The second promise of low morbidity has not yet been proven as few data have been published on this topic. The expectation of reduced side-effects seems to be based more on 'common sense' rather than data.The side-effects of axillary surgery are often underestimated by surgeons, and current measuring instruments are often lacking in detail for axillary symptoms. The ALMANAC group have developed a new axillary subscale to the FACT B-4 quality of life questionnaire,which has been shown to be very sensitive in detecting changes in common axillary symptoms such as sensory disturbance and shoulder stiffness. This new subscale is being used in the randomised phase of the ALMANAC trial,which has currently randomised over 500 patients, to compare the morbidity of conventional axillary surgery with sentinel node biopsy.The definite proof of the advantage of sentinel node biopsy is required since the only rationale for the procedure is a reduction of morbidity over that produced by axillary clearance. Although the symptomatic results will be seen in the near future, the potential problem of increased local recurrence will take longer to emerge.

188 INVITED

Sentinel node negative and no treatment: Is it safe?

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We have been performing axillary sentinel node biopsy (SNB) in breast cancer since 1996. Approximately 3000 patients have undergone SNB at our center approximately 1600 of whom had a negative SN and underwent no further axillary treatment. Among these 516 patients were enrolled in a randomized trial, 259 were randomized to SNB, 166 had a negative SN and did not receive further axillary treatment. Among the 257 patients randomized to axillary dissection, 166 had a negative axilla. After a mean follow up of 26 months, there have been no axillary events among the 166 patients who received SNB. Indicating that no treatment in SN negative cases is at least as safe, from the oncological point of view, as axillary dissection.

Six months after the operation, the intensity of pain, presence of paresthesia, arm mobility, appearance of the axillary scar judged and circumference of the operated arm were assessed in 100 consecutive AD arm patients and 100 consecutive patients who did not receive total axillary dissection as the SN was negative. There was less subjective pain and numbness and better arm mobility in patients who only SNB only.

These data suggest that no treatment of the axilla in SN negative cases safe. An further indicate that routine axillary dissection should be abandoned in favour of SNB. In patients with a negative SN who receive no further treatment the risk of understaging is small and largely compensated for by more accurate histological examination of the SN. A preliminary examination of all 1600 patients who have received SNB so far fully supports the conclusions reached on our trial patients.

189 INVITED

Clinical relevance of sentinel nodes outside the axilla

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The hypothesis is that identification and investigation of sentinel nodes outside the axilla will improve staging and will lead to better outcomes.

Till date, nodal involvement is the best prognostic factor. It has been sufficiently proven that understaging of lymphatic dissemination by insufficient nodal sampling results in inferior survival rates. This may be due to under utilisation of adjuvant systemic treatments or insufficient loco-regional control. From this one can draw the general rule that better-lymphatic-staging will result in better outcomes; either by less over treatment resulting in less morbidity without losing significant survival benefits, or by rightfully applying adjuvant treatments with accompanying survival benefits.

Traditionally, lymphatic dissemination is sought in the axilla. From old mastectomy series including supraradical lymph node dissections with internal mammary chain (IMC) nodes removal, it is well known that IMC dissemination may occur in -larger tumours- up to 20% (5–10% isolated IMC metastases). Further, isolated IMC nodal dissemination caries the same worse prognosis as isolated axillary lymph node metastases. Thus knowing IMC nodal status -or better lymph node status outside the axilla- may enhance prognostic information.

Lymphatic mapping by using lymphoscintigraphy has renewed interest in lymphatic dissemination to extra axillary sites. Interestingly, cutaneous or subcutaneous injection of tracers will hardly ever lead to sentinel nodes outside the axillary regions. Injection of radiolabeled tracers of intermediate particle size (80–200 nm, Nanocolloid) in small volumes in the parenchyma of the breast or in the tumour will lead in 15–25% of the patients to sentinel node outside the axilla, as has been shown by us and a number of series. Extra axillary nodes are located in the internal mammary chain, intramammary infra- or supraclavicular.

We performed lymphatic mapping by preoperative scintigraphy, the use of patent blue dye and intraoperative probe on 606 patients. Lymphoscintigraphy depicted in 27% (164/606) of procedures extra-axillary sentinel nodes. The 119 sentinel nodes depicted in the IMC (18%), 86% (102/119) could be harvested and contained metastases in 17% (17/102). In 52 patients other non-axillary nodes were excised (identification rate of 70%) and 12 (23%) contained metastases. In all, in 3% of all patients extra-axillary lymph node metastases were found while the axillary nodes were negative.

Non-axillary sentinel node biopsy had therapeutic consequences in 5% of the whole population and in 18% of the subgroup with non-axillary drainage. The most apparent therapeutic consequences were: adjuvant systemic treatment in patients considered as good prognosis by an axillary negative nodal status, omitting adjuvant radiotherapy in IMC node negative cases and applying IMC radiotherapy in node positive cases.

Extra-axillary sentinel node biopsy is associated with low morbidity and will improve staging and must therefore improve outcomes.

Thursday, 21 March 2002 14:45–16:15

SYMPOSIUM

Intraoperative radiotherapy: rationale, techniques, results

190 INVITED

Intraoperative radiotherapy: rationale, techniques, results

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In order to avoid a prolonged course of external irradiation, several Authors treated patients with low or high dose-rate iridium implants to the primary tumor bed alone as part of breast conserving protocol. Local control rate was very high (from 92 to 100%) in all trials but one. It is worthwhile to mention that in all trials reported above the cosmetic result was comparable to conventional approach and the incidence of distant metastases and overall survival was similar to those treated with a combined radiation treatment.

The experience on 201 patients treated at the European Institute of Oncology with Intraoperative Radiotherapy as a whole treatment allows a positive preliminary conclusion. The procedure is simple and rapid, the training of the staff easy, the acute side-effects are minimal and not serious. The patients' satisfaction is high, as the long period for the external radiotherapy is avoided.

IORT dramatically reduces radiation exposure of the skin, of the lung, and of the subcutaneous tissues and completely avoids the irradiation of the controlateral breast, contributing to a very low incidence of radiation-induced sequelae.

191 INVITED

Targeted intra operative radiotherapy (Targit) for early breast cancer: Rationale and early clinical experience

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Early local recurrence of breast cancer most commonly (over 90%) occurs at the site of the primary tumour. This is true whether or not radiotherapy is given and irrespective of the margin status. Whole-organ analysis of mastectomy specimens on the other hand, reveals that 63% of breasts harbour occult cancer foci and 80% of these are situated remote from the index quadrant. Therefore, these occult cancer foci may be clinically irrelevant. Hence, after breast conserving surgery, it may not be necessary to treat the whole breast with the usual 6 week long course of post-operative radiotherapy that is not only inconvenient and costly, but may cause many women from geographically remote areas to choose mastectomy. *Targ*eted *i*ntra-operative radio*t*herapy (*Targit*) to the peri-tumoural area alone might provide adequate local control. 'Intrabeam' (*PeC*) is a portable electron-beam driven device that can deliver therapeutic radiation (soft x-rays) in 20–30 minutes within a standard operating theatre environment. The pliable breast tissue - the target - is wrapped around a spherical applicator - the source - providing truly conformal radiotherapy. The prescribed dose is 5 & 20 Gy at 1 cm and 0.2 cm respectively, from the tumour bed. The biologically effective dose is

7 & 53 Gy for _/_ = 1 and 20 & 120 Gy for _/_ = 1.5. In our pilot study of 26 patients (age 30–80 years, T = 0.42–4.0 cm), we replaced the routine post-operative tumour bed boost with targeted intra-operative radiotherapy. There have been no major complications and no patient has developed local recurrence, although the median follow-up time is short at 29 months. The cosmetic outcome is satisfying to both the patient and the clinician. Having established the feasibility, acceptability and safety in the pilot study, we started in March 2000, a randomised trial that compares *Targit* with conventional post-operative radiotherapy for infiltrating duct carcinomas, with local recurrence and cosmesis as the main outcome measures. Patient accrual in this trial has been excellent and it has attracted several international collaborative groups. If proven effective, *Targit* could eliminate the need for post-operative radiotherapy potentially saving time, money and breasts.

192 INVITED

Intraoperative electron irradiation (IOERT) in breast cancer: Methodological description of a 7 years instutional experience

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Purpose: To analyze retrospectively the outcome and cosmetic results of breast cancer patients in which IOERT was used as a component of treatment.

Patients and Methods: From October 1993 to October 2000, 21 breast cancer patients recieved IOERT. Age ranged from 35 to 75 years (median 53 years). Conservative surgery was perfomed in 14 (66%). Tumor stages were: 3 I (14%); 12 IIA (T_1N_1–T_2N_0); 3 advanced (1 T_2N_2; 2 inflamatory); 3 loco-regional recurrences. Histological subtypes were: 12 invasive ductal (57%), 3 lobulillar, 3 intraductal, 2 inflamatory carcinoma and 1 phylloides sarcoma. Postoperative treatments included external radiotherapy (76%), chemotherapy and hormonotherapy. IOERT target was the surgical tumor bed (negative-close margin 95%), with applicator size range from 5 to 10 cm Ø, electron energies from 4 to 12 MeV, single doses from 8 to 15 Gy and multiple field employed in 3 procedures.

Results: Median follow-up time is 36 months (range 8 to 91 months). 81% of patients are alive (76% NED). No local recurrence has been detected: 3 patients developed distant metastasis (bone and lung). In breast preserved patients cosmetic results are categorized as excellent. No acute or late toxicities have been exclusively related to the IOERT component of treatment.

Conclusion: In the context of an expert IOERT institution this radiation boosting technique used as a component of treatment is feasible to introduce in the multimodal management of localized breast cancer. Cosmetic and local control results are attractive, in particular for breast conserving approaches. Information is limited regarding its potential value in recurrent disease and locally advanced post-mastectomy patients.

193 INVITED

The Milan trial

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Local recurrences after breast conserving surgery occur mostly in the quadrant harbouring primary carcinoma. The main objective of postoperative radiotherapy should be the sterilization of residual cancer cells in the operative area while irradiation of the whole breast may be avoided. We have developed a new technique of intraoperative radiotherapy of a breast quadrant after the removal of the primary carcinoma. A mobile linear accelerator with a robotic arm is utilized delivering electron beams with four energies from 3 to 9 MeV. Through a perspex applicator (available with different diameters - from 4 to 10 cm and angles) the radiation is delivered directly to the reconstructed portion of mammary gland around the tumor bed, stretching out the skin from the radiation field. In the first phase, since February 1999 to November 2000, different dose-levels were tested from 10 to 21 Gy on 101 patients without important acute side effects. According the radiobiological models, can be estimated that a single fraction of 21 Gy is equivalent to 60 Gy delivered at 2 Gy daily. All patients underwent quadrantectomy and axillary dissection and/or sentinel node biopsy. Seventeen patients received a dose of IORT of 10 to 15 Gy as an anticipated boost while 86 patients received a dose of 17-19-21 Gy intraoperatively as a complete treatment. No major late effects have been observed with a follow-up of 12-24 months. The cosmetic outcome was very good. A phase III randomized study comparing IORT at the dose of 21 Gy (prescribed at yhe 90% isodose) and a conventional course of external irradiation (60 Gy/30 fractions) is oingoing since November 2000 and is expected to finish in 3 years. During the first 12 months more than 180 patients fullfilling the inclusion criteria (age more than 48 years, histologically confirmed unifocal infiltrating carcinoma of the breast, maximum diameter of the tumor 2.5 cm) have been enrolled.

The IORT treatment was very well accepted by all patients, either due to the rapidity of the radiation course in case of IORT as a whole treatment or to the shortening of the subsequent external radiotherapy in case of IORT as an anticipated boost. We believe that single dose intraoperative radiotherapy after breast resection for small mammary carcinomas may be an excellent alternative to the traditional postoperative radiotherapy, which deserves a clinical evaluation through a large-scale randomized controlled trial.

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SYMPOSIUM

Molecular biology

194 INVITED

Growth factor regulation of angiogenesis, lymphangiogenesis and metastasis

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Angiogenesis and permeability of blood vessels are regulated by vascular endothelial growth factor (VEGF) via its two known receptors VEGFR-1 and VEGFR-2. The VEGFR-3 receptor tyrosine kinase is related to the VEGF receptors, but does not bind VEGF and its expression becomes restricted mainly to lymphatic endothelia during development. We have found that homozygous VEGFR-3 targeted mice die around day 10 of embryonic development due to failure of cardiovascular development and that heterozygous missense mutations of VEGFR-3 inactivating the tyrosine kinase activity are associated with human hereditary lymphedema. We have also purified and cloned the VEGFR-3 ligand, VEGF-C. Transgenic mice expressing VEGF-C developed a hyperplastic lymphatic vessel network and show evidence of lymphangiogenesis. However, proteolytically processed VEGF-C was also capable of stimulating VEGFR-2 and was weakly angiogenic. VEGF-C induced vascular permeability, but its point mutant, which retained lymphangiogenic properties and activated only VEGFR-3 did not.. VEGF-D is closely related to VEGF-C, similarly processed and binds to the same receptors. Thus, VEGF-C and VEGF-D appear to be both angiogenic and lymphangiogenic growth factors. VEGF-C induced the growth of peritumoral lymphatic vessels and was associated with lymphatic metastasis in transgenic mice. VEGF-C overexpression also led to lymphangiogenesis, intralymphatic tumor growth and lymph node metastasis in an orthotopic model of human breast carcinoma in immunoincompetent mice. Furthermore, soluble VEGFR-3, which blocks embryonic lymphangiogenesis, blocked these changes. However, VEGFR-3 is also induced in blood vessels of various types of human cancer. Ongoing experiments address the role of the VEGFR-3 signaling pathway in embryonic and tumor angiogenesis and the mechanisms of lymphatic metastasis.

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