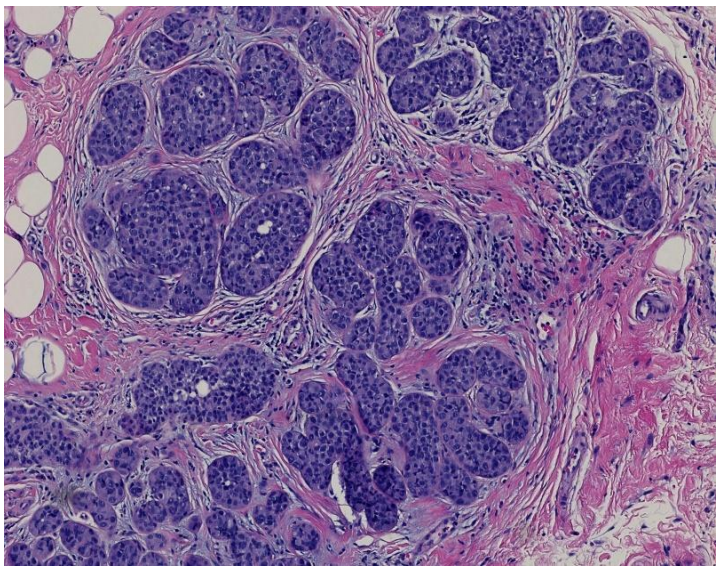

Figure 3A:

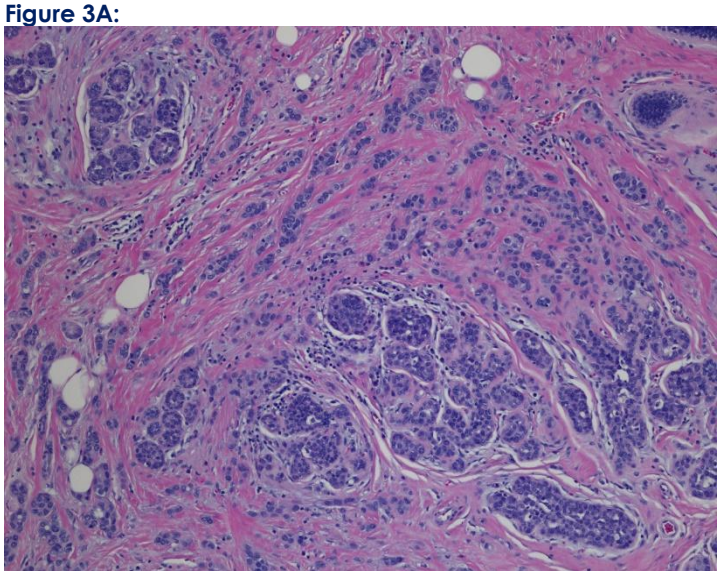

Figure3B: shows lobular carcinoma in situ and Figure 3B

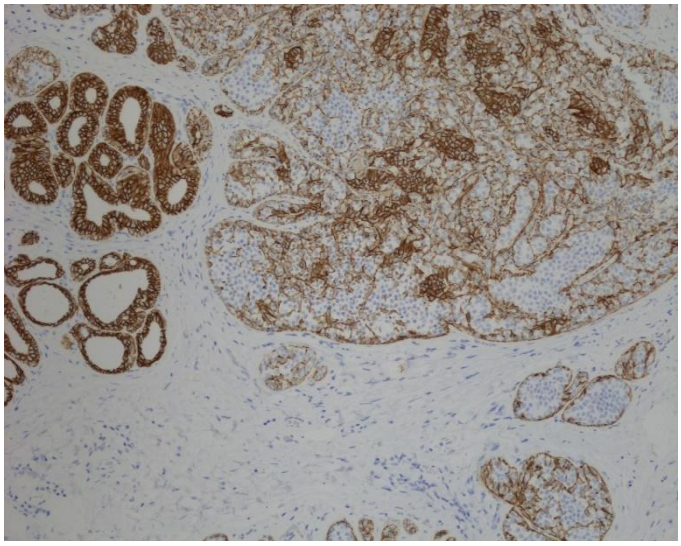

Figure 3C: where lobular carcinoma in situ is negative for the marker (Immunostain, magnification x10).

Representative examples of lobular carcinoma. Figure 3A shows lobular carcinoma in situ and Figure 3B shows invasive lobular carcinoma next to foci of lobular carcinoma in situ (Hematoxylin and eosin, x10). E-cadherin immunostain is shown in Figure 3 C where lobular carcinoma in situ is negative for the marker (Immunostain, magnification x10).

Histologic grading

Breast cancer are graded into three grades (I-III) according to the Nottingham modification of Bloom-Richardson system (SBR) based on the cytologic features evaluating nuclear size and degree of nuclear hyperchromasia and pleomorphism, growth pattern evaluating the extent of glandular/tubule formation and mitotic activity (16-18). Each of these three elements is assigned a score on a scale of 1 to 3 with a final grade determined by the sum of the three scores: where grade 1 well differentiated tumors have a score of 3-5, grade two have a score of 6-7 and grade 3 have a score of 8-9.

Unfortunately, the above described system, albeit it is the only accepted grading system accepted, lacks precision in assessing all three parameters including nuclear grade, mitosis and tubular formation, leading to an element of subjectivity with significant interobserver variability. Furthermore, it was not suited for grading in situ lesions or the other non-ductal invasive carcinoma types. Several investigators have attempted to improve the accuracy of grading BC for better correlation with prognosis and survival. Our group has recently proposed a new grading system including the routine evaluation of nuclear features combined with automated proliferation index (N+P) system], using a digital imaging system, eliminating the growth pattern of tumor for better representation of tumor biology. Similar to the SBR grading system, each of the nuclear and automated proliferation index components was assigned a score on a scale of 1 to 3 with the final grade determined by the sum of the two scores. The automated MIB-1 count was likewise scored into three categories: score 1:≤9%, score 2:10-25%, and score 3:> 25%. This system has the advantage of being used for not only invasive ductal carcinomas, but for all other invasive carcinomas, including lobular, other special type carcinomas and non-invasive carcinomas [19-21].

Our studies compared the N+P system with the SBR grading system and correlated them with a variety of clinicopathological parameters including patient's overall survival, tumor size, angiolymphatic invasion, LN status, and biomarker status including estrogen receptor (ER), progesterone receptor (PR), p53, epidermal growth factor receptor, BCL-2 and Her-2. Although there was an agreement between the two systems with histologic and prognostic parameters studied, there was 37% disagreement when grading individual tumors. Fifty-three percent of SBR grade II tumors were "downgraded" to N+P grade I, and 7% were "upgraded" to N+P grade III.

Distinction among the different histologic grades for overall survival curves was better indicated by N+P than SBR grading systems [19-21].

Molecular Classification

The underlying basis for the development of malignancy is a series of genetic mutations resulting in dysregulation of normal cellular replication resulting in the ability of uninhibited cell growth and tumor formation. In BC, a number of important genetic mutations have been discovered that characterize tumor biology. This molecular characterization confers information about how aggressive a tumor is, which has important prognostic implications. Further, knowledge of the mechanisms that provide a survival advantage for the tumor has led to the development of agents targeted to these pathways resulting in tumor cell death. Most notable in the case of BC are the development of drugs against the ER and Her2 receptors, which are overexpressed in some tumors. The estrogen receptor was the first molecular marker discovered to have a role in breast cancer. This receptor became important clinically with the discovery of the therapeutic benefit of selective estrogen receptor modulators (SERMs), such as tamoxifen and raloxifene in reducing BC recurrence in tumors with ER positivity. Aromatase inhibitors were later introduced after SERMs as another effective therapy for decreasing estrogen in postmenopausal women.

Recently, proposed classification schemes used gene expression microarray analysis, to categorize BC phenotypes based on their molecular features. The purpose of these classification systems is to facilitate identification of tumor markers that may serve as indicators of prognosis and potentially as therapeutic targets. Breast cancers are categorized into at least five major molecular subtypes: luminal A, luminal B, normal breast like, Her2, and basal-like (BL) Figure 4. Representative examples of immunostains for invasive breast carcinomas positive for estrogen receptor in A, progesterone receptor in B and Her2 in C (magnification, x10). (Figure 4) [22-31]. However, the utility of such assignments of molecular subtyping, especially the BL subgroup, also known as triple negative tumors (ER, PR and Her2 negative), has generated much interest and has been called into question by scientists, pathologists, and oncologists alike.

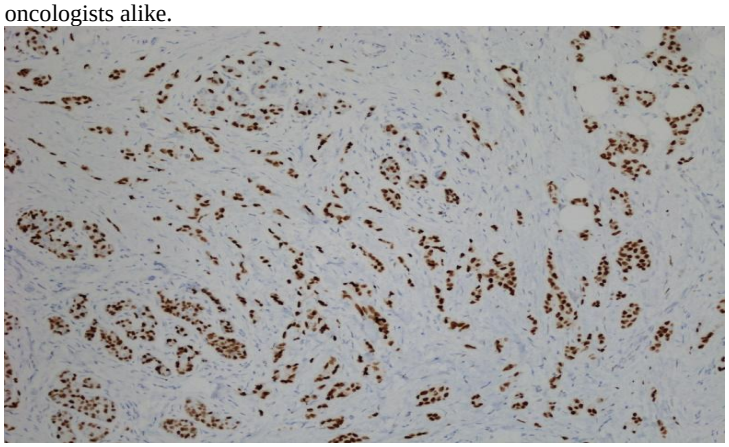

Figure 4A:

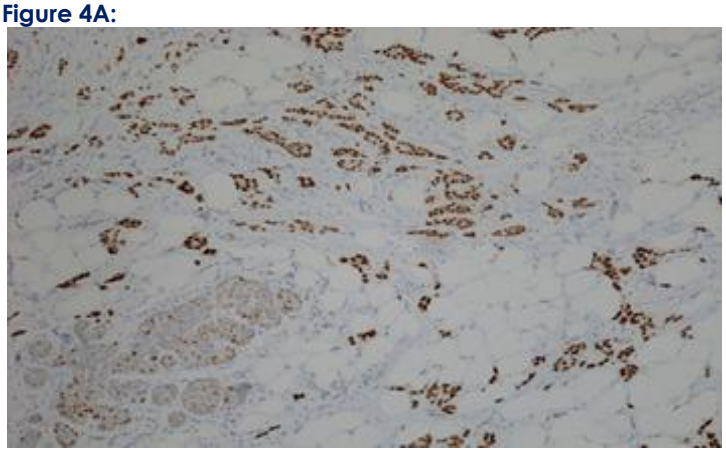

Figure 4B:

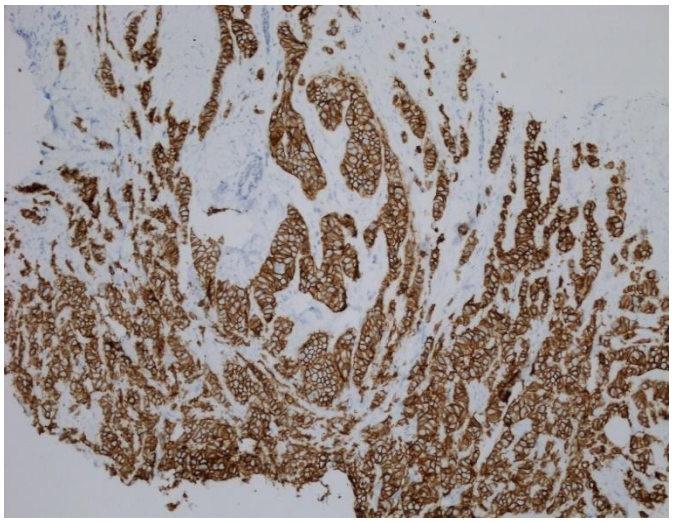

Figure 4C:
Representative examples of immunostains for invasive breast carcinomas positive for estrogen receptor in A, progesterone receptor in B and Her2 in C (magnification, x10).

Triple-negative (TN) tumors are highly aggressive, rapidly growing, hormone-unresponsive tumors that tend to be diagnosed at a later stage, affect younger women, and are associated with shorter overall survival. TN tumors have recently been shown to be molecularly, pathologically, and clinically a heterogeneous subgroup, although the majority are BL [24,29].

Treatment

Treatment of breast cancer has evolved over the years. Currently treatment strategies are tailored for each patient based on her clinical status and the characteristics of that particular patient and her tumor. Options varying from using a single treatment modality to various combinations of surgery, chemotherapy, radiation, hormonal therapy and/or immunotherapy [31,32]. Factors such as patient's age and general health status, as well tumor characteristic including type, histologic grade, burden, location, size, number of lesions, extent of nodal involvement and biomarker and genetic status should be taken into consideration before recommending treatment options.

Surgical options have undergone tremendous changes over the last several decades. Since its introduction by Halstead, radical mastectomy was the only treatment option provided. Later on, breast conserving surgeries were introduced such as simple mastectomy, modified radical mastectomy, partial mastectomy, segmental mastectomy, quadrantectomy, lumpectomy and skin-sparing and nipple-sparing mastectomies allowing for reconstruction with artificial implants [33-35]. Metastatic involvement of LNs is the single most important prognostic factor in BC exclusion and inclusion criteria are essential for diagnostic precision, accurate prediction and overall improvement of patient care. The traditional axillary LN dissections were quickly replaced by sentinel node procedures significantly reducing morbidity and treatment cost for early stage BC patients.

Radiotherapy is used in early BC after breast conservation surgery and in locally advanced BC patients post mastectomy. Breast radiation is an integral part of breast conserving surgery. Postoperative radiotherapy is strongly recommended following surgical excision [36-38]. Whole breast radiation therapy alone reduces the 10-year risk of locoregional and distant recurrence by 15% and the 15-year risk of breast cancer-related mortality by 4%. Boost irradiation gives a further 50% relative risk reduction. Many radiation techniques are currently utilized to treat patients with the goals of maximizing treatment of the targeted lesions and minimizing risks to surrounding organs. Three-dimensional conformal radiation therapy (3DCRT) with/without wedges or field-in-field method, intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), hybrid technique, helical tomotherapy, and Tomo direct are examples of proposed radiation treatment options for BC patients in the literature.

Similar to surgical and radiation modalities, major advances in chemotherapy for BC has led to a significant decrease in mortality rate from BC in the last decade. Many challenging factors such as tumor stage and characteristics including hormonal status, Her2 status and molecular type dictate among others the choice of specific chemotherapeutic agents. Luminal BCs, also known as hormone receptor positive represent the vast majority (60-70%) of BC cases.

Endocrine therapy with agents such as tamoxifen, aromatase inhibitors is the mainstay for treatment. Additional agents such luteinizing hormone-releasing hormone analogs and selective estrogen receptor degraders (fulvestrant) could be used for patient's refractory to the other hormonal therapies. Anti-Her2 monoclonal antibodies such as trastuzumab, epratuzumab are targeted therapeutic agents for treatment of Her2 positive BC either alone or in combination with other traditional chemotherapeutic agents.

Novel targeted therapies

Unlike hormone positive and/or Her2 positive BCs, the TN molecular type is the most difficult to treat. For years standard chemotherapy with conventional cytotoxic agents such as taxanes, anthracycline, alkylating agents such as cyclophosphamide and platinum drugs remained as the only therapeutic options for such aggressive form of the disease. Over the past few years, with the better understanding of the biologic heterogeneity of BC, recent advances have been made in the discovery of new targeted drugs that are very promising. Many clinical trials are underway investigating several promising agents. Drug combination such as poly(ADP-ribose) polymerase (PARP) inhibitors tor carboplatin to standard chemotherapy, anti-angiogenic agents, EGFR inhibitors and src inhibitors are promising cancer therapeutic agents. Perhaps nothing as intriguing as the concept of immunotherapies nowadays.

Programmed cell death ligand 1 (PD-L1) encoded by the CD272 gene on chromosome 9, is a 40kDa transmembrane protein that is expressed on a variety of normal cells including NK cells, macrophages, dendritic cells, B cells, epithelial cells and endothelial cells. Recent data suggest that the PD-1 pathway may be an active immune checkpoint in a variety of cancers [39-43]. Normally when the immune system detects cancer cells it activates cytotoxic T cells. Once the T cells are activated, they infiltrate the tumor microenvironment, recognize the tumor cells and starts killing them. Targeting the PD-1/PD-L1 pathway may prevent inhibitory T-cell signaling and reactivate T cells to mediate tumor killing. A growing body of evidence has clearly shown that certain "immunogenic" tumors that overexpress PD-L1 can evade destruction by the immune system. PD-L1 has been reported to be expressed on tumors cells and stromal tumor-infiltrating immune cells (ICs). Few studies have evaluated the expression of PD-L1 in BC [44-46]. While BC is one of the less immunogenic cancers, some data suggest that the PD-1 pathway might be active in certain subtypes. PD-L1 expression was shown to be increased in TN/BL breast cancer cells. Breast cancers infiltrated by PD-1 positive ICs was associated with worse survival in Luminal B and triple negative BC types. Recent studies suggest that PD-L1 positive BCs were associated with more aggressive features including younger age at diagnosis, large size cancers, LN positivity, ER negativity and distant recurrence. Paradoxically the PD-L1 positive BCs were associated with significantly improved survival.

While this is an exciting time for immunotherapy, we are still far from understanding the exact relationship between PD-L1 expression by ICs and cancer cells and other immunologic features of the breast tumor microenvironment. We, and others, have previously shown that the value of PD-L1 detection by immunohistochemistry as a valuable marker is confounded by many unresolved issues such as different detecting antibodies, different staining protocols and platforms and different cutoff points in addition to variable tissue preparations and variable tumors with different characteristics. Our recently published study has shown an excellent agreement between the three PD-L1 antibodies, including Dako (22C3), Ventana (SP263) and BioCare antibodies, with highly significant Kappa values ($p \leq 0.001$) (47). PD-L1 expression was more likely to be associated with higher tumor grade, TN molecular subtype, hormone negative and highly proliferative tumors ($p < 0.001$) (9).

Given the high concordance, it is not surprising that all three antibodies demonstrated the same associations with all pathologic and clinical parameters studied. Thus, as in the case with quantitation of PD-L1 in lung cancer and melanoma, pathologists might have the option of utilizing less expensive reagents for the evaluation of this marker in BC. It is inconceivable to perform a unique FDA-cleared assay for each marker and disease following the recommendation of certain biopharmaceutical-sponsored or investigator-driven study. Indeed, many investigators have recently recommended an urgent need to harmonize approaches for PD-L1 testing independent of biopharma for realistic economic and practice expectations in PD-L1 assessment for targeted therapy.

In our second manuscript we explored the expression of PD-L1 in tumor cells along with the expression of CD3, CD4, CD8, CD20 and CD68 markers in tumor microenvironments of a cohort of patients with matched primary BC and metastatic disease in regional LNs (48). Expression of the different markers was be correlated with several clinical and pathological parameters. There was 100% agreement for PD-L1 expression on tumor and ICs between BC and matched LN. PD-L1 is differentially expressed in primary BC and regional nodal disease. Expression correlated with higher grade, hormone receptor negativity and highly proliferative tumors ($p < 0.001$). In LNs, the high positivity rate was driven by TN status (70% vs 5%) ($P<0.0001$). In contrast, there was significantly near total absence PD-L1 expression in distant metastatic lesions compared to BC and LNs (2-4% in Mets vs 17-20% in BC and LN, $p=0.009$). ICs density varied in BC and metastatic tumors with predominance of CD3 and CD68 and near total absence of CD20 cells. PD-L1 expression was mainly associated with CD68 cells. There were consistent higher numbers of CD3 (CD8 > CD4) than CD20 cells in primary and metastatic tumors. Correlation of PD-L1 expression in BC and its microenvironment may be useful for development of new treatment strategies. Most of the previous studies focused in evaluating PD-1 expression in the different types of lymphocytes including CD3, CD4, CD8, CD19, CD20 and surprisingly ignoring the evaluation of PD-L1 expression in macrophages. Tumor-associated macrophages play an important role in tumor progression, metastasis and recurrence after treatment. Recent evidence suggests that macrophages are key players in PD-1/PD-L1 cytotoxic T cell signaling and activation. The potential role of macrophage derived paracrine signaling is a critical factor for effective immunotherapy. Correlating the regulatory role of macrophages and overall treatment response could lead to potential targets that could overcome resistance to immunotherapy. Our study is one of the very few that has focused on evaluated PD-L1 expression in the macrophages and correlating it's with the different histopathologic and clinical parameters.

In conclusion, we as well other investigators have successfully categorized breast cancers depending on the PD-L1 expression in tumor cells and infiltrating ICs. It might be important to test tissue for PD-L1 positivity in primary, locally metastatic and distant metastatic disease separately since there is a differential expression between the same tumors. There is tremendous potential for development of treatment strategies based on the PD-L1 expression in tumors and their microenvironment. It is hoped that we would able to identify certain types of breast cancer that has the potential of evading the immune surveillance and become successful in metastasizing. Successful identification of such aggressive primary and/or metastatic cancers would be very helpful in selecting patients for appropriate immunotherapy as well as accurate prediction and overall improvement of patient care.

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