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Symposium 4D: Advances in breast cancer

S4D-1. Pathological assessment for targeted therapy

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Breast cancer is the commonest malignancy in women with an estimated 1 million women worldwide developing breast cancer each year. It is a heterogeneous disease with multiple sub-types and varying prognosis; hence the choice of therapy is dictated by information provided by the pathological assessment. The examination of the standard H&E is still an efficient, cost-effective and powerful way of providing data to inform classification and clinical management. The pathological sub-type (tubular versus basal-like), grade (1 versus 3), size, vascular permeation and nodal status will together dictate the decision regarding endocrine, chemo and radiotherapy. None-the-less, the developments in our understanding of the molecular and cellular basis of cancer initiation and progression is providing tools for refining breast cancer taxonomy and is opening up new avenues for the targeted treatment of breast cancer. Staining for oestrogen receptor (ER), Progesterone receptor (PgR) and HER2 is becoming standard practice and increasingly gene amplification studies for HER2 have also been incorporated into the testing. These molecular tests help us to stratify breast cancers into meaningful groups for prognostication and treatment. The use of tamoxifen or an aromatase inhibitor and the addition of chemotherapy with or without trastuzumab (Herceptin) are dictated by the results of these studies. Recently, the basal-like carcinomas have been increasingly recognised. These tumours are often, though not invariably, triple negative (ER, PgR and Her2 negative). However, they are often positive for Epidermal Growth Factor Receptor (EGFR) and anti-EGFR therapies are being considered for this subset of breast cancer. Much has also been learned about familial predisposition, especially due to mutations in the BRCA1 gene. These tumours have a distinct morphology and the molecular phenotypes are suggesting novel ways to target the tumour cells. Since many BRCA1 tumours are also basal-like, it is hoped that data from these studies will also inform the management of sporadic basal-like cancers. Microarray technology, looking at the expression of thousands of genes simultaneously has been used to sub-classify breast cancer and 'signatures' for prediction of 'responsive versus non-responsive' cancers have been reported. Although much remains to be done in terms of validation, the technology holds much promise for development of novel targeted therapies.

S4D-2. In situ breast carcinoma

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In situ carcinoma of the breast is defined as a malignant epithelial proliferation that is confined within the duct space, without extension beyond the basement membrane into the surrounding stroma. While ductal and lobular carcinoma in situ (LCIS) are the two entities encompassed under this rubric, LCIS is considered as part of the spectrum of lobular neoplasia and traditionally regarded as a risk marker rather than a direct precursor of invasive disease. Recent molecular evidence however, has challenged this concept of LCIS, with some of such lesions potentially progressing to invasive lobular carcinoma. Ductal carcinoma in situ (DCIS) comprises the majority of in situ carcinomas diagnosed in the breast.

Its incidence has increased substantially with the advent of mammographic screening, but rates are becoming more stable in countries with established screening programmes. DCIS is a heterogeneous entity radiologically, morphologically and biologically, with high nuclear grade DCIS being more aggressive with a greater likelihood of recurrence and progression to invasive disease. Biological studies on DCIS have affirmed the predictive ability of nuclear grade and necrosis in its classification, yet there are still controversies in optimum management of this disease. Diagnostic challenges in DCIS include distinction from atypical ductal hyperplasia from low nuclear grade lesions at one end of the spectrum, while assessment of microinvasion in high nuclear grade DCIS may be problematic with the oft encountered distortion and stromal fibrosis that accompany. Specific and unusual DCIS subtypes such as the spindle cell DCIS may be inadvertently underdiagnosed as usual type epithelial hyperplasia. An understanding of morphologic criteria for the diagnosis of both DCIS and LCIS is needed to allow histologic recognition, in order for appropriate management to be instituted.

S4D-3. Telomerase in breast cancer

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Tumour cells have the unique ability to proliferate indefinitely, hence achieving a state of immortality. This is crucial for neoplastic progression as it allows these cells to express the aggressive properties of cancer without the censure of biogical ageing. In contrast, normal somatic cells are subject to a "mitotic clock," a phenomenon linked to telomeric shortening with each round of cell replication, so that eventually the loss of genetic material reaches a critical stage and the cells undergo senescence and death. Some cells escape this stage through mutation of "death" genes (such as p53 and RB), and continue dividing. However, with further telomeric shortening, another critical stage (mortality stage II) is reached whereby cells die. Hence, to achieve immortality, neoplastic cells have to bypass these two stages. Telomerase is a ribonucleoprotein capable of synthesizing telomeric DNA onto chromosomal ends using a segment of its RNA component as a template. It is believed that telomerase plays a key role in neoplastic cell immortalization by restoring telomere length. First discovered in Tetrahymena and other eukaryotes in 1989, it has been convincingly demonstrated in humans in 1995. Studies using the telomeric repeat amplification protocol (TRAP) assay have detected strong telomerase activity in germ cells (ovary and testis) and various tumours but weak or no activity in normal somatic tissues. It is noteworthy that telomerase activity has been detected in about 75-90% of breast carcinoma in-situ lesions, 88-94% of invasive breast carcinoma, 5-14% of tissues adjacent to breast cancer and none of normal breast tissue. Studies from the University of Malaya show findings consistent with trends above. In addition, we have found mean telomere lengths of 3.1, 1.9, 1.0 kbp for non-neoplastic breast tissues, fibroadenomas and invasive breast carcinomas respectively, supporting the concept of a crisis level of telomere shortening that triggers telomerase activation. Besides diagnostic implications, studies showing a significant correlation between telomerase activity and tumour size, lymph node status and stage have underscored the prognostic utility of telomerase assay. As the average telomere length in breast cancer cells is substantially shorter than normal tissues, the probability that telomerase inhibitors could lead to arrest and death of cancer cells without adverse effects on normal tissues, poses an attractive therapeutic approach.