Breast Conservative Surgery For Operable Invasive Ductal Carcinoma After Neoadjuvant Chemotherapy Or Hormonal Therapy - A Challenge For Breast Surgeon: A Review Based On Literature And Experience

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Abstract

Neoadjuvant chemotherapy or hormonal therapy is based on biological data and enables more patients to be treated with breast conserving surgery for locally advanced T2 and T3 without significantly increasing the rates of ipsilateral breast recurrence. Careful consideration of an optimal preoperative planning aims at accurately determining the patterns of primary tumour down staging and at the amount and location of any residual tumour in the breast, besides converting patients from mutilating surgery candidates to candidates for breast conservative procedure. The use of induction chemotherapy has the potential to improve the cosmetic results but free margins must be achieved and surgery must be planned in onco-plastic surgery. Axillary lymph node clearance is still the gold standard surgery in the treatment of the axilla. Sentinel lymph node biopsy can be done for clinically N0 patients but only in control trials.

Keywords

Neoadjuvant systemic therapy, breast cancer surgery

Introduction

Neoadjuvant chemotherapy or induction systemic chemotherapy began in the 1970’s for locally advanced or inflammatory breast cancers(1, 2). In the 1980’s, this therapeutic strategy was extended for operable breast cancer of more than 3cm and/or in central position in order to avoid modified radical mastectomy if a good downsizing of the tumour allows a breast conserving surgery(2, 3, 4, 5). The goals of neoadjuvant systemic therapies are:

- Free margins for invasive and in situ carcinoma;
- Local recurrence is less than 10 percent at 10 years;
- Overall and disease free survival is at least the same compared to after modified radical mastectomy followed by adjuvant systemic therapy;
- That these objectives must result in good psychological results for well informed patients;(6)
- To have an in vivo test of sensitivity to the systemic therapies (chemotherapy +- target therapy or hormonal therapy) and theoretically to destroy micro metastases before surgery of the primary tumour and by consequence to improve overall and relapse free survival(7, 8)

Objective and Methods

The goal of this paper is to help surgeons plan for breast conservative procedures after neoadjuvant therapy for T2, T3 N0 N1 M0 breast cancer. The method used was to review the results of trials on neoadjuvant therapy and the surgical technique proposed in the literature and our own experience as breast cancer surgeons. This paper focuses on surgery after systemic neoadjuvant therapies for operable breast cancer.

Preoperative work-up before Systemic Neoadjuvant Therapies

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A precise clinical staging must be established before neoadjuvant systemic treatment must be done in close collaboration with the radiologist and medical oncologist. Clinical examination by the breast surgeon is essential.

Clinical size of the mass should be described with accuracy, and its location inside the breast in standing and lying position. The skin over the tumour can be tattooed\(^9\). The opposite breast must also be examined. Clinical examination of the homolateral and contra lateral axilla and supraclavicular area must be performed. Radiological work-up of the breast must be done with bilateral mammogram and homolateral breast ultrasonography (US), US of axilla, and breast MRF\(^{10,11}\). Size, shape of the mass and its location must be described.

MRI of the breast is important in order to have a precise size of the tumour and to know if the tumour is multicentric or multifocal. MRI may change the strategy of neoadjuvant chemotherapy and conservative procedure to modified radical mastectomy and adjuvant systemic therapy in 20 to 30% of operable breast cancers with more than 4cms\(^22,23\).

Core biopsy of the tumour is absolutely necessary before starting systemic therapy to be sure that it is an invasive breast carcinoma. This will provide all prognostic factors from the primary tumour:

- Histological type, grading, oestrogen and progesterone receptor status, Ki-67 and eErb2 profiles;\(^{14}\)
- During core biopsy, one or two liga clips or other metallic guide marker must be put in the tumour, so that in case of complete clinical or radiological response (CCR), the surgeon knows with accuracy the location of the primary tumour before systemic therapy;\(^{12,13,14}\)
- The identification of molecular predictors of prognosis and response to cytotoxic agents - mainly to ANTHRACYCLINES, TAXANES and hormonal therapies - is still a research priority with potential effects on the clinical management of locally advanced breast cancer;\(^{15}\)
- On the core biopsy before neoadjuvant systemic therapy, gene expression profiling studies result in a classification of breast cancers in several major groups which include Lumina A and B (ER+Cerb2), Human epidermal growth factor 2 (HER2) positive, basal-like and a normal breast-like groups;\(^{16,17}\)
- Genomic predictors to drug sensitivity (pharmacogenomic) have been used for neoadjuvant systemic therapy with promising results. The pathologist plays a key role in establishing an accurate prognosis and he should focus on the possibility of using the most appropriate neoadjuvant systemic therapy;\(^{17,18}\)
- A systemic work-up must be performed before neoadjuvant systemic therapy for the tumour over 3cm or for a tumour with palpable metastatic axillary lymph nodes. Other specific work-ups such as tumour markers CEA, CA15-3, liver U/S, bone scan and chest x-ray must be done if the patient has particular warning signs of metastasis. MRI Brain, MRI Spine, liver, kidney and heart function tests must be performed before neoadjuvant chemotherapy. PET/Scan would be useful when all the test for metastatic deposits are negative but the tumour markers are high;\(^{14,19,20}\)

**Work-up during neoadjuvant systemic therapy**

Clinical evaluation of the tumour must be done before every course of neoadjuvant chemotherapy and after two months of hormonal therapy. Mammography and U/S of the breast are performed after 3 courses of chemotherapy and after 3 months of hormonal therapy. An increase in size of the tumour must be considered as a resistant tumour to the treatment (less than 5% of the cases)\(^{21}\). In such case, a new strategy must be discussed between the surgeon and medical oncologist (modified radical mastectomy or new neoadjuvant systemic therapy). In case of stabilisation or regression of the tumour, the same neoadjuvant therapy regimen

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must be followed. The surgeon must be fully involved in the follow-up of the patient during the treatment. MRI of the breast 3 weeks after the first course of neoadjuvant chemotherapy or three months after hormonal therapy is a very important examination. Kinetic and intensity of reinforcement after contrast on dynamic MRI is correlated to the volume of the residual tumour tissue after treatment. After one course of chemotherapy, we can know which tumour may respond to the treatment.(12, 13, 21, 22)

MRI of the breast during neoadjuvant systemic treatment is an important indication for prognosis and the therapeutic sensibility on the tumour.(22, 23) An MRI of the breast must be done at the end of neoadjuvant systemic therapy to know the following:

• The residual tumour size - conservative procedure is indicated if the downsizing is more than 50%;
• If the tumour is solitary - whether it is multicentric or multifocal because conservative surgery is performed only for localised tumour;
• How the tumour shrinks - conservative treatment can be done when the shrinkage of the tumour is concentric and if it shrinks in separated blocks of residual tumour surrounded by tumour necrosis. In such case, mastectomy is the best option.(22, 23, 24, 25)

MRI of the breast before surgery has a key role. As far as the morphology and size of the tumour after preoperative systemic therapy is concerned, the surgeon can plan the surgical strategy, mastectomy or conservative procedure. The patient must be informed of the decision before surgery.

Microcalcifications without residual tumours after preoperative chemotherapy are not good indicators of residual viable tumour cells. Microcalcifications in the area of primary tumour may persist and may be due to tumour necrosis. These are very useful for the surgeon because they give a good indication of the location of the primary tumour when there is complete clinical and radiological response. The surgeon must remove all the microcalcification foci. An x-ray of the specimen must confirm that all the foci of microcalcification are removed with good margins.(9,10)

Multiple core biopsies during preoperative chemotherapy on the residual tumour are only performed for clinical research(15). Dynamic analysis (biological response) and comprehensive analysis (genetic profiles, qualitative transcriptase and protease) will provide predictive and prognostic information in near future.

PET/Scan of the breast (FDG/PET) in the early assessment of response to neoadjuvant chemotherapy in evaluation and diminution of the tumour metabolism during chemotherapy is an indicator of a good response. We cannot conclude that there is no residual tumour at the end of the preoperative chemotherapy if FDG/PET is considered negative. PET could be used to fix the date of surgery for chemo resistant tumour.(19, 20)

At the end of the neoadjuvant systemic treatment, a multidisciplinary decision must be taken by the surgeon, medical oncologist and the radiologist. The patient and her family must know very clearly why such a strategy is planned for her breast: modified radical mastectomy or conservative procedure. She must also understand that a final decision will be taken during and after conservative procedure.

Surgical Treatment of the Breast

Modified radical mastectomy is indicated:

• When the tumour is in different quadrants of the breast, but in case of multifocal tumour, modified radical mastectomy is not necessarily indicated and breast conservative surgery may be done if good free margins can be achieved;
• When the shrinkage of the tumour is not concentric;
• For premenopausal patients, when there is a high family sensitivity to breast cancer and in BRCA mutation carriers, mastectomy is the most effective strategy to avoid local recurrence for this group of patients. As we know, mastectomy does not benefit in survival, breast conservation could be considered if there is a near or complete
response after preoperative chemotherapy.

- After modified radical mastectomy, an immediate breast reconstruction can be considered.
- Skin sparing mastectomy and immediate breast reconstruction is proposed by some authors if the downsizing or the multicentricity or multifocality does not allow for breast conservation; the number of the patients treated and their follow-up are very limited; this technique cannot be recommended outside of controlled clinical trial.

For all these cases, neoadjuvant chemotherapy is proposed before mastectomy to raise the possibility of cure in spite of locally advanced operable breast cancer. Conservative surgery is acceptable only if the surgeon can perform a wide local excision of the residual tumour with free margins (>1cm around the tumour) and with a good cosmetic results. After surgery and adjuvant radiation therapy, the breast must be soft, not painful, with good shape and volume.

The most challenging situation for the surgeon is when there is a complete clinical and radiological response after preoperative systemic therapy. The surgeon must be a member of multidisciplinary team following the patient during the preoperative treatment and it is very important to have metallic markers inside the tumour during the first core biopsy.

After neoadjuvant chemotherapy or hormonal therapy, the surgical technique is the same as classical conservative procedure. In our experience, to avoid as much as possible positive margins and to have optimal local control, wide local excision must remove as much as possible breast glandular tissue around the residual tumour or around the metallic marker in case of complete clinical response but allowing a good shape of the breast. Resection of the gland must go down to the pectoral’s fascia. If the tumour is near the skin, the ellipse of skin is removed over the tumour.

If the tumour is retro areolar, the nipple areola complex must be removed with the residual tumour and for central tumour, a large core of glandular tissue must be removed around the tumour. Two liga clips must be put inside the tumour bed on the pectoral’s muscle to localize accurately the tumour if boost of radiation therapy is needed. A good gland exploration by palpation must be done by the surgeon after wide local excision of the tumour. Any suspicious nodule must be removed and sent for frozen section. After a good haemostasis, the breast must be rebuilt following the rules of onco-plastic surgery with no drain inside the tumour bed.

Breast conservative procedure is safe after neoadjuvant chemotherapy. The rate complication as hematoma infection and necrosis is as rare as after conservative surgery without preoperative therapies, but surgery must be performed at least 3 weeks after the last course of chemotherapy and 4 weeks after target therapy. Adjuvant radiation therapy can be started safely 2 to 3 weeks after surgery.

The status of the margins is very important issue because it is the best established factor for local recurrence. The probability to find residual tumour on the margins is high for large tumours and younger patients. The probability to find residual invasive or in situ carcinoma when the margins are 2-3mm could be up to 17%. When the margin is locally positive for DCIS, the risk of residual tumour is 89% and when it is multifocal it is 100%.

Frozen sections on the tumour are not recommended by the International Guidelines because accurate evaluation of the status of the margins after neoadjuvant systemic therapy is extremely difficult. The specimen must be sent to the radiology department for a specimen x-ray to know the macroscopic margins around the metallic landmark. When there is a palpable residual tumour, the specimen must be examined per operatively macroscopically by the pathologist. He can give the surgeon the macroscopic size of the residual tumour and the minimal distance in millimetres from the tumour to the margins. The size of the residual tumour is compared with the size of the primary lesion. When there is no palpable tumour (complete clinical response) the specimen can be only
studied in the paraffin sections.

After an accurate histopathological study by a breast cancer specialist, the patient will face three situations:

1. There is a residual carcinoma but all margins are free of invasive or in situ carcinoma and lymphovascular invasion, conservative surgery is the good option;

2. The free margins are close to the tumour (<5mm) or invaded by invasive or in situ carcinoma; modified radical mastectomy is the best option if a new WLE will give a bad cosmetic result. But we must outline that the risk of mastectomy after a well planned wide local excision is less than 15%.

3. There is no clinical and radiological residual tumour in 15 to 30% of the cases (CCR), the surgeon must remove widely the gland around the metallic markers because there is a great discordance between the pathological results and clinical and radiological response.

Pathological complete response (PCR) is found only in 10 to 15% of the cases. For NSABP B18 study, after neoadjuvant chemotherapy 248/1573 cases had CCR but only 89 (13%) were PCR. These results explain the high risk of local recurrence when after CCR, the patient has only adjuvant radiation therapy without local control by surgery. The patient must be informed before the surgery that a mastectomy must be done in spite of planned conservative procedure during the operation or after the pathological results.

In conclusion, we must outline that neoadjuvant systemic treatment can be difficult to accept by very anxious ladies who wish to be quickly freed from their tumour and to undergo mastectomy in spite of conservative treatment. We know that neoadjuvant systemic therapy does not improve overall survival over systemic adjuvant therapy and has only a prognostic impact on disease free survival and overall survival rate when there is a PCR. Modified radical mastectomy followed by adjuvant therapy could be the best option for these patients.

Treatment of the Axillary Lymph Nodes

Because the risk of invading lymph nodes in the axilla is high (50%) for tumour over 3cm, and MD ANDERSON’S studies had clearly shown that only 23% of the positive axillary lymph nodes (FNAC) become negative after preoperative chemotherapy, an axillary lymph node dissection is still the gold standard treatment of the axilla. We must also outline that the overall survival at 5 years is less than 50% when the axilla is still positive after preoperative chemotherapy and 80% for negative axilla. The persistent positive axillary lymph nodes are strong prognostic factor.

When the axilla is clinically (N0) or US negative before or after neoadjuvant chemotherapy, sentinel lymph node biopsy can be an option to avoid unnecessary axillary lymph node dissection for pN0 patients, but the technique is not yet standardized and must be done only in well-controlled clinical trial.

For large tumours with high risk of lymph node invasion, the sentinel lymph can be completely invaded by metastases and not found by a sentinel lymph node mapping. After neoadjuvant chemotherapy, the risk of false negative may be due to the intra glandular tissue necrosis due to the down staging.

Conclusion

For locally advanced operable breast cancers, meta analysis and many clinical trials confirm that neoadjuvant chemotherapy with or without target therapy or hormonal therapy increases breast conservation rate (75%) at the cost of an increase risk of local recurrence rate; however, this rate is not compromised even if the patient receives adequate surgery with free margins and even if the tumour undergoes complete remission. Surgery after neoadjuvant therapy needs a well trained breast surgeon in onco-plastic surgery. Indication of preoperative systemic treatment for operable breast cancer must be taken after multidisciplinary approach with the breast surgeon. He must know onco-plastic surgery of the breast and aware of the advantages and inconveniences of breast conservative surgery.

after neoadjuvant systemic therapy. He must work in close collaboration with the medical oncologist, the radiologist and the pathologist who depend on his key role for the optimal management of breast cancer patients. In 2010, Axillary Lymph Node dissection is still the standard treatment of the axilla after the neoadjuvant systemic treatment.

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