

Thursday, February 26, 1998

16.00–17.45

Session 5 Integrated Therapy: Changing Surgical Procedures for Breast Cancer

S17 The axilla; To clear or not to clear? That is the question!

M. Blichert-Toft. *Rigshospitalet, DK-2100, Copenhagen*

The title suggests that "whether or not to clear the axilla" is still a matter of controversy in the treatment of operable breast cancer. In most guidelines for surgeons in the management of symptomatic breast cancer it is emphasized that histologic node status should be obtained on all invasive tumors either by sampling or clearance of the axilla. No physical examination, no imaging techniques and no tumor markers can replace axillary dissection for staging. Further, axillary node status in potentially curable breast carcinomas is still considered the single best predictor of outcome and the primary determinant for use of systemic therapy. Finally, there is growing approval of the role of loco-regional tumor control leading to increasing attention to removal of involved axillary nodes.

Today, the question to be asked is not "whether or not to clear the axilla". Rather, the question should go: How do we separate node negative patients from those who are node positive without clearing the axilla in all probands. No surgeon would advocate to dissect the axilla in node negative patients provided that nodal status could be procured by using a different technique.

The pros are illustrated by results from the Danish Breast Cancer Cooperative Group, DBCG. In DBCG protocols axillary dissection is compulsory.

National surgical quality standards on axillary dissection will be given together with proposals indicating extension of the surgical procedure. The relationship between tumor diameter and axillary nodal involvement is illustrated and the importance of axillary surgery with the intention to cure is stressed. DBCG results show a frequency of node positivity ranging from 17% in tumors 0–9 mm up to 77% in tumors >50 mm in diameter. The percentage of tumors with 4 and more positive lymph nodes amounts 23% in Npos tumors 0–9 mm. Further, the critical number of lymph nodes to be removed in order to avoiding irradiation of the axilla will be given appropriate attention. Finally, the recognition of excellence in surgical treatment on a national scale with due reference to outcome is considered. It is concluded that meticulous surgery can improve overall survival by quite 10% in absolute terms due to a more accurate staging and better loco-regional disease control.

S18 The axilla; To clear or not to clear? That is the question!

U. Veronesi. *European Institute of Oncology, Milan, Italy*

Axillary dissection is performed for staging purposes. With the increasing rates of very small carcinomas the removal of axillary nodes results in totally healthy nodes in a high proportion of cases. A large number of women therefore suffer from an unnecessary and unpleasant operation which removes a good quantity of normal tissue of the immune system.

A new method (sentinel node biopsy) has been discovered to avoid this blind procedure and to stage the axilla with a minimally invasive procedure. The sentinel node biopsy has a correct predictive power on about 97% of cases.

S19 Pre-surgical chemotherapy

R. Margolese. *Jewish General Hospital, Montreal, Quebec, Canada*

One of the goals for pre-surgical adjuvant chemotherapy for breast cancer patients is the reduction of tumor size to favor conservative breast surgery. There is good biologic rational for this, but the clinical problems the surgeon encounters are quite different from those in traditional breast conserving surgery.

Evidence in favor of pre surgical chemotherapy is derived from experience with the primary treatment of locally advanced breast cancer where initial chemotherapy is extremely effective. Preliminary studies in head and neck tumors and sarcomas also indicate high responsiveness to presurgical therapy. Thus presurgical therapy offers advantages of potentially increased disease free survival and, secondarily, reduction in size of tumor.

The patient population will include many with small or minimally palpable tumors and a substantial number of clinical complete responses will occur. Since clinical response may not assure pathological disappearance of tumor it is still necessary to perform local excision and problems in identifying the exact site of the original tumor can arise.

The National Surgical Breast Project has conducted workshops for its mem-

bership in addressing these issues and a summary of findings will be presented. These involve accurate mapping of the original site, use of preoperative needle localization for persisting microcalcifications, and specific skin markers or tattoos.

One special problem is the issue of control of margins. Tumors may not shrink in a uniform fashion similar to melting ice cubes and there is concern that downsizing the scope of the operation will not maintain the excellent local control rates now obtained in conservative breast surgery. This problem will be documented and techniques for management discussed. Correlations with original tumor size and extent of response may be useful guides to surgical technique.

S20 Integration of plastic surgery in the course of breast cancer surgery to improve final cosmetic result and radicality of tumor excision

J.-Y. Petit. *European Institute of Oncology, Milan, Italy*

In case of mastectomy, the integration of plastic surgery is currently widely admitted. Immediate breast reconstruction with implant or with autologous tissue procedures is frequently proposed to the patient before the mastectomy. However, breast conservative surgery (BCS) is recognized as the treatment of choice in most cancers. Breast conservation is proposed in more than 70% of the primary cancers treated at the IEO of Milan. Such a high percentage of preservation has been made possible thanks to the integration of plastic surgery at the time of the primary surgery. The size of the tumorectomy remains a matter of discussion. Based on the Milan II trial and the R. Holland pathological studies, Veronesi recommended the so called "local radical surgery". A free margin of 2 cm implies a final specimen of at least 5 to 6 cm in diameter for a tumor size of 1 cm. In small or medium size breasts, such resection results in wide glandular defect and poor esthetic results in case of direct closure. Plastic surgery derived from reduction mammoplasty procedures allow much better final cosmetic results which is the goal of the conservative treatment. In 25% of our BCS cases, the plastic surgeon is called upon by the general surgeon to close the glandular defect. However, such glandular remodelling changes the size and the position of the breast. Therefore, in 15% of these cases, a symmetry procedure of the opposite breast has been performed. The reduction of the opposite breast should be taken as a good opportunity to check the glandular tissue. Therefore, a special attention should be given to contralateral mammogram in order to focus the glandular resection on the most dubious areas. Four per cent of occult carcinomas, the half of them were infiltrating, have been found in a series of 350 symmetry procedures performed during a breast reconstruction at the G Roussy Cancer Institute. In conclusion, a close collaboration between oncologists and plastic surgeons is required not only to obtain the best cosmetic results but also to allow a better radicality of the tumor resection and an histological check up of the contralateral breast.

Friday, February 27, 1998

8.30–10.00

Session 6 Integrated Therapy: Primary Adjuvant Systemic Therapy

S21 Preoperative therapy (PROP) for breast cancer

B. Fisher. *National Surgical Adjuvant Breast and Bowel Project (NSABP), Pittsburgh, PA, USA*

NSABP B-18 was conducted to evaluate the worth of PROP for the treatment of stages I and II breast cancer.

Goals: 1) to determine if PROP could more effectively prolong disease-free survival, distant disease-free survival (DDFS), and overall survival (S) than the same chemotherapy given postoperatively (POP); 2) to evaluate response of a primary tumor to PROP and correlate that response with DDFS and S; 3) to determine if PROP permitted more lumpectomies (LUMP) and decreased the incidence of ipsilateral breast tumor recurrence after LUMP; 4) to determine whether PROP "downstaged" axillary nodal status, as indicated by more negative nodes.

Methods: Patients (Pts.; 1523) were stratified according to age, clinical tumor size, and clinical nodal status, then randomly assigned to either LUMP and axillary dissection, or modified radical mastectomy, followed by 4 cycles of Adriamycin/cyclophosphamide (AC) every 21 d, or AC then surgery. All pts ≥50 years received tamoxifen for 5 yrs. LUMP pts. also received postoperative

XRT either after surgery (the "PROP group" – 760 pts.) or after postoperative adjuvant chemotherapy (the "POP group" – 763 pts.).

Results: Effect of PROP on Local-Regional Disease: 35% of tumors had a clinical complete response (cCR) to PROP and 45%, a clinical partial response (cPR). PROP pts. and pts with responsive tumors were more likely to undergo a LUMP. More pts. whose tumors were ≥ 5.1 cm underwent a LUMP. PROP resulted in axillary nodal downstaging, and there was a highly significant correlation between tumor response to PROP and pathologic (path.) nodal status. About 25% of pts, with a cCR had no residual tumor on histologic exam of the resected specimen; 11% had only noninvasive intraductal carcinoma, and the rest had invasive tumor on path. exam. **Relation of PROP to Outcome:** Through 6 yrs., outcome of all PROP pts. was virtually identical to that of pts. treated with POP. There was a correlation between breast tumor response to PROP and outcome. The best outcome occurred in pts. whose tumors showed a path. complete response.

Conclusion: Outcome with PROP or POP is similar. A significant correlation exists between breast tumor response to PROP and outcome. PROP increases the use of LUMP, esp. in pts. with large tumors.

S22 Is primary chemotherapy useful in all patients?

S. Scholl, P. Beuzeboc, B. Asselain, J.-Y. Pierga, P. Pouillart. *Institut Curie, Paris, France*

Based on the concept of breast cancer as a systemic disease, the administration of primary chemotherapy was the logical next step, aiming at eradicating micrometastatic disease with the potential to increase cure rates. Yet, published clinical trials testing primary versus adjuvant chemotherapy have shown only minor or no statistical significant benefit. Did we go wrong? The latest update of the Curie trial (S6: 390 pts with an 8 y median follow up) showed a minor survival advantage for the primary chemotherapy group (Wilcoxon 0.09; Breslow 0.05). Clinical response, our surrogate end point, was achieved in 2/3 of all patients and was highly predictive of outcome in our series. It was moreover significantly associated with high S phase and young age. Patients aged <35 years had a higher RR (2.46) for metastatic recurrences despite better response and higher mitotic rates, suggesting that the treatment may have been suboptimal for this subset.

Clinically palpable nodes, high mitotic rates and absence of objective clinical responses were independent predictors for poor survival. Conversely, high risk tumours with high mitotic activity and/or good clinical regression are most likely to benefit from chemotherapy and may benefit from prolonged and intensified therapies. Since response can best be assessed by primary chemotherapy, patients at risk and with highly proliferative tumours (S phase $>3\%$) might best be treated with primary chemotherapy for a minimum of two courses while *mdr* induction and response can be monitored. Patients with low risk tumors and little mitotic activity as well as patients who do not respond are unlikely to gain from prolonged primary chemotherapy while suffering the discomfort and anxiety as well as the potential for enhanced genetic instability associated with cytotoxics. Following local treatments these patients may become candidates for targeted antibody or vaccine therapies as these become available. Results of a phase I trial directed against MUC1, a vastly overexpressed tumor antigen (detectable in serum as tumor marker CA153) administered in a vaccinia virus carrier showed some promise.

were randomized to receive RT before or after 4 cycles of CAMFP. The 5-year failure rates were not different, but the (uncensored) rate of DM was significantly greater in the RT-first arm. However, the risk of local failure was higher in the CT-arm. These results suggest that for pts at moderate-high risk of metastases, it is preferable to give a 12-week course of CT followed by RT. However, 1) it is not certain if this applies to longer courses of CT or to pts at low risk and 2) alternative ways of combining RT and CT which maximize both local and systemic control should be explored. Concurrent full-dose RT and either CMF or dox-containing CT has unacceptable results. We recently completed a study of concurrent full-dose CMF and reduced-dose RT (3960 cGy/22 fx to the whole breast followed by a boost of 1600 cGy/8 fx.) in 105 pts with 0–3 positive nodes with good early results.

In conclusion, the available information regarding combining CT and RT is limited and often conflicting. Differences in the details of the treatment (surgery, RT, and CT) may be factors. In the meantime, clinicians might modify the sequence in individual patients based on the patient's risk of metastases and the margins of resection.

S25 Novel approaches using radiation techniques

Lars E. Rutqvist. *Karolinska Hospital, Stockholm, Sweden*

New information has recently emerged concerning the role of adequate local control of breast cancer through the use of postoperative locoregional therapy in conjunction with adjuvant cytotoxic chemotherapy. The updates of the Danish DBCG 82b trial and the British Columbia Trial have confirmed a significant overall survival benefit with postoperative radiation therapy in patients with high-risk disease. These trials together with in-depth analyses of previous studies suggest that the mechanism of the survival benefit is eradication of subclinical locoregional deposits of tumour cells with a potential for further dissemination if left untreated. Despite these findings several questions remain largely unanswered concerning the optimal way to integrate radiation therapy into routine clinical practice. For instance, which subgroups are likely to benefit from comprehensive treatment including the peripheral lymphatics as opposed to treatment of the breast/chest wall alone? Until results are available from future controlled trials the Stockholm Breast Cancer Group has adopted a provisional policy of offering locoregional radiation therapy to subgroups of patients whose 10-year cumulative risk of local failure (in the postmastectomy setting) in the absence of radiation exceeds 15–20%. On the basis of results from the Stockholm Breast Cancer Data Base including c. 3,200 patients treated with surgery alone or surgery plus adjuvant chemotherapy, cumulative risks of this magnitude concern all patients with 4 or more positive axillary nodes, but also subgroups of patients with node-negative disease or 1–3 positive nodes in case of a large histopathological tumour size (>20 – 30 mm) or a high proliferative activity. The available randomized trials and overviews have convincingly demonstrated that it is essential to minimize long-term radiation side effects in the myocardium in order to achieve an overall survival benefit. Such effects are positively correlated with the cardiac dose-volume. An adequate treatment technique is therefore essential, particularly if the internal mammary nodes are included in the target. Individual treatment planning should be encouraged since some patients have an "unfavorable anatomy" with the heart located anteriorly in the mediastinum. Such patients may receive a high cardiac dose-volume even with conventional tangential field irradiation that does not include the internal mammary nodes. In summary, recent information highlights the fact that radiation therapy plays an important part in the primary management of many breast cancer patients. However, an adequate treatment technique that minimizes the risk of late cardiac effects is paramount in order not to compromise the potential treatment benefit in terms of overall survival.

Friday, February 27, 1998

10.30–12.30

Session 7 Integrated Therapy: Radiation Therapy/Endocrine Treatment

S24 How to combine radiation (RT) and systemic (ST) therapies

J.R. Harris. *Harvard Medical School (HMS), Boston, MA, USA*

Clinical trials have demonstrated both the effectiveness of adjuvant ST and the equivalence of BCT and mastectomy; consequently, clinicians commonly are faced with combining RT and ST following CS. In addition, recent studies have suggested that regional RT after mastectomy and adjuvant CT improves survival. Thus, combining RT and ST has become an issue following mastectomy. The options for combining RT and chemotherapy (CT) are variable. RT and tamoxifen can be delivered concurrently.

Clinical trials are required to resolve this issue. We performed such a trial in which 244 pts at moderate-high risk for relapse (209 were node-positive)

S26 The molecular biology of the estrogen receptor (ER) aids in the understanding of tamoxifen resistance and breast cancer prevention with raloxifene

V.C. Jordan. *Lurie Cancer Center, Chicago, IL, USA*

The recent crystallization of the ER with estradiol or the new antiestrogen raloxifene has provided an invaluable insight into drug resistance to tamoxifen (Brzozowski et al *Nature* 389:753–759, 1997). Tamoxifen can stimulate the growth of both breast and endometrial tumors in the laboratories. One theory to explain this phenomenon is mutation of the ER. However, there is only evidence for one natural mutation (Wolf and Jordan *Breast Cancer Res. Treat* 31:129–138, 1994). Aspartate 351 is changed to tyrosine and the mutant ER increases the estrogenicity of raloxifene (Levenson et al *J. Steroid Biochem Mol. Biol.* 60:261–268, 1997). It has been known for forty years that a correctly positioned aminoethoxy side chain is essential for antiestrogen action. Now we know from the crystal structure of the ER raloxifene complex that the side chain must interact with aspartate 351 to produce the conformational change in the ER that blocks estrogen action. Amino acid 351 is the key to antiestrogenic activity; a mutation prevents the change in conformation resulting in estrogenic