Towards patient-tailored surgical treatment in breast cancer
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Concluding remarks and future prospects
CONCLUDING REMARKS

There is an ongoing trend towards patient-tailored treatment in breast cancer which ultimately will decrease overtreatment and avoidable morbidity. Accurate patient selection is the basis of patient-tailored treatment. Patient selection requires methods to assess the need for a certain treatment. The challenge for a clinician is to combine all relevant information, to improve the patient selection and to critically appraise standardized treatment protocols.

The sentinel node biopsy procedure is an accurate technique to determine the nodal staging and the need for further axillary treatment in patients with a clinically negative axilla. The standard axillary treatment of patients with a tumour-positive sentinel node is an axillary lymph node dissection. However, in the AMA-ROS trial we assess the value of axillary radiation therapy, expecting the morbidity to be lower compared to axillary clearance. The extent of nodal involvement, apart from the sentinel node involvement, remains unknown when axillary clearance is replaced by axillary radiation therapy. This thesis shows that absence of knowledge regarding the extent of nodal involvement does not have a major impact on the administration of adjuvant systemic therapy. This finding controls the validity of future trial results and refutes the argument that an axillary lymph node dissection has to be performed in order to obtain information for adjuvant decision making.

Patient tailored treatment is an important gain of neoadjuvant chemotherapy since in vivo the tumour response can be assessed without requiring long term follow-up. Better understanding the response to chemotherapy of different breast cancer subtypes can improve the patient selection for neoadjuvant chemotherapy and ultimately for chemotherapy in the adjuvant setting.

Oestrogen receptor-positive breast cancer showed a low pathological complete remission rate (pCR) compared to triple negative and HER2-positive tumours. However ductal oestrogen-receptor positive patients showed a high increase in breast-conserving surgery after neoadjuvant chemotherapy. So, although the majority of patients did not achieved a complete remission, they showed a significant shrinkage of the tumour burden. Oestrogen-receptor-positive lobular carcinomas, on the other hand, showed a low pCR rate, a low increase in breast conserving surgery and a high rate of incomplete resections requiring subsequent mastectomy. However, the subgroup of pleiomorphic and HER2-positive lobular carcinomas did show a good response to neoadjuvant chemotherapy.

Besides the histological characteristics of a tumour, the 70-gene expression profile, a prognostic biomarker, also showed predictive potential. A pCR is unlikely to be achieved in tumours that have a good
prognosis-signature and tumours with a poor prognosis-signature are more sensitive to chemotherapy. These results imply that the selection of patients for neoadjuvant chemotherapy can be improved by combining histological and molecular information regarding the breast tumour.

Patient selection again plays an important role in decision making regarding the type of surgery after the administration of neoadjuvant chemotherapy. MRI, if used correctly, is an accurate imaging modality to select patients for breast-conserving therapies after neoadjuvant chemotherapy. The patients selection for breast-conserving surgery can be improved by taking into account the residual disease extent on the pre-surgery MRI, the tumour type based on hormone and HER2 receptor status and the tumour size before neoadjuvant chemotherapy.

Another surgical issue is the staging and treatment of the axillary lymph nodes. The initial nodal status yields prognostic information and affects radiotherapy planning. Therefore, assessment before neoadjuvant chemotherapy by using ultrasound guided fine needle aspiration and – if negative- by sentinel node biopsy is recommended. In the group of patients with cytological proven lymph node metastases before the start of neoadjuvant chemotherapy, it is desirable to identify patients with an axillary pCR to treat them more conservatively. The MARI procedure (Mapping the Axilla with Radioactive Iodine seeds) and FDG-PET/CT are potential methods to select these patients. If the axillary lymph nodes do not respond to neoadjuvant chemotherapy, it is required to perform an adequate ALND after neoadjuvant chemotherapy by removing at least ten lymph nodes to provide adequate local control.

**Future prospects**

The EORTC AMAROS trial is expected to finalize the patient accrual by the end of 2010. It is assumed that the axillary recurrence free rate in the axillary lymph node dissection treatment group at five years equals 98%, and we want to show that the axillary recurrence free rate in the radiotherapy group at five years is not less than 96%. With a one sided log-rank test for non inferiority with alpha=0.05 and beta=0.2, 52 events are needed. Given a low axillary recurrence rate currently observed in the AMAROS-trial, it will be exciting if the number of events is going to be reached. If at three years after the end of accrual, the number of axillary recurrences has not been reached, the primary analysis will nevertheless be performed. A follow-up of three years ensures an average follow-up of 6-7 years. Furthermore, it ensures that we will have follow-up for all patients in the period where axillary recurrences become evident most probable, i.e. within the first two years. Until the final analysis of the AMAROS trial, performing an axillary lymph node dissection will remain the standard treatment. To my believe, axillary radiation therapy is a safe and
adequate alternative with less morbidity for patients with a positive sentinel node in the near future. Not all patients with a positive sentinel node may need axillary treatment, particularly those in whom the perceived risk of additional disease is low. Approximately 50% of patients with a positive sentinel are found to have no further additional disease. Furthermore, systemic therapy, which is generally administered in patients with a tumour-positive sentinel node may eradicate additional lymph node metastases. In addition, radiation therapy after breast-conserving surgery includes the caudal part of the axilla and may contribute to the elimination of additional metastases. These hypotheses are reflected by the extremely low axillary recurrence rate after omitting completion axillary lymph node dissection in sentinel node positive patients. Bilimoria et al. retrospectively assessed the differences in recurrence and survival for sentinel node alone versus sentinel node with completion axillary clearance in 97,314 patients from the American National Cancer Data Base. Compared with sentinel node biopsy alone, completion axillary lymph node dissection did not significantly improve the axillary recurrence rate or survival. Several other studies reporting the axillary recurrence rate after a positive sentinel node biopsy alone show a similar low axillary recurrence rate, 0-3%. However, in the MIRROR study, the largest cohort study in the Netherlands assessing the impact of micrometastases and isolated tumour cells in the sentinel node, omission of further axillary treatment in patients with micrometastases resulted in a significantly higher 5-year axillary recurrence rate (1.2% versus 6.2%, HR 4.45 95%CI 1.46 - 13.54).

These findings provide the rationale for a randomized study comparing a sentinel node biopsy alone (i.e. wait and see) versus axillary treatment in a selected patient population. We designed a new EORTC trial addressing this question, named the POWER trial; Positive sentinel node, Wait and See or Excision by Randomisation. Within this trial we would like to selectively randomize patients with a positive sentinel node between sentinel node procedure only and axillary clearance, based on the a-priori risk of having additional nodal involvement. Several nomograms (Memorial Sloan Kettering Cancer Centre, Mayo, Cambridge, Stanford) and scores (MDA, Tenon, Saidi) are developed to estimate the risk on additional nodal involvement. These models are prospectively compared by Coutant and colleagues. They conclude that the Tenon score and the MSKCC nomogram outperform other methods in all patients. Since the MSKCC nomogram is user friendly and well known in Europe and the United States, we decided to use this nomogram to estimate the a-priori risk of additional lymph node metastases. In the EORTC POWER trial, patients with a low risk on additional lymph node metastases will be randomized between a sentinel node biopsy only and completion axillary lymph node dissection. Patients with a high risk will be treated with a completion axillary lymph node dissection. An advantage of using this model is that patients selection will not only be based on the size of the sentinel node metastasis. Patients with micrometastases and unfavourable tumour and sentinel node characteristics will be classified in the high risk group.
reason to perform an axillary lymph node dissection is to achieve adequate loco-regional control and not to improve survival, therefore the endpoint of this study will be axillary recurrence rate after five years. After the final results of the AMAROS trial will be published, axillary lymph node dissection will be replaced by axillary radiation therapy, if the latter is proven to be non-inferior with less morbidity. Thus, in the future the patient selection for axillary treatment will be further improved. I expect that patients with a positive sentinel node will only receive axillary radiotherapy if they have a high risk on additional axillary metastases. All other sentinel node positive patients will have no further local axillary treatment. In the POWER trial a translational research project will be performed, aimed to identify a gene-expression profile predictive for lymph node involvement in patients with early breast cancer. If a reliable gen-expression profile can be established, the sentinel node biopsy procedure might become redundant.

Patient-tailored treatment has considerable potential in the neoadjuvant setting. At present, the selection of patients for neoadjuvant chemotherapy is based on clinical and pathological variables, in particular tumour size and the presence of lymph node metastases. Theoretically, all patients who are eligible for adjuvant chemotherapy could be treated with neoadjuvant chemotherapy. The decision, however, to administrate adjuvant chemotherapy is currently made after surgical resection of the primary tumour and the sentinel node biopsy procedure. This prohibits the selection of patients for neoadjuvant chemotherapy. Prognostic biomarkers, like the 70-gene profile (MammaPrint®) and the recurrence score (OncotypeDX®), allow early risk estimation, since it can be determined in tumour biopsies before surgery. At present, the MINDACT trial is addressing whether the 70-gene profile correctly identifies those who benefit from adjuvant chemotherapy. In this trial, treatment selection based on the 70-gene signature as compared to clinical risk assessment may show that it does not compromise the overall outcome. In the future, all patients with a poor prognosis 70-gene signature, having a worse survival, could potentially be treated with neoadjuvant chemotherapy. Patient selection should not only be based on the prognosis of the patients, but also on the probability that a tumour will respond to chemotherapy; the prediction of chemosensitivity. Several small studies have shown that the genetic expression profiles of cancer that are highly sensitive to chemotherapy differ from those of less responsive tumors. Large studies are needed to validate these predictors and determine the true performance characteristics of these tests. The thesis shows the predictive value of the receptor-based subtypes and the 70-gene signature. A promising direction of research is to examine the hypothesis that different markers and biological pathways may be involved in determining prognosis, response and resistance to therapy in different molecular subgroups of breast cancer. In addition, several studies assess the value of neoadjuvant endocrine therapy in pre-selected oestrogen-positive patients. Ultimately, patients will be selected for neoadjuvant chemotherapy based on their genetic route...
map showing the need for chemotherapy (prognosis) and showing to which type of chemotherapy they will respond or be resistant (drugs sensitivity). Gene expression signatures should allow a better tailoring of treatment for breast cancer in the next few years. Improving response monitoring during neoadjuvant chemotherapy will contribute to a higher level of patient-tailored treatment. Response monitoring of the primary tumour with FDG-PET shows promising results. Future research will weigh the value of FDG-PET/CT imaging against dynamic contrast-enhanced MRI to evaluate response of the primary tumour. It is expected that these modalities will complement one another in two ways: 1) MRI provides information on perfusion, whereas FDG provides tumour information on cell metabolism 2) FDG-PET/CT may provide earlier assessment of tumour response than MRI for subgroups of patients. In addition, the thesis shows the potential of FDG-PET/CT assessing the axillary response. Further research will determine cut-off points in SUVmax to discriminate between favourable and unfavourable responders with the objective to adjust the treatment to the axillary response. In favourable axillary responders an axilla-conserving treatment may be given and in unfavourable axillary responders the chemotherapy regimen may be changed.

To increase the number of patients treated with axilla-conserving therapy after neoadjuvant chemotherapy, the accuracy of the MARI-procedure will be further assessed. Fifty-two patients with residual axillary disease after neoadjuvant chemotherapy have to be included to prove that the true-positive rate will be above a minimally acceptable limit of 90%. If the accuracy of the MARI-procedure is proven, the discussion remains which patients could be offered a more axilla-conserving therapy; patients with a complete remission or also patients with a partial remission. These patient groups have yet to be specified. However, axilla-conserving surgery will become one of the major benefits of the administration of neoadjuvant chemotherapy in the near future.
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