E11. Controversies in classification for pathologists

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Introduction

This presentation covers three areas of controversy relating to pathological diagnosis and classification of breast cancer. Firstly the question of over-diagnosis, secondly the impact of gene expression array and protein expression technology in identification of new types or classes of breast cancer, and thirdly the issues relating to introduction of such techniques into routine clinical practice.

Breast screening and over-diagnosis of breast cancer

Breast screening detects a wide spectrum of breast cancer, ranging from microfocal low-grade ductal carcinoma *in situ* (DCIS) to large high-grade invasive cancer [1]. Detection and treatment of microfocal low-grade DCIS is considered over-treatment by some as there is evidence of slow progression to low-grade invasive cancer in only a proportion of cases. However it has been proposed that detecting some forms of *in situ* cancer, particularly high-grade DCIS, would prevent the development of high-grade invasive cancer in a similar fashion to detection of cervical intraepithelial neoplasia stage 3 (CIN3) of the cervix, which is known to prevent progression to invasive high-grade cervical carcinoma. It is well recognised that many low-grade, special invasive cancers are identified at breast screening. Such tumours have an excellent prognosis, but may be so indolent that they would never have presented clinically or have threatened the life of the patients. It has been proposed alternatively that a proportion of these low-grade invasive tumours might de-differentiate over time into more aggressive, less well-differentiated tumours, although this remains controversial. Identification and removal of such cancers when they are at a low grade would avoid such progression. Detection of high-grade invasive cancers when they are small is clearly a means by which screening could reduce breast cancer mortality. In support of this possibility, it was shown in the Two-counties trial in Sweden that histological grade 3 invasive cancers detected when less than 10 mm have an excellent prognosis, while it is widely recognised that large high-grade invasive cancers have a poor prognosis. In addition the presence of vascular invasion and lymph node metastasis, which are associated with development of metastatic disease, are rare in grade 3 tumours <10 mm, grade 2 tumours <10 mm and grade 1 tumours <20 mm, indicating that detecting tumours under a certain size should be beneficial [2].

Recognition of new classes of breast cancer

Recent high-throughput genomic studies have offered the opportunity to challenge the molecular complexity of breast cancer and provided evidence for classifying breast cancer into biologically and clinically distinct groups based on gene expression patterns [3,4]. Such new molecular taxonomies have identified many genes, some of which are being proposed as candidate genes for sub-grouping breast cancer. Such studies have been applied on a relatively small number of tumours and require validation in large series and comparison with traditional classification systems prior to acceptance in clinical practice. This can be achieved using high-throughput tissue screening tissue microarray (TMA) technology, which allows concomitant analyses of many proteins on a large number of tumour samples and provides new opportunities to examine combined protein expression profiles in breast cancer to determine their relevance and ability to challenge existing taxonomy. Recent studies have confirmed that similar classes of breast cancer can be identified using this approach and have extended this approach to identify specific new and important entities [5,6]. For example, the basal phenotype of breast cancer as defined by expression of CK5/6 and/or CK14 is associated with poor prognosis and shorter outcome in terms of shorter overall survival and disease-free interval.

Prognostic and predictive factor classification of breast cancer

The established prognostic features of invasive breast carcinoma include tumour size, lymph node stage, histological grade, tumour type and presence of vascular invasion. The disease has a markedly variable course but outcome can be predicted by use of these prognostic factors; a group of women with 'curable' carcinomas who will not receive significant benefit from adjuvant

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therapy can be identified, whilst others will succumb relatively rapidly to the disease. Because of this widely differing clinical outcome prognostic factors, and more recently predictive factors, are routinely required. In breast cancer, oestrogen receptor (ER) and HER-2 are the best, and at present the only widely applied examples of specific tests used to predict response to a specific therapy in breast cancer management in selection of appropriate treatment. With expanding knowledge of molecular biology of cancer and the availability of the Human Genome Project we are now experiencing a rapid increase in understanding of the molecular pathology of breast cancer, how it may be applied to classification, and its potential to identify molecular targets for drug development. Pathology laboratories will play a pivotal role in developing methods to assess potential efficacy based on signalling pathway changes, identify surrogate endpoints for early clinical trials, identify markers predictive of response, identify mechanisms of response, and integrate diagnostic and predictive testing into routine cancer management. The recent high-profile introduction of gene expression array and polymerase chain reaction (PCR)-based molecular assays to assist in prognostic stratification serves to illustrate the changing nature of this field and the fact that it is inevitable that new technology will find a role in routine practice [7–9]. The key issues at present with respect to such technologies are: (i) whether it can offer additional value over standard high-quality morphological and phenotypic assessment of breast cancer; (ii) reproducibility of results [10]; and (iii) how such 'research assays' can be translated into routine standardised clinical assays.

References

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