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

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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

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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

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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-γ, IFN-α, IL-12), a TH2 (IL-4) or a mixed (IL-10) response; c) elicits (IL-2, IFN-γ and IL 12) a systemic reaction that protects against incipient metastases (IL-2, IFN-γ, 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

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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

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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/10^6cells/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