Symposia

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Molecular pathology of breast carcinomas

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The biologic and pathologic features of breast carcinomas have beer extensively studied with the goal of identifying markers that might accurately predict the clinical outcome, and or the response to anti cancer treatment of breast cancer patients. Unfortunately, the usefulness of biologic information in tumor management remains highly controversial. Indeed, the Clinical Practice Guidelines for the use of tumor markers in breast carcinoma, proposed in late 1997 by the American Society of Clinical Oncology, conclude that data are still insufficient to recommend the use of biologic markers for prognosis. When considered singly, parameters such as c-erbB-2 overexpression, p53 alteration, and hormone receptor expression appear to yield relevant information about disease progression and/or response to therapy but not enough reliable for the clinical use. For their use in association, however difficulties in interpretation arise whenever parameters of good and poor prognosis are found in the same tumor. Furthermore, many prognostic variables identified in univariate analyses as relevant for breast carcinoma lose their prognostic significance upon multivariate analyses, indicating their association to other factors with a higher prognostic power. To investigate the association between variables, we studied a large retrospective series of breast carcinoma patients using the multiple correspondence analysis, which enables graphical examination of associations among categories. By this analysis, two distinct subsets of breast carcinomas were identified. These two subsets display different clinical outcomes and different responses to chemotherapy.

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Progress in the molecular diagnostics of lymphoma

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Molecular diagnostics find two main applications in the management of lymphoma: as adjuncts to morphology and immunohistology in diagnosis, and as means to detect low level residual disease despite clinical remission.

In diagnosis immunoglobulin and T-cell receptor gene rearrangements have long been used to determine B- or T-cell lineage. With the REAL classification it has become easier to associate molecular findings with specific illnesses. CD30+ anaplastic large cell lymphoma associated with the t(2;5) carries a favourable prognosis, whilst rearrangements involving c-Myc at 8q24 suggest a more aggressive tumour type, frequently Burkitt's lymphoma. Subdivision of diffuse large cell lymphomas according to the presence of Bcl-6 rearrangements distinguishes those with more favourable prognosis. To date few studies have demonstrated prognostic significance from molecular findings alone. In most diseases it is the patterns of protein expression rather than genetic alteration which provide the best prognostic information.

Extensive studies of consistent chromosomal rearrangements have yielded a variety of targets for detection of small numbers of lymphoma cells at the molecular level, mainly using the PCR. The rearranged immunoglobulin or T-cell receptor genes provide widely applicable targets, whilst specific rearrangements such as those involving Bcl-1, Bcl-2, Bcl-6, Bcl-10, c-Myc or ALK/NPM are more sensitive but constrained by the illness concerned.

The t(14;18) translocation of follicular lymphoma has been most studied but even here the association between the detection of Bcl-2/IgH and the presence of active lymphoma is not straightforward. Patients with prolonged remissions may still have the translocation detectable without developing recurrent disease, the PCR gives positive results in a small proportion of healthy donors and PCR studies of the blood become negative in some patients in whom only a partial clinical response is achieved. There is nonetheless good evidence to suggest that therapy which makes the translocation undetectable is better than therapy which does not.

Newer methodologies hold considerable promise for molecular diagnostics: dense array hybridisation will permit the analysis of complex patterns of gene expression as an aid to diagnosis. Real-time quantitative PCR will allow better use to be made of information about minimal residual disease. Comparative Genomic Hybridisation will allow the identification of new targets for these studies. An important next step along the way to using these techniques for guiding therapy will be the development of standard methodologies to allow the results of different centres to be compared.

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New prognostic and predictive factors in colorectal cancer

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The improved pre-, per-, and postoperative imaging techniques presently used in colorectal cancer have as yet not made tumour staging good enough for safe selection of patients to additional therapy and appropriate surveillance regimes. During the latest two decades much effort has been spent on developing methods to identify minimal residual disease (MRD). Predominantly, tumour cells in the bone marrow have been in focus as the major indicator organ, but also tumour cells at other sites of much interest, that is the macroscopically negative regional lymph nodes of the resected specimen, the peritoneal cavity, and the peripheral blood, have been investigated. Only a few out of several studies using immunohistochemistry with antibodies mainly against cytokeratins or CEA in single or a few sections from dissected regional lymph nodes have been able to show any prognostic impact of detected single or small clusters of tumour cells. Tumour cell enrichment by gradient centrifugation followed by positive or negative cell separation using magnetic beads targeted with antibodies against tumour-associated antigens present on the cell surface, in the cytoplasm, or in the nucleus, has improved the possibility to detect few turnout cells among a huge number of benign cells in the bone marrow, blood, or peritoneal cavity. Immunocytochemistry on cytospins using double-staining techniques or multiparameter flow-cytometry has made it possible to further characterize the fenotype. There are studies reporting on the prognostic significance of tumour cells predominantly in the bone marrow. Common antibodies, for example the 17–1A, anti-cytokeratins, and anti-CEA antibodies, are only tumour-associated and not tumour-specific, leading to the occurrence of some false positives in benign control samples, why results must be interpreted with caution. More lately, the use of molecular-based techniques, such as FISH and RT-PCR, have been developed for true diagnosis of MRD. Besides using primers for CEA and cytokeratins, the RT-PCR technique has shown most promising results when using primers for Ki-ras and p53.

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New prognostic and predictive factors in ovarian cancer

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In ovarian cancer, only a few features such as residual tumor, stage, histologic type and grade, performance status and age have gained general acceptance as factors of independent prognostic value on the basis of multivariate analyses with some of these factors, the discriminating power of which is restricted to an already partly determined patient situation such as histologic grade in early stage and residual tumor in advanced stage disease. The only clinically established factor predictive for response to first line therapy is the early fall in CA-125. Beyond patient- and tumor-related factors, the quality of treatment defined as center factor or the degree of specialization of the surgeon can be of additional prognostic relevance. No established factor exists so far to select primary standard chemotherapy. Chemosensitivity testing based choice of primary therapy has yet to demonstrate its superiority over standard drug choice. Response to subsequent chemotherapy in platinum pretreated patients is significantly dependent on tumor burden and histology only, but not on time from last treatment. The