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INVITED

**The contribution of radiotherapy to breast conservation***J. Kurtz. University Hospital of Geneva, Radiation Oncology, Geneva 14, Switzerland*

Breast-conserving therapy has clearly become the preferred loco-regional approach for the majority of breast cancer patients in West European countries, where early-stage presentation is the rule and access to radiotherapy is relatively easy. This privileged position is undoubtedly the consequence of unequivocal findings from certain key randomised clinical trials, all of which are well known. However, it is also quite clear (and sometimes forgotten) that breast conservation was not *invented* by clinical trialists. Breast-conserving techniques had been practiced with some success on a limited scale since the 1930s, based upon the known effectiveness of radiotherapy (RT) in the treatment of breast cancer. With the introduction of cobalt machines treatment of operable breast cancer by radical RT doses became technically feasible, often associated with "excisional biopsy" for debulking of macroscopic disease ("primary RT"). Local control and survival associated with these techniques seemed satisfactory, but widespread acceptance of breast conservation awaited publication of the NSABP Trial B-06 in 1985. The trials not only proved the equivalence of breast-conserving and ablative approaches, but they introduced new rigor into the practice of conservation surgery. As a consequence surgery came to be considered the primary treatment, with RT relegated to an adjuvant role. However, even with optimal surgical quality local recurrence rates in unselected patients remain unacceptable in the absence of breast irradiation. Fractionated whole-breast RT (50 Gy/25 fractions) remains the standard, resulting in a reduction of local failure by a factor of about 3–4. A localised boost has been demonstrated to further improve local control in the reference quadrant, where most local failures occur. Analysis of clinical trial data suggests that breast RT not only increases local control, but also improves long-term breast preservation rates and reduces the risk of uncontrolled local disease, metastasis, and breast cancer mortality. This lecture will discuss three key research questions: Can more convenient dose-fractionation schedules be advocated? What are the respective roles of RT limited to the tumour-bearing area compared with whole-breast RT? For which patients might conservative surgery without RT be safely proposed?

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**Breast conserving surgery: the contribution of neoadjuvant treatment***L. Mauriac. Institut Bergonié, Department of Medicine, Bordeaux, France*

Neoadjuvant treatment was successfully applied in the 70, mainly with chemotherapy for advanced and inflammatory breast cancers. Without any randomised trial, it became obvious that primary chemotherapy allowed for local treatment in good carcinologic conditions and was able to improve outcome of such poor prognostic tumors. In the 80, the concept of neoadjuvant chemotherapy was applied to operable tumors whose size was too big to be treated with initial conserving surgery. Several phase II studies were conducted before phases III trials were able to respond the questions raised:

- survival is neither improved nor worsened by neoadjuvant chemotherapy in comparison with adjuvant chemotherapy;
  - breast conserving surgery can be obtained more than one out of two whereas mastectomy would have been the optimal classical treatment;
  - the third initial objective to test chemosensitivity is still in the research fields.
- The present/future of neoadjuvant treatment has to go to several ways:
- to improve the means to increase breast conservation by use of non cross resistant chemotherapeutic regimens (anthracycline-taxanes) or of new compounds directed against specific molecular markers;
  - to test predictive factors of response to neoadjuvant chemo- or endocrine therapy;
  - to use surrogate markers, such as obtention of pathological tumor response, to assess efficiency of treatment regimens and to evaluate accuracy of disease response monitoring (MRI, pet-scan);
  - to use imaging of expression of particular gene products to direct biologically targeted therapy.

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**Saving the breast: an important motivation for women in favour of early detection***G. Freilich. Royal Free/University College London School of Medicine, The Cancerin Centre, London, UK*

Since the dawn of civilisation, women have believed that breast cancer is synonymous with disfigurement, disability and death. Right up to the mid-1970s, having breast cancer was incomparably more traumatic and

devastating an experience than it is today. Faced with the threat to her survival, the standard treatment required the removal of a woman's breast, usually to the extent of a Halstead radical mastectomy. Adjuvant therapies were crude and damaging. The patient suffered the mutilation of her body and bore the stigma of having the disease; she feared rejection by her partner, friends and even her family. She saw herself as deformed, stripped of her femininity and therefore sexually unattractive and an individual of less worth.

Into that society, where few people even mentioned the word 'cancer' and not too many felt comfortable about uttering the word 'breast', prominent American women such as Betty Ford and Happy Rockefeller revealed their diagnoses and extent of their surgery to the world. The effect of such disclosures was revolutionary. Regardless of social status, women everywhere realised their vulnerability to a disease that was normally mentioned only in whispers. On the other hand, they saw for the first time the positive role model of women with breast cancer – women who were alive, looked well and functioned normally in society.

Ford, Rockefeller and one or two other contemporaries had sown the seeds of breast cancer awareness; their personal courage opened the way towards public understanding of the scale of the disease and its impact.

Coincidentally, those historical disclosures occurred during a period of great social, technological and scientific progress. Of specific importance was a) the development of mammography, b) the ground-breaking technique of breast conserving surgery and c) the introduction of Tamoxifen. These advances formed three cornerstones of modern breast cancer management. They also provided the necessary stimulus for powerful public education campaigns to be developed with the aim of dispelling the myths and misconceptions and of promoting the importance of early detection and diagnosis.

This presentation will discuss the contribution made by advances in breast surgery towards motivating early detection, influencing survival and enhancing quality of life.

**Friday, 19 March 2004****14:15–15:45****SYMPOSIUM****Optimal management of the patient with an HER2 overexpressing tumour**

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INVITED

**Challenges in assessing overexpression***J. Baselga. Hospital Universitari Vall de Hebron, Department of Medical Oncology, Barcelona, Spain*

Targeted biologic therapies offer new treatment options for patients with breast cancer but also present therapeutic challenges: patient selection and screening strategies, appropriate use and duration of treatment, and integration with other therapeutic agents. These issues will be examined as they pertain to treatment of metastatic breast cancer (MBC) with HER2-targeted monoclonal antibodies (trastuzumab and rhuMAB2C4), and with small molecule inhibitors targeting epidermal growth factor receptor (HER1/EGFR; erlotinib and gefitinib, or anti-HER1/EGFR antibodies (cetuximab and ABX-EGF).

Trastuzumab has shown the greatest clinical efficacy, including survival benefit, in MBC patients that have the highest HER2 levels, defined by a immunohistochemistry [IHC] score of 3+, or HER2 gene amplification as determined by fluorescence in situ hybridization [FISH]. Recent data from two large adjuvant trials demonstrate a poor correlation between IHC analysis performed within clinics compared to IHC or FISH done in central laboratories. In the adjuvant NSABP-B31 study, an 18% of the community-based assays, could not be confirmed by HercepTest IHC or FISH by a central testing facility. Likewise, a poor concordance (74%) between local and central testing for HER2 status was observed in the N9831 study. This two report provides a snapshot of the quality of HER2 assays performed in laboratories nationwide. Positive FISH status correlates with improved survival of MBC patients receiving trastuzumab. Additionally, FISH is generally more reproducible than IHC in assessing HER2 status. For biologics directed at HER1/EGFR, including gefitinib, erlotinib and cetuximab there does not appear to be a direct relationship between expression levels and efficacy, although HER1/EGFR levels have been reported to have prognostic value. Other aspects of HER1/EGFR-related proliferative activity may provide more direct correlation with clinical efficacy, such as levels of ligand involved in autocrine-loop stimulation, or levels of phosphorylation of HER1/EGFR or downstream molecules. The activity of rhuMAB2C4, which prevents dimerization of HER2 with HER1/EGFR and other HER family molecules and the resulting proliferation signaling,