

Review

Options and Limits of Surgery after Pre-operative Chemotherapy in Breast Cancer

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Abstract. *The primary administration of chemotherapy leads to a reduction in size of tumors, increasing the possibility of breast-conserving surgery in both locally advanced, inoperable and primary operable mamma carcinomas. This, however, increases the rate of local relapse and the rate of mastectomy over the course of the disease, even although the EUSOMA guidelines are not exceeded. Whether the pre-surgical administration of chemotherapy with pathological complete remission actually increases the disease-free rate and overall survival remains to be determined. Further clinical studies are required to establish the reliability of sentinel lymph-node biopsy; currently, axillary lymphadenectomy is still the standard therapy. The response of the tumor to therapy, in correlation with predictive factors and the molecular-genetic profile, could make more individualized treatment regimes possible in the future.*

There is currently a paradigm shift with regard to the "adjuvant" treatment of breast cancer. Proceeding from the model of a systemic disease (1) requiring systemic therapy accompanied by a reduction in the radicalism of local surgery (2), leads to a multi-modal therapy concept. If numerous adjuvant studies have shown an increase in the disease-free (DFS) and overall survival (OS) rates (3), the same success should also be possible with primary systemic therapy. In this regard, the first study of primary systemic therapy in locally advanced, initially inoperable breast cancer was carried out (4). With regard to the benefit of primary therapy for women

undergoing curative treatment, animal experiments showed that, after excision of the primary tumor, significant metastatic deposits proliferated (5) within 24 hours and remained for 7-10 days. At the same time, growth-stimulating factors were found in the blood and the metastatic capillarization increased. Pre-operative chemotherapy reduced proliferation, leading to an increase in the survival time of the animals (6, 7). In addition, carcinomas in an early stage are more chemo-sensitive since, with an increasing number of cells, the probability of chemotherapy-resistant cell clones also increases (7). Given these results, it is understandable that women are offered a primary systemic therapy, with the additional option of breast-conserving surgery. However, balancing a potential reduction in DFS and OS rates for good cosmetic results must be seriously considered. The review examines clinical studies regarding the reliability of surgical methods and the effectiveness of sentinel node lymphadenectomy in breast cancer. Whether there should be a paradigm shift is also discussed.

Option: Breast Conservation after Primary Systemic Therapy

Both internationally and according to the German national S3 guidelines of the AGO (German Study Group for Oncology), primary systemic therapy is the standard therapy for local, advanced, primary inoperable or inflammatory mamma carcinomas with a level of incidence (LOE) 1c and degree of recommendation A (high recommendation, dependent on the existence of randomized studies with controls (8)). The standard chemotherapy regime comprises anthracyclines or anthracyclines followed by taxanes, for at least 4 cycles. As an alternative in postmenopausal, receptor-positive women, third-generation aromatase blockers can be used as a primary endocrine therapy. If the primary tumor is operable, but cannot be resected in a

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breast-conserving manner, or if surgery is contraindicated, then primary systemic therapy is an alternative.

Numerous studies have been carried out and can be classified with regard to: randomized or non-randomized, combination therapy or monotherapy, simultaneous or sequential, change in dose and duration of the dose, as well as point-in-time of the therapy with respect to surgery (9). All these studies attempted to answer the question of whether primary systemic therapy has advantages over adjuvant therapy with regard to the DFS and OS rates and to long-term breast conservation.

In the numerous non-randomized investigations, the patients at various stages of the disease received different chemotherapy regimes. In the study by Amat *et al.* (10), it was shown that administration of 6 cycles of docetaxel as a single agent corresponded to a 72% breast-conserving surgery rate with a pathological complete remission (pCR) of 20%. A similarly high pCR (24%) was achieved by Ezzat *et al.* (11) in a phase II study with 3-4 combination cycles of paclitaxel and cisplatin, although the rate of breast-conserving therapy was only 29%. In the non-randomized studies, the average response rate was generally over 80% (10-16), regardless of the therapy regime administered or the period of time it was applied. The PCR was between 3% and 27%. Interestingly, in recent studies this figure was lower than expected. In 22 women with locally advanced breast carcinoma Wantani *et al.* (17) achieved a pCR of 9% and Espinosa *et al.* (18) achieved a pCR of 18% in 51 women. Taxanes were used in both studies. The reason for the low pCR could be the small size of the patient collective or the large size of the tumors (stage III). It could not, however, be determined from the non-randomized studies whether there was a correlation between pCR and lumpectomy. For example, Bonadonna *et al.* (13) reported a pCR of 3% with a lumpectomy rate of 85%, whereas Espinosa *et al.* (18), who reported a pCR of 18%, carried out breast-conserving surgery in only 12% of the cases. Similarly, Ezzat *et al.* (18) reported a pCR of 24% and a lumpectomy rate of only 29%; Barni *et al.* (19) obtained a 71% rate of breast conservation without giving a figure for pCR. The average rate of breast conservation in all the non-randomized studies was 57%. The results regarding survival found in randomized studies are presented below.

From the first comparisons between adjuvant and primary chemotherapy, both regimes were shown to have the same success rate. After an increase of breast-conserving operations in primary inoperable mamma carcinomas from 0% to 63% in contrast with adjuvant therapy, the same studies were undertaken for primary operable carcinomas (20). There was a clear improvement in the rate of breast-conserving therapy with primary chemotherapy, both in studies carried out at the outset such as that reported by Scholl *et al.* (21) with 4xFAC (5-fluorouracil, cyclophosphamide, doxorubicin) or the Royal

Marsden trial (22) with 4x mitozantrone and methotrexate (+/- mitomycin-C), as well as in later investigations in the framework of the EORTC 10902 (23) with 4xFEC (5-fluorouracil, cyclophosphamide, epirubicin), of the ABCSG 07 (24) with 3xCMF (cyclophosphamide, methotrexate, 5-fluorouracil) or of the NSABP-B18 (25) with 4xAC (doxorubicin, cyclophosphamide). In the largest comparative study (NSABP-B18), including 1,495 women, there was a significant difference between adjuvant and primary therapy of 60% and 67%, respectively ($p=0.002$). This means that breast conservation can be increased to a limited degree after neo-adjuvant therapy, with the greatest advantage associated with tumors larger than 5 cm. A comparison of the studies on breast conservation showed a great variation in the conservation rate, between 22% and 89% (26). This can also be explained by the fact that very different types of surgery and procedures are used for tumors of the same size.

In addition to the goal of achieving a good cosmetic result with high patient satisfaction, maximum reliability with respect to DFS and OS has to be achieved. According to the NSABP-B18 study, which had the longest follow-up of 9 years, there were no differences between primary and adjuvant therapy in this respect: the DFS was 55% vs. 53% ($p=0.5$) and the OS was 69% vs. 70% ($p=0.8$), respectively. Other studies showed equivalent (22, 23) or even a significant increase in OS after neo-adjuvant therapy: 86% vs. 78% ($p=0.039$) (21). In conclusion, it can be said that primary therapy is equivalent to adjuvant therapy.

The question is how to achieve even better results. The existing studies confirmed that a good remission, especially for pathological complete remission, could improve survival (27). Here, the estimated probability of relapse depends on the size of the tumor, the nodal status and age. It has been hypothesized that an increased pCR results in an increase in OS. This had led to neoadjuvant studies in which new substances such as the taxanes have been administered and changes in cycle and dose have been introduced.

One of the most important studies on the taxanes with respect to response rates, as well as to DFS and OS, was the NSABP-B27 study, where the standard arm with 4xAC was compared with the 4-fold sequential administration of docetaxel both pre- and post-operatively (27). In the collective of 2,411 patients, primary taxane administration led to a doubling of the pCR ($p\leq 0.001$), in agreement with the results of the ECTO trial (28) where the primary administration of 4xdoxorubicin/paclitaxel, followed by 4xCMF resulted in a comparably high pCR (23%). Diéras *et al.* (29) also achieved a doubling of the pCR (16%) using a pre-operative dose of 4xAP (doxorubicin, paclitaxel) instead of 4xAC. Of interest is that this high and significant pCR was not confirmed by independent pathologists (8% vs. 6%). The direct comparison of 162 women with an anthracycline combination chemotherapy, 4xCVAP (cyclophosphamide,

vincristin, doxorubicin, prednisolone) followed by 4xdocetaxel resulted in a doubling ($p=0.04$) of the pCR (30).

Investigations were also undertaken to examine monotherapy with the taxanes in comparison to standard combinations. Buzdar *et al.* (31) obtained a lower pCR in monotherapy with 4xpaclitaxel (8%) than with the standard therapy of 4xFAC (17%). As a result, the same research group developed a dose-dense study model comparing the standard 3-week cycle of 4xFAC and paclitaxel with a weekly administration (32). With the more dose-dense regime, the pCR doubled (15% vs. 28%). In comparing the taxanes using a dose-dense regime with a sequential regime, the results of the GEPARDO study (33) showed the clear advantage of the sequential regime ($p\leq 0.001$).

Thus, it is possible to improve pCR results and a 20% rate is achievable. On the one hand, this is the result of the use of taxanes. In contrast with the large fluctuations in the non-randomized studies with very different tumor sizes the pCR remained constant at 20%, in the randomized studies. On the other hand, the pre-operative cycle increase to 8 with a taxane-containing chemotherapeutic agent administered 4 times led to an increase in the pCR (34). Regimes with anthracycline-containing agents resulted in a clearly lower pCR (35, 36), indicating that the pCR depends on the therapy regime.

The use of taxanes also increased the number of breast-conserving operations significantly (29), with the extension of the cycle in the Aberdeen trial ($p\leq 0.01$) (30) and in the GEPARTRIO trial ($p\leq 0.01$) (37). This, however, was not confirmed in the NSABP-B27 (27) study, which had a lumpectomy of approximately 62% in all 3 arms.

The hypothesis that an increase in the pCR can lead to an improvement in the OS and the DSF has been confirmed in several studies (38, 39). In the Aberdeen trial (30) there was a significant increase ($p=0.005$) in the OS rate. Diéras *et al.* (29) showed that, after 18 months, the DFS was higher with the administration of taxanes than with anthracyclines (87% vs. 79%). However, after 31 months, the values for the 2 chemotherapeutic agents were approximately equal. Still, there was a clear correlation between pCR and DFS, since 92% of the patients with pCR were healthy, whereas only 69% of those without pCR were healthy. Thomas *et al.* (36) showed that there was a significant correlation between pCR and OS ($p=0.002$) after a follow-up of 13.9 years. Follow-ups in other studies are, however, still needed to confirm this hypothesis. It is known that the pCR is an important surrogate marker for a more favorable course of the disease and that the pCR is dependent on several biological markers, *i.e.*, a uni-focal, receptor-negative carcinoma with low differentiation responds better to chemotherapy (29, 39-41). Mauriac *et al.* (40) determined that receptor-positive carcinomas responded very well to the first 2 cycles but not after, thus giving rise to the question

of how many cycles receptor-positive patients should receive. Mauriac *et al.* also showed that with tumors with a high proliferation index (Mib1 >40%) there was a linear reduction of the size of the tumor from cycle to cycle, in contrast with tumors that had a lower proliferation index. Invasive lobular carcinomas or carcinomas with a high *in situ* proportion had a smaller reduction in size, although they did have a demonstrable cyto-reduction.

The administration of trastuzumab in Her2/neu-positive patients also seems to have a positive effect on the pCR. Currently, the TECHNO study of the AGO with 4xEC (epirubicin, cyclophosphamide), followed by 4xtaxol plus herceptin and the NOAH study with paclitaxel, adriamycin, CMF and herceptin are underway. Last year at the ASCO, Buzdar *et al.* (42) presented a study with 4xpaclitaxel followed by 4xFEC, both with and without herceptin, in which the herceptin group had a response rate of 67% compared to 25% for the non-herceptin group. This was confirmed by Coudert *et al.* (43), who used 6xdocetaxel and herceptin, achieving a pCR of 41%.

An alternative treatment is the administration of primary endocrine therapy in postmenopausal, receptor-positive patients. Tamoxifen was compared in studies with the third-generation aromatase blockers. Significantly higher response rates (36% vs. 55%) and, therefore, breast-conserving therapies (35% vs. 45%), were achieved with the aromatase blockers (44, 45). In a recently published study, a pCR of 23% in local advanced breast carcinoma was achieved with the 3-month administration of anastrozole (46). Also of interest is a study by Semiglazov *et al.* (47), who found no difference in clinical response between primary endocrine chemotherapy with an aromatase blocker and primary chemotherapy with doxorubicin and paclitaxel. The tendency for increased breast-conserving surgery could be seen with the administration of hormone therapy as opposed to chemotherapy (33% vs. 24%) with, however, no difference in DFS ($p\geq 0.5$).

In conclusion, with respect to surgical options, significant improvements have been made with locally advanced breast carcinomas, but the proportion of breast-conserving operations with primary operable carcinomas is on the increase. Whether and how the lesions should be pre-operatively localized is still open to question. As for the rate of OS, additional follow-up data has to be gathered. It is possible that the surgical advantage initially gained with breast conservation is limited by an increased rate of local relapse.

Local Relapse Rates after Breast-conserving Surgery

The goal of every operation is R0 resection with a cosmetically satisfactory result. The percent of patients who would originally have received a mastectomy but now

receive breast-conserving surgery varies greatly and individually according to the surgeon. For example, in the NSABP-B18 (25) and the ECTO (28) studies less than 30% of the cases underwent breast-conserving surgery, whereas this figure in the AGO study was 52% (48). In general, the primary tumor is operated on in its new margins after primary therapy (according to AGO guidelines: LOE 3b, recommendation level C). However, it is precisely at this point that the question of whether the shrinkage of the tumor is "concentric or honeycombed" (23, 49) arises. Dixon *et al.* (45) reported that there was more breast-conserving surgery and fewer local relapses following endocrine therapy, since histological examination of the tumor tissue after chemotherapy appeared different than after endocrine therapy. These authors' impression was that endocrine therapy shrinks the tumor concentrically, whereas chemotherapy, while it reduces the number of cells in the tumor, sometimes does not reduce its extent. No explanation was given for this difference.

The original rate of 82% for breast-conserving surgery, achieved by Scholl *et al.* (21) was reduced to 61% after a 5-year follow-up, since the patients had to undergo a secondary mastectomy due to local relapse (27%). The literature reported relapse rate is between 3% and 27%, depending on the time of the follow-up and the therapy regime. For example, there was a clearly lower rate of local relapse in the Aberdeen trial (30) with sequential administration of a taxane than without (90% DFS vs. 71% DFS, $p=0.03$). The NSABP-B18 after 9 years showed no increase in relapse in either arm. However, the rate of relapse increased from 11% to 14.5% in the primary systemic arm for the group of patients where a change in indication from mastectomy to breast-conserving surgery had been made after primary chemotherapy, as compared to those patients for whom the initial indication for mastectomy was unchanged (Mamounas *et al.*) (50). Furthermore, it was determined that, in both arms, the patients under 50 who were receptor-negative, node-positive, or who had a tumor larger than 5 cm and had a partial remission with primary therapy had significantly more relapses than patients who did not display one or more of these parameters. On the other hand, Eiermann *et al.* (28) found a connection between the therapy regime and relapse rate since, in both arms of the ECTO trial with initial surgery, 15 women suffered a relapse, whereas only 2 suffered a relapse in the primary systemic arm (the 1,355 patients were approximately equally distributed among the 3 arms).

In conclusion, the local relapse rate depends on the prognostic parameters. Nonetheless, the overall relapse rate is <15%, which fulfills the EUSOMA guidelines. However, whether the increase in patient satisfaction with the cosmetic result (EORTC trial 10801) (51) only represents a shift in time until a relapse occurs remains unanswered.

Whether more operations for the individual patient, increased emotional trauma and higher costs for society are the results also remain to be seen. The data for adequate individual patient recommendations are still lacking.

Sentinel-node Biopsy (SNL) following Primary Systemic Therapy

The method of choice after primary systemic therapy is level I and II axillary lymphadenectomy. It has been shown that a positive nodal status is an important prognostic marker (52), which correlates directly with the pCR (53). In the NSABP-B18 trial there was a significant reduction of positive lymph nodes in the adjuvant group (41% vs. 57%). Several groups have examined whether complete axillary clearance is necessary in patients where primary chemotherapy eliminates axillary disease, including numerous studies with small patient populations and one with 428 patients (50). An SNL detection rate of 82-100% with a false-negative rate between 0% and 33% was common in all the studies. However, as Charfare *et al.* (26) correctly noted that this encompassed different tumor stages, therapy regimes and methods of lymphatic mapping. Taking all the studies together, there was a detection rate of 89% with a false-negative rate of 11%.

Additional results, with larger patient collectives, are necessary before the question of whether a change in regime with regard to axillary dissection can be evaluated.

The indication for post-operative radiotherapy is still a topic of debate (54), but should be decided on prior to the start of chemotherapy.

Primary therapy is a treatment option corresponding to the AGO guidelines, but has not yet provided a basis for a change in paradigm in the treatment of mamma carcinoma. Thus, studies with the goal of therapy optimization by means of changing chemotherapeutic agents, dose-intensification and reduction of intervals, are still being carried out.

Of great benefit are gene expression analyses, DNA microarrays and proteomics, which can be performed prior to, during and after treatment and which are designed to detect new predictive markers. On the other hand, *in vivo* chemosensitivity tests can be used to develop new, more individualized treatment concepts. For example, Pusztai *et al.* (55) discovered a protein peak with paclitaxel which was less pronounced with FAC. Women who showed this protein peak also showed after-surgery markers of micrometastasis. This might justify a post-operative systemic treatment. Microarray investigations have shown a correlation between good clinical response and gene changes during chemotherapy – that is, "clinically responsive tumours show early biological changes which may be predictive of long-term outcome benefit" (56). Hannemann *et al.* (57) confirmed that, in tumor response, a "gene

expression pattern of 30 genes distinguishes" the pre-therapy from the post-therapy status, with no change occurring when there is no response to therapy.

These results will allow conclusions to be drawn regarding treatment regimes and enable new treatment concepts to be developed.

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