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 independant 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.

Friday, February 27, 1998 **10.30–12.30**

Session 7 Integrated Therapy: Radiation Therapy/Endocrine Treatment

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

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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) 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

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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 trail 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 routing 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 trails 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 trails 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.

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

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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 structive 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