# Symposia

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## Predictive and prognostic factors – Clinical relevance

S. Scholl, P. Beuzeboc, P. Pouillart. *Department of Clinical Oncology, Institut Curie, 26 rue d'Ulm Paris, France*

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 hormonotherapy, 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.

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

Th.J. Vogl, Th. Diebold, O. Söllner, R. Felix. *Virchow, Klinikum, Radiologische Klinik, Augustenburger Plat, 13353 Berlin, Germany*

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.

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## Primary chemotherapy for early breast cancer: A revolution in progress

I.E. Smith. *Breast Unit, Royal Marsden Hospital, London, UK*

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/m$^2$ daily × 6 months along with conventional epirubicin 60 mg/m$^2$ iv and cisplatin 60 mg/m$^2$ 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.

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

H. Bartelink. *The Netherlands Cancer Institute/Antoni van Leeuwenhoek Huis, Amsterdam, The Netherlands*

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

the need for a high radiation dose. On the other hand reducing the volume of the excision specimen and separate removal of primary tumor and lymph node metastases will lead to much improved cosmetic results, as shown in a recent major trial of the EORTC. In this trial 5569 patients were randomized to investigate the curative potential of a boost dose of radiotherapy, as part of the breast conserving treatment. The precise localization of the tumor bed by the surgeon will help the radiation oncologist in a much more accurate delivery of the radiation boost dose, therefore optimizing the local control rate in patients with early breast cancer.

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## New approach to staging the axilla by endoscopic axillary lymphadenectomy (EAL) in early breast cancer

F. Suzanne, C. Emering. *Unité de Sénologie CHU de Clermont-Ferrand Université d'Auvergne, France*

Staging of axillary lymphnodes remains the essential factor of prognosis in breast cancer. Actually some teams are very reluctant to do it because of the high morbidity in conventional surgical adenectomy. Not the most for its early complications: lymphorrhea, lymphocele but for its delayed complications lymphoedema, shoulder stiffness and arm swelling. To avoid all those problems a lot of solutions were invented: axillary lymphadenectomy limited to the picking of the only "sentinel" lymphnode. None of those methods is fully satisfying. Morbidity is still important in functional lymphadenectomy: picking of the "sentinel" node seems not to be enough. We propose a new way of adenectomy in the axilla: liposuccion of the axillary fat and endoscopic picking of all the remaining lymphnodes. Fat aspiration leeds to an anatomical and conservative dissection of the axilla preserving the vessels, the nerves and permits an electif and complete removal of all the lymphnodes by this way adenectomy fulfills his prognostic and therapeutic aim.

Early morbidity is very low and transitory, delayed morbidity is near to zero without any lymphoedema. It seems as if liposuccion and EAL (Endoscopic Axillary Lymphadenectomy) will be the technique of lymphadenectomy in the next millenium for early breast cancer.

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## Quality control aspects in surgery

M.R. Christiaens. *Dept. Surgery-Senology, University Hospital Gasthuisberg, Leuven, Belgium*

For a long time surgery was the keystone of any treatment of breast cancer. Last years, one has the impression that surgery is not that important any more since outcome seems to be defined by stage of the disease at time of diagnosis and the use of adjuvant treatment. The evolution to more breast conservative treatments has put a lot more strain on the surgeon and the radiotherapist, since not only locoregional control and survival, but also cosmesis is considered an important endpoint.

Most of the patients are primarily treated outside the frame of clinical trials, so decision making and selection is based on individual experience, believe of the surgeon or patients' preferences. The surgical procedure itself – even within the frame of prospective trials, where surgery is considered 'standard'- is submitted to a large range of variation as has been detected by an EORTC pilot study on that matter. Pathology reports not only reflect the way surgery has been performed but also the thoroughness of the pathologist. On these uncontrolled bases, adjuvant treatment regimens are tailored and investigated in prospective trials.

Better education and special training in breast disease are necessary. A computer assisted decision making process and accurate documentation of the surgical procedure and pathology may lead to a better understanding of how decisions are taken and build up a more accurate data base to analyse process and outcome in a prospective way.

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## Mechanisms of vaccination with cytokine gene-transduced cells

C. Forni, K. Boggio, F. Cavallo. *Department of Clinical and Biological Sciences, University of Turin, 10043 Orbassano, Italy*

**Purpose:** Gene therapy is certainly a powerful tool. Yet it is also a seductive concept. This, coupled with the difficulty of establishing of appropriate controls has lead and is continuing to lead to over-optimistic conclusions. There is thus an urgent need for a tenable definition of its potential.

**Methods:** A transplantable, aggressive and metastasizing mammary carcinoma (TSA) that spontaneously arose in a BALB/c mouse and mammary tumors arising in *neu* transgenic BALB/c mice were used as a model to explore the potential of vaccination with cytokine gene engineered cells in: a) inducing a protective immunity in normal mice; b) curing incipient spontaneous metastases; c) curing small and large solid tumors; d) preventing tumor development in transgenic mice.

**Results:** The cytokine released by engineered tumor cells: a) influences the characteristics and efficacy of the local reaction; b) leads to the induction of a memory reaction towards parental tumor cells skewed toward a TH1 (IL-2, IFN-$\gamma$, IFN-$\alpha$, IL-12), a TH2 (IL-4) or a mixed (IL-10) response; c) elicits (IL-2, IFN-$\gamma$ and IL 12) a systemic reaction that protects against incipient metastases (IL-2, IFN-$\gamma$, IL-12), but hampers (IL-12) established tumors marginally only; d) protects (IL-12) against the development of spontaneous tumors.

**Conclusion:** Manipulation of the antitumor response through vaccination with cytokine-engineered cells is a real prospect. Selection of the inducing cytokine makes it possible to shape the features of a primary inflammatory reaction and the ensuing antitumor memory. These findings are leading towards a more distinct evaluation of the potential of cytokine-gene engineered cells in protecting cancer patients with minimal residual disease, or those expected to have a recurrence after a long disease-free interval, and in subjects with high risk of cancer.

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## Gene therapy for melanoma

Georg Stingl, Achim Schneeberger. *DIAID, Department of Dermatology, University of Vienna Medical School, Austria*

Gene therapy approaches for the successful combat of cancer include several conceptually different strategies: (i) enhancement of the tumor's immunogenicity; (ii) modification of the host immune system, e.g., by transducing tumor-infiltrating lymphocytes with TNF or IL-2 genes or by expressing tumor antigen genes in professional antigen-presenting cells; (iii) modification of other host tissues, e.g., by transfer of cytotoxic drug resistance genes into hemopoietic progenitor cells; (iv) introduction of corrective genes (e.g., wild-type p53) into tumors; (v) transfer of enzymes for prodrug therapy, e.g., introduction of the viral thymidine kinase gene into tumor cells which then become sensitive to ganciclovir.

In the case of melanoma, most gene therapy trials are conducted with melanoma cells the immunogenicity of which has been augmented by transfection with genes encoding cytokines (e.g., IL-2, IL-7, GM-CSF) and/or costimulatory molecules (e.g., CD80).

We and others have shown (i) that highly tumorigenic mouse melanoma cell lines lose their tumorigenicity upon transfection with IL-2, (ii) that mice injected with IL-2-transduced melanoma cells are protected when challenged with wild-type tumor cells, and (iii) that administration of IL-2-transfected melanoma cells into mice can induce the elimination of preexisting cancer cell deposits. Based on these encouraging results, we have tested the safety and immunostimulatory potential of an IL-2-based, autologous melanoma vaccine in patients with stage IV disease. Results obtained are promising and provide the basis for a phase II study aiming at evaluating the therapeutic efficacy of such vaccines.

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## Vaccination with GM-CSF transduced melanoma cells: A promising treatment

E.M. Rankin[1], M. Gallee[1], B. Kremers[1], S. Clift[2], H. Spits[1]. [1]*The Netherlands Cancer Institute, Amsterdam, The Netherlands;* [2]*Somatix Therapy Corporation, Alameda, California, USA*

GM-CSF is the most effective cytokine in vaccines designed to generate an anti-tumor effect and induce long-term tumor specific memory in animal models (Dranoff et al, PNAS 1993; 90: 3538–43). We have explored this approach in patients with advanced, metastatic melanoma using autologous tumor cells transduced with huGM-CSF and the MGF-S retroviral vector. 28 patients have been randomised to 5 or 50 × $10^6$ cells (secreting 40–800 ng GM-CSF/$10^6$cells/24 hr) q 3 wk × 3. The vaccinations are safe and well tolerated. The local and immunological effects are greater at the higher dose. A lymphocytic infiltrate at the vaccine site at d3 changes at d8 to one in which eosinophils, Langerhans cells and a vasculitis predominate. Conversion of the DTH response occurs in all patients. Increases in the number of precursor CTLs have been seen in blood and in distant metastases. We have seen stabilisation of previously progressive disease for longer than 6 months without further intervention in 5 patients, and in a further 3 again