

Symposia

592

Predictive and prognostic factors – Clinical relevance

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Much progress has been accomplished towards identifying breast cancer patients who will most certainly be cured or, on the opposite, have a very high risk of recurrence. We have made little progress in matching patients with particular forms of therapy to which they are most likely to respond.

Although we can evaluate "dynamic" features such as high proliferation rates of tumor cells, high motility and invasive behaviour, as well as interactions with stromal cells and inflammatory cell infiltrates, we still lack a precise understanding of the detailed molecular mechanisms prevailing in each individual tumor. Similarly, our treatment options have all been empirical attempts to win the battle and are based on population studies. In a neoadjuvant chemotherapy trial in which tumor response and patients outcome was assessed as a function of classical prognostic parameters we could show that young age as well as tumors with *high proliferation rates* (>5%) were significantly associated with response after 4 courses of chemotherapy. On the opposite, patients with low proliferation rates and positive steroid receptors commonly respond well to hormone therapy, but many patients do not fit these two extremes. About 20% of unselected tumors and about 2/3 of inflammatory type carcinomas overexpress the c-erbB2/neu oncogene and might best be treated with a combination of chemotherapy and a specific treatment such as anti-neu antibodies. High tumor motility and invasive behaviour correlate with high vascular density and anti-angiogenic drugs are being assessed in clinical trials. It is generally accepted that established tumors are capable to *downregulate immune surveillance*. Preventive immunizations against the breast tumor associated mucin antigen MUC1 (>90%) might find a place in the adjuvant therapy of patients with a high risk of recurrence and predictive factors for successful immunization will be discussed.

593

The radiologic challenge of early diagnosis in patients with breast cancer. The value of new imaging modalities for the diagnostic procedure

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In respect of the fact that statistically one of nine women will develop a malignant tumor of the breast during their lifetime and that this tumor entity has become the most frequent cause of death in women, the early diagnosis is an important factor of improving the prognosis. Though in the last few years high efforts have been made to establish new imaging modalities for the noninvasive differentiation of benign and malignant changes and the early diagnosis of tumor recurrence, there is still need for further improvements. Subject of this lecture will be to review the indications for the different imaging modalities with an emphasis on new technologies and to set up an optimal diagnostic procedure.

Even in the presence of "high tech"-methods as MR-mammography (MRM) and Positronemissionmammography (PEM), the conventional mammography remains the only suitable screening method for breast cancer. For routine patients with a homogenous structure in mammography and without any anamnestic, clinical or mammographic abnormalities, no further imaging modalities are necessary. Also in patients with characteristic benign microcalcifications, an additional high resolution B-scan ultrasound examination is sufficient for diagnosis. Numerous studies have shown, that the sensitivity of conventional mammography in combination with ultrasound in patients with normal dense fatty breast is between 97% and 100%. Further examinations have to be performed in patients with a dense radiopaque breast, patients with a clinically suspected malignant tumor or tumor recurrence and also in patients with a proven malignant tumor for the exclusion of a multifocal or bilateral tumor growing. B-scan and doppler sonography have become a well established imaging method because of

the high feasibility of this method and the easy application. Especially in the differentiation between a solid mass and cystic lesions sonography has an increasing importance. In patients with absent palpable or very small lesions, however, the diagnostic security of sonography for the exclusion of a malignant tumor is low. In future, the additional use of power doppler mode may help for higher diagnostic security. Thermographic and transillumination examination were not well accepted for a long time due to a persisting high number of false diagnosis. Recent developments of laser doppler imaging, that creates an high resolution image of tissue perfusion, have promising results and have to be evaluated in further clinical trials. The different SPECT-techniques and even more the PET-techniques have also gained an increasing importance with a high sensitivity and specificity for even small tumors. The spatial resolution of these techniques, however, is relatively low and they have to be combined with other imaging modalities. Computed tomography remains an imaging modality of second choice due to the low soft tissue contrast and the applied radiation dose and will be used only in patients with contra-indications for MRM.

594

Primary chemotherapy for early breast cancer: A revolution in progress

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Primary (neo-adjuvant or pre-operative) chemotherapy for early breast cancer is a major new development with important implications for the future management of the disease. With this approach the traditional roles of treatment are reversed and chemotherapy is given as first-line therapy *before* rather than after surgery. Several groups have shown that primary chemotherapy given conventionally will achieve objective tumour regressions in 70% or more of patients, with complete clinical remission rates at around 15–25%. Recently we have shown at the Royal Marsden that an infusion-based chemotherapy using continuous infusional 5-FU 200 mg/m² daily × 6 months along with conventional epirubicin 60 mg/m² iv and cisplatin 60 mg/m² iv q 3 weeks achieved a 98% response rate with a complete remission rate of 66% in a phase II pilot study of 50 patients. This schedule is now being compared with conventional AC (adriamycin, cyclophosphamide) in a multicentre national trial. Important new issues are raised with this approach. Is surgery necessary in patients achieving complete clinical remission? In our current studies 39/185 patients receiving primary/pre-operative chemotherapy were electively allocated not to have subsequent surgery but to proceed straight to radical radiotherapy on the basis of complete or near complete clinical remissions. So far, with short follow-up, there is a suggestion of a slight increase in local recurrence rate in these patients but no survival difference. A randomised trial has just commenced to address this question formally.

In conclusion, prospects for primary chemotherapy suggest the potential for major change in our front-line management of early breast cancer.

595

Optimal results in breast conserving therapy: The interaction between the surgeon and radiation oncologist

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A large spread in treatment outcome both in local control and cosmetic outcome is seen if one compares institutes where patients undergo breast conserving therapy. Reduction of these variations and improvement of these results can be obtained by a joint effort by both surgeons and radiation oncologists. Knowledge of prognostic factors associated with local failure rate after surgery and radiotherapy together with careful pathological examination of the operation specimen form the pivotal elements in this cooperation. Re-excision in order to obtain microscopically free margins in patients with invasive breast cancer and extensive ductal carcinoma is a typical example which results in a lower risk of local recurrence and avoids