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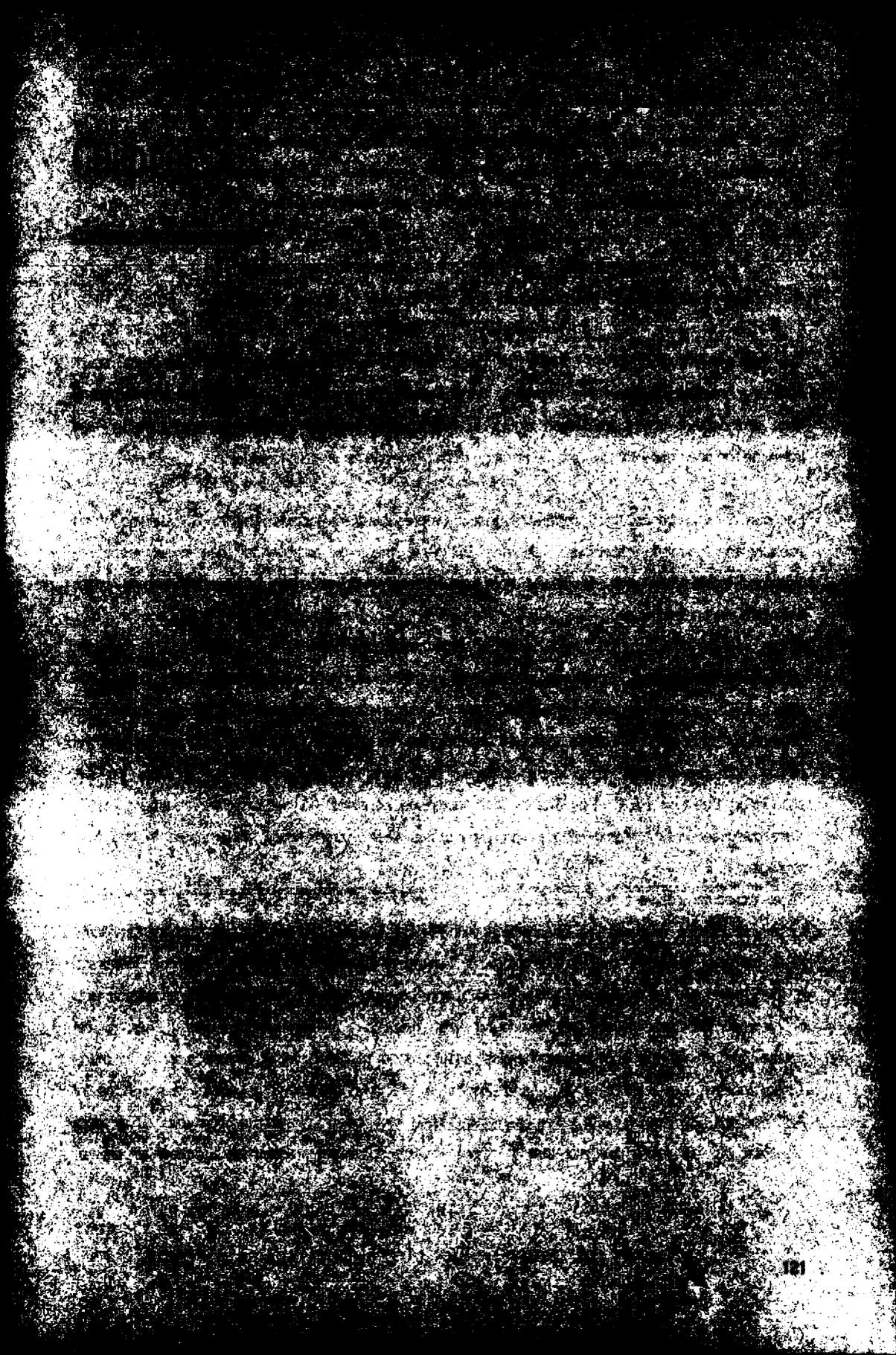
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One of the primary goals of chemotherapy research in breast cancer is to obtain a better understanding of risk factors for developing distant metastases and of breast cancer sensitivity to drugs. This thesis focuses on the latter, discussing two central issues:

- I. Prediction and implications of response to chemotherapy;
- II. MDR proteins, their detection and their role in chemosensitivity.

The experimental work for this thesis had been finished, by the beginning of 2003. More recent publications regarding predictive markers, MDR related proteins and response to chemotherapy have provided no significant new insights, so that the conclusions drawn from the literature and from the original data in this thesis remain valid:

For predictive purposes, the proliferation index (represented for instance by Ki-67 staining) and possibly the hormone receptors (ER and PR) are the only established markers of response; increased proliferation and decreased hormone receptor expression are associated with a better response to chemotherapy.

In a number of studies HER2 status was associated with responsiveness to specific chemotherapy regimens. Conflicting results prevent definitive conclusions to be drawn from these data. HER2 status does however rapidly gain interest in clinical decision-making: the possibilities of receptor-targeted immunotherapy with agents like trastuzumab are being further explored in clinical and pre-clinical experimental settings, with some early successes^{365 366}. Data on the association between HER2 amplification and increased sensitivity to anthracycline treatment, which were discussed in the introduction chapter, have not been systematically implemented in treatment strategies.

Other molecular markers such as MDR1/P-Gp, the MRP's, BCRP, p53, Bcl-2 and p27 all fail to reliably predict response to chemotherapy in clinical studies. In vitro studies strongly implicate ABC proteins in MDR but clinical proof is lacking. Although there appears to be increased mRNA expression of at least MDR1/P-Gp (and possibly MRP1) after anthracycline treatment, no reproducible association can be found with response to chemotherapy or further clinical course. Importantly the immunohistochemical assays used to detect MDR related proteins in many (also recent, e.g. Larkin et al³⁶⁷ and Filipits et al³⁶⁸) publications that claim associations of ABC protein expression with chemosensitivity have not been proven to be valid. The data presented in this thesis suggest that it is not possible to reliably detect ABC protein expression

in paraffin embedded samples using immunohistochemistry. A (combination with) RNA based technique is mandatory for proper assessment of the drug pumps in clinical samples.

As is demonstrated in this thesis and most recently in another study by Burcombe et al³⁶⁹, the clinical response to chemotherapy of a tumor is not an adequate prognostic factor. Clinical response lacks proper correlation with pathological response. Only a pathological complete remission, occurring in roughly 15% of patients, actually predicts improved outcome. In this respect the preliminary findings from the NSABP protocol B-27 are very interesting: the preoperative addition of four cycles docetaxel in 1500 of 2400 early breast cancer patients who received four cycles neoadjuvant AC treatment, resulted in an increase of the pathological complete remission rate from 14% to 26% ($p < 0.001$)³⁷⁰.

An important development of the past five years in the field of (breast) cancer predictors and prognosticators is gene expression profiling, using microarray analysis. In contrast to investigation of singular parameters, chosen because of the more or less logical assumption of their involvement in the disease or in success of therapy, genome-wide screening non-selectively assesses thousands of genes. Unfathomable amounts of relevant and irrelevant data are obtained, putting the simple observer at a loss. Relevant findings must be reconstructed by complex biostatistical methods that are beyond the scope of this thesis (reviewed by Aittokallio et al³⁷¹ and by Leung et al³⁷²). Microarray technology has been used in clinical studies, as was first reported for breast cancer by Perou et al, who did some explorative work in a small set of tumors, some having received anthracycline therapy³⁷³. Several later studies have identified gene expression profiles with potentially useful clinical implications, also with regard to chemotherapy and its use in breast cancer patients. Most authors use microarray analysis to define predictive or prognostic gene expression profiles and subsequently apply those profiles in an independent validation group. This appears to be a more successful strategy than any conventional classification based on "logically" studied (molecular) parameters. Van de Vijver et al characterized patients with high-risk of distant metastases (hazard ratio 5.1) from a group of 295 primary breast cancer patients³⁷⁴. Chang et al described a profile predicting response to neoadjuvant docetaxel for 24 patients³⁷⁵. Ayers et al have described a gene expression profile associated with response to neoadjuvant paclitaxel and FAC chemotherapy³⁷⁶. Published series to date are mostly small, and in terms of altering therapeutic practice, no clinical consequences have as yet been drawn from the data. Michiels et al have recently reassessed seven microarray studies, concluding with the caution that the classifying gene profiles in the reviewed

papers are insufficiently validated³⁷⁷. Whether and how this debate will be resolved remains to be seen. Meanwhile the evolution of microarray research continues and has also been applied specifically to the investigation of ABC genes and MDR: chips comprising only ABC genes³⁷⁸ and a combination of ABC genes with other possible MDR related genes³⁷⁹ have been successfully tested in cell lines. Studies of clinical samples will no doubt follow shortly. It is not to be expected that gross new findings will result from this, as in fact these chips duplicate the work on individual MDR genes that has already been done, showing no significant influence of their expression on chemosensitivity. The main advantage of these chips will be in the ease to assess multiple tumors and genes and thus in the power of greater numbers. Concerted expression and subtle differences of expression will more easily be brought to light.

Both microarray and other techniques will benefit from technical advancements: Improvement of technologies to increase the yield of both DNA and RNA from archived materials can open the door to formalin-fixed and paraffin embedded tumor specimens that have long been largely idle in pathology departments.

Further refinement of laser capture technology can help isolate specific regions or cells of interest from tumor samples. Expression of genes and proteins possibly related to chemoresistance can thus be studied exclusively in cancer cells from clinical specimens, in contrast to the present day use of bulk material. Regional differences in protein expression within a tumor may explain resistance of minor parts of that tumor. Isolation of RNA from selected tumor cells can validate or definitively negate the unreliable immunohistochemistry findings to this extent.

It is remarkable that regardless of the vast scientific efforts and of all the spectacular new findings the use of chemotherapy for breast cancer today is still determined mostly by very low-tech parameters. Certainly it must be hoped for that prediction of behavior of breast cancer will become feasible on an individual level, enabling tailored therapy for each patient.