BREAST CANCER
CONSERVATIVE AND RECONSTRUCTIVE SURGERY

Extended abstract
UDC: 618.19-006:616-089.8:504.06

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Breast conserving and reconstructive surgery for breast cancer - indications and contraindications in DCIS and minimal cancer - state of the art

KEYWORDS: Breast neoplasms; Breast-conserving surgery; Breast reconstruction

Breast, mammary gland, symbol of maternity and femininity, is accessory skin gland. Breast is often affected by numerous pathology conditions. Breast cancer is the most frequent cause of death in women.

BASIC PRINCIPLES IN DIAGNOSIS AND THERAPY OF BREAST CANCER

At the onset of breast symptoms woman should be immediately submitted to specialized institution. Despite the fact that the most of the lesions in the breast are benign, one should always think that the incidence of breast cancer is increasing.

Surgeon, radiologist and pathologist are representing a diagnostic team. Surgeon must be educated in diagnosis, therapy and prognostic factors in breast cancer as he could provide an adequate information to the patient. Surgical treatment for breast cancer involves mastectomy, breast conserving operation and/or mastectomy with reconstruction, so reconstructive and plastic surgeon should also be a member of the team.

Mammography and ultrasonography are obliged part of clinical examination. Modern technology enables stereotaxic, computed guided biopsies, ultrasound guided biopsies of the breast cyst, etc. Radiologist should be trained in all these procedure.

Implementations of breast cancer screening and early detection have provided the increase of detection of small cancers (<10 mm) and cancers in situ. An adequate histology examination and evaluation of risk factors is the goal of pathologist in efforts to establish biological prognostic factors.

Chemotherapy and radiotherapy are of course the integral part of treatment of breast cancer, in respect on stage of the disease. Therapeutic team involves surgeon, radiotherapist, medical oncologist, and pathologist and radiologist (1).

Implementation of National diagnostic and therapeutic protocol is of essential value in standardization of diagnosis, therapy and follow-up in cancer patients (United Kingdom, Danish Breast Cancer Cooperative Group-DBCCG '77, Serbia, etc.) (2).

Advantages of specialized treatment, especially educated surgical oncologist, in patients outcome have been reported (3).

Diagnosis of breast cancer Surgical oncologist has the key role in diagnosis of breast cancer, as well as coordinating of specialized team.

Three steps in management of palpable breast lesion:

1. Clinical examination of trained surgeon
2. Mammography and/or Ultrasonography if necessary
3. Fine Needle Aspiration Biopsy (FNAB) or core biopsy.

If diagnosis couldn't be obtained an open biopsy for histology examination is indicated. One shouldn't always insist on frozen-section examination in respect of possible false results.

Women with positive family history for breast cancer have an increased risk for developing the disease. Approximately 5-10% has the inherited breast cancer, and should undergo genetic examination.

Standard procedures in patients with suspect breast tumor At least 80% of patients with palpable breast lesions should be examined as soon as possible, at most in the first 5 days.

In more than 90% of patients the diagnosis should be obtained by preoperative FNAB or core biopsy.

Suggested open, excision biopsy should be performed in 2 weeks in 90% of cases.

In specialized institutions benign/malignant lesions ration is less than 1:1 (not involved abscesses or breast secretions) (4).

Treatment options and planing The patients with breast cancer should be treated in specialized institutions. Only trained surgeon should operate the breast cancer. If breast reconstruction is planed, plastic surgeon should be involved.

Invasive breast cancer The patient must be timely informed about the treatment approaches, types of operations and possibilities. Patient's agreement for operation is the key stone in planing the treatment.

Possible operations are:

1. Breast conserving operation with dissection of axillary lymph nodes and consecutive radiotherapy of breast remnant,
2. Modified radical mastectomy,
3. Modified radical mastectomy with immediate or delayed reconstruction

Lymph node dissection of axillary lymphatic enables:

- precise histology staging
- information of prognostic parameters
- prevention of regional relapse

It is the most important in obtaining the prognosis in breast cancer (5).

The most of surgeons suggests dissection of lymph nodes of first and second level. If the nodes in third level are suspected of metastases, dissection should be performed. Number of dissected lymph nodes is disputable. In goal of good local and regional control, and diagnosis of lymph node metastases, dissection of two or all three levels is suggested (6).

The average number of lymph nodes is about 25, and it depends on surgeon's skill and pathology examination (7).

Radiotherapy of axillary lymphatic in case of complete dissection is not advisable because of high percentage of lymphoedema.

Non-invasive breast cancer At the time of diagnosis non-invasive breast cancer is potentially curable. Mastectomy presents the therapy of first choice; nevertheless it could be over-treatment for some patients. Inadequate treat-

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The manuscript was received: 12. 10. 2001.

Accepted for publication: 19. 10. 2001.

ment of *in situ* carcinoma leads to invasive ones and worse prognosis. At this moment there is no consensus about the best treatment approach for *in situ* breast cancer (8).

Lobular carcinoma *in situ* (LCIS) has higher risk to become invasive cancer. It depends on number of acinars and nuclear grade. The majority of experts suggest only follow-up, although the extent of surgery is from biopsy to bilateral mastectomy (9).

Ductal carcinoma *in situ* (DCIS) precedes invasive cancer. The therapeutic dilemmas still exists. Mastectomy should offer almost 100% of curability. The relapse risk after breast conserving surgery goes from 5 to 60%. This risk depends on size of lesion, extent of excision and free margins, histology subtypes, etc. Breast conserving surgery followed by radiotherapy should provide the same results, but is still controversial (10).

Axillary dissection is not recommended in non-invasive lesions.

In respect to existing dilemmas these patients should be randomized in clinical trials.

Quality assurance Breast cancer department should employ specialized surgeon educated in this filed, as well as radiologist, pathologist, medical oncologist and radiotherapist.

Diagnostic and therapeutic decisions are multidisciplinary.

About 90% of patients planed for surgery should be operated in the first 3 weeks.

Also, 90% of patients after breast conserving operations shouldn't undergo more than 2 operations.

Free margins of the excised tissue must be at list 10mm and confirmed by pathologist. Histology grade of lymph nodes must be established in invasive breast cancer. At list ten lymph nodes should be dissected.

Postoperative radiotherapy of axillary region is not necessary in cases complete dissection. In extensive DCIS breast-conserving surgery is not recommended.

Follow-up The patients should be followed on 6 months controls for the first 5 years and after that once a year. Follow -up must consider clinical examination, mammography once a year or in two years in respect on risk factors, Chest X-ray, whole body scans, Ultrasonography, CT, MRI (according to clinical findings), tumor markers, etc. Follow-up is protocolized.

SENTINEL LYMPH NODE BIOPSY (SLNB)

Sentinel lymph node is the first node draining the primary tumor. Correctly identified and histology examined it could point on lymphatic spreading of cancer. At the present, combination of blue-dye and radionuclide gives the best results in identification of SLN. It is suggested that surgeon should perform at list 20 biopsies in order to get skilled for the method.

The aim of SLNb is to estimate axillary lymph node involvement and to avoid unnecessary dissection in absence of lymph node metastases. In cases positive results, dissection is obligated in order to reach adequate locoregional control and prevent distant metastasizing of breast cancer.

It is suggested that SLNb should be performed in stage I and II of the disease. Poor surgical technique and bad estimation of lymph node involvement could lead to Sirius mistakes (11)

Surgeon as the factor of prognosis The main assignment of surgeon is to provide local and regional control of the disease. Local and regional relapse is usually a sign of systemic spreading, distant metastases, with consequent lower survival rate. Surgical technique is therefore very important in locoregional control.

BREAST CONSERVING SURGERY (BCS) IN BREAST CANCER

The aim of breast conserving surgery is to equalize the therapy results with mastectomy, as well as to provide better quality of life in patients with breast cancer. Cosmetic aspect is therefore very important in BCS.

Skin incision has two basic principles:

- to provide free margins of the specimen
- to be cosmetically satisfactory

The place of incision is guided by the tumor site, but well hidden. Periareolar incision for tumor in central quadrant of the breast is not recommended because of poor cosmetic results. Therefore, mastectomy with reconstruction or infra-mammary incision is alternative.

Excision is indicated if the upper skin is involved.

Infra-mammary approach provides easy bimanual exploration of complete gland. It is especially recommended for tumor in medial quadrants (13).

Lumpectomy (tumorectomy) At the beginning of BCS era, quadrantectomy or bi-quadrantectomy for breast tumor was mandatory, very often with bad cosmetic results. Lumpectomy with 1 cm of free margins is satisfactory, both in oncolgical and cosmetic aspects.

Following the skin incision, lumpectomy is performed with scalpel or scissors at list 1 cm from palpable tumor to pectoral fascia. The excised specimen is cubical. Deliberating pectoral fascia enables good exploration of the remaining tissue and gives the possibility of reconstruction with glandular flap.

Reconstruction of glandular tissue Some authors do not suggest glandular reconstruction and wait till fibrous tissue fulfil the defect (14).

The others, consider glandular reconstruction necessary. It could easily be done with resorpitve sutures when the defect is small. In cases of large tissue defects, glandular flaps are used either from pectoral or lateral sides. Usually mastopexy or reduction of the other breast is not necessary (15).

Skin closure Skin closure is performed in two layers. Inverted resorptive sutures in fatty skin tissue and intradermal non-resorptive sutures for skin.

Drainage Aspiration drain for 2-3 days.

Axillary dissection Skin incision for axillary dissection is usually separated. Two types of incision are suggested:

- parallel to lower edge of great pectoral muscle
- in skin crease normally to pectoral muscle (8 cm)

Following the incision, skin flaps are formed from lower edge of great pectoral muscle to anterior edge of dorsal latissimus muscle. The extent of dissection is usually two levels (acc. Berg) (16).

Subcutaneous mastectomy Subcutaneous mastectomy is indicated in cases of multicentric DCIS or preventive surgery for breast cancer. It is always followed with implantation of sub pectoral endoprosthesis.

Skin incision is usually infra-mammary. The whole gland is separated from pectoral fascia and chest wall. Separation from the skin, especially in retro-areolar region, should be carefully in order to provide radicality and conserve blood supply for the skin. This procedure should be done with scissors. The thickness of the flaps should be 5-8mm. The most delicate part of operation is removal of axillary tail and distinction between axillary tissue. Axillary tail and retro-areolar site are marked with sutures and sent to histology examination.

The operation is continuing by placement of endoprosthesis under the pectoral muscle. The best cosmetic results are in small, non-ptotic breasts.

Reconstructive surgery in patients in early stage breast cancer Despite the fact that majority of women in early stage breast cancer undergo BCS and postoperative radiotherapy and eventually chemo and/or hormonotherapy, reconstructive surgery has the same importance. It is particularly important in patients who had mastectomy for early stage breast cancer for following rea-

sons:

- small breast which consider bad cosmetic results following BCS
- Tumor in central quadrant of the breast
- DCIS with extensive intra-canalicular spreading, or multiple DCIS with unclear margins.

Mastectomy with reconstruction does not have negative influence on survival of patients with breast cancer (17,18,19).

Postoperative radio and chemotherapy do not compromise wound healing and don't increase postoperative complications after reconstruction (20,21).

The choice of reconstructive technique depends on breast volume and treatment modalities. Breast reconstruction could be done with implant or myo-cutaneosus flaps, immediately or delayed after adjuvant treatment.

Implantation of definitive or expander endprosthesis is generally easy procedure that doesn't significantly prolong mastectomy. Expanders are filled from time to time (2-3 weeks). When the satisfactory volume is reached, the expander is removing, and definitive prosthesis implant in capsular cavity. Chemotherapy is not contraindicated simultaneously. Radiotherapy could slightly impact the wound healing and in a small percentage could cause skin retraction, but is not contraindicated. Radiotherapy of regional lymphatics is not contraindicated as well.

Reconstruction with myo-cutaneous flaps (rectal abdominal muscle-TRAM or dorsal latissimus muscle-LATISS) on vascular branches is rather popular technique.

Each technique has its own advantages and is chosen by individual approach.

Loco-regional treatment depends on stage of the disease. In cases of distant metastases, loco-regional therapy is not curable, so systemic approach is the treatment of choice. In cases where the disease doesn't affect first lymphatic barrier, surgery and/or radiotherapy can provide good loco-regional control (22).

In the early stage breast cancer, diagnostic procedures could fail in detection of occult distant metastases 10mm (23).

Tumor markers, especially CA 15-3, are not quite reliable. They can give a suspicion, but are not absolute sign of metastases (24). Therefore, further therapy shouldn't be applied even in high values of tumor markers.

The aim of loco-regional treatment is to provide information's about the extent of the disease and prognostic parameters, so adjuvant chemo and/or hormonotherapy could be consider.

Advantages in surgical techniques of axillary dissection have provided decrease in postoperative sequels (motor and sensitive innervations, lymphocoelae, lymph oedema of the arm, etc.) (25,26,27).

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Archive of Oncology 2001;9(Suppl 2):76-7.

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Breast cancer conserving surgery - quality of life

KEYWORDS: Breast neoplasms; Breast-conserving surgery; Breast reconstruction

INTRODUCTION

Conserving or radical surgery in operable breast cancer is a dilemma, which draws attention of both surgeon oncologists, and patients.

The past three decades of the last century were sufficient time distance to enable making of the series of sick patients who were cured with radical or conserving breast surgery. Through analysis and evaluation as well as follow up of patients with this disease, it is possible to make adequate conclusions on the value of one surgical method.

The conserving surgery (CS) concept in early curing of breast cancer has emerged from the possibility for detection of breast cancer in zero or clinically first stage of the disease. Progress of the medical technology and appearance of new diagnostic methods, and mammographs of high sensitivity, as well as by application of xeromammography and digital mammomat and computer directed mammography, enabled that starting from non-palpable lesions, small tumours of l cm may be detected.

It is well known, in the biology of tumour, that malignant potential is being augmented with geometrical progression when transiting from subclinical stage into the clinical phase. In this stadium only, tumour is accessible to palpation to surgeon, i.e. to physician, and very often to the very patient, as well.

In the oncological surgery there existed a period of outstanding radicality, in the first half of the 20th century, in curing of malignant tumours. Even breast surgery was not immune to such approach, which brought to the performances of extended mastectomy - amputations of Halsted or Urban type. These mutilant operations caused permanent consequences: impaired esthetic appearance and poor cosmetic result, as well as organic sequela, leading to invalidity.

Lost torso, problems in functional mobility of arm, paresthesia, limited mobility in shoulder, and arm oedemas, as additional moments, remaining permanent after such operations.

As a consequence of the lost of breast - organ being the best symbol of femininity, physical and emotional traumas and complexes emerge, particularly in young patients.

Lately, we are witnesses of the fact that age limit for appearance of breast cancer is moving towards the younger population (from 30 - 40) so, having in mind that after operation she is going to be permanently deprived of her image, makes her mentally instable.

PATIENTS AND METHODS

When first trials on breast conservation surgery were published, 20 years ago (Guy's, Milan I, II Villejuif, NSABP B-o6), they were received with interest. Well designed, randomised, and documented, trials showed long free interval in selected cases in curing of breast cancer (To, T1abc, T2 to 25mm, No-1, Mo). This encouraged other surgeons, oncologists, to start CS performance.

In our Institute, the first breast CS were performed during 1980 (author's remark).

The concept - resection from the edges of primary tumour, as far as possible, was altered by the optimal, i.e., free - margin edge, of 2 cm at the most, into the healthy tissue.

As with CS tumour is being resected, removing in that case more or less of the glandular tissue, the following titles were inaugurated: tumourrectomy, lumpectomy (segmentectomy) and quadrantectomy.

The volume of CS on the breast depends on the histological findings. If it refers to DCIS and LCIS, i.e., carcinoma In-situ, then tumourectomy or lumpectomy is managed, without dissection of axilla. In other cases, of the invasive carcinoma findings, regardless to the histological type, Igl axillary dissection is managed.

Dissection of lymphatic knots (I,II,III) of axilla, being the first obstacle, makes the constituent part of breast.

In various authors, a level of dissection of lymphatic knots of axilla is from: excrement of the lower floor, standard dissection of lower and medium floor, to the radical dissections of all three floors, including apical knots. Lately, over the last 10 years, by introducing sentinel biopsy, radicality of axilla dissection is being altered. Some authors insist that with negative sentinel biopsy, it is not necessary to manage Igl dissection in the first act.

Our attitude is to make frozen-section check-up of one lymphatic knot, prior to decision on CS, and should it be negative, to approach to conservation surgery. The first CSs were booked for tumours located in the upper outer quadrant of breast, so quadrantectomy and axillary dissection were performed through one incision. Later on, authors demonstrated that through two incisions, particularly in localization of tumour in other quadrants , the planned resection of primary tumour, might be safely done., while axillary dissection may be performed through other incision. In this way, the appearances of keloid scars is prevented, if incision is more than 10 cm long, as well as fibrosis of the remainder of breast. Also, in this way, it is possible to prevent lymphostasis, in the breast skin. One of the difficulties in operation of voluminous breast is to solve vacuum upon quadrantectomy, which may be achieved by mastopexy.

Further improvement in CS in the sense of better aesthetic and cosmetic incidence is achieved by combination of excision of primary tumour, silicone filled up cavum, with silicone partial prosthesis in combination with oncoplastic breast operations.

In continuation of curing in CS performance, radiotherapy is applied transcutaneously, to the remainder of breast, with 45 Gy, eventually with boost dose of 10 Gy to the tumour bed. Radiation of regional lymphatics is applied in cases of medial localisation of tumours and with lymphatic knots in axilla (N+3 and more). Application of adjuvant chemical/hormone therapy depends on the size of tumour (< 10 mm) grades HG II, III; finding of lymphatic knots (N+) and receptory status (ER+,PGR+).

It is of great importance to point out the fact that decision making for the determined type of breast surgery must be performed after detailed conversation made between surgeon and patient, and upon agreement made by the patient for conservation surgery treatment.

RESULTS AND DISCUSSION

Standard parameters of evaluation: appearance of local relapse i.e., local recurrence in the remainder of breast tissue, i.e., skin and metastasis at a

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The manuscript was received: 12. 10. 2001.

Accepted for publication: 19. 10. 2001.

great distance, as well as the survival period, are identical both in conservation and radical surgery.

Surgery and radiotherapy may induce consequences, therefore the same must be taken into account when evaluating success of the breast CS only to mention the most important:

- skin changes: chronic inflammation, retraction, fibrosis, and lymphostasis;
- arm mobility: in elevation, rotation, and retroflexion;
- arm oedema: with or without lymphangitis;
- neuromuscular changes: pains, paraesthesis, paralysis, neuropathy.

In breast CS, it is very important to evaluate aesthetic, i.e. cosmetic outcome (image), and their influence to the patient's life quality. The cosmetic result is important because it is one between two factors, together with local controls, which are the reason for the choice of this therapeutical model. Evaluation of cosmetic outcome must be objective (qualitatively and quantitatively) by documented image - photography upon surgery, and, prior to radiotherapy, and finally, after completed locoregional therapy, as well as one year after on the follow-up. For interpretation of aesthetic view in CS, there is a scale of category: good, fair, poor and nonmeasurable. The symmetry of alveola and breast contour is being measured as well. For the complete evaluation of the success of the surgery, we must take into consideration functional sequela, which may be wounds - late and permanent.

For assessment of the CS value, the estimation of results of conservation and radical operations is essential (under the same conditions).

Comparison of own results to the results achieved by other authors, i.e., trials, is of great importance.

In the latest recommendation obtained by EORTC and UICC, the evaluation of the patients quality of living, is to be determined by means of score application chart, which includes functional results and psychical condition of patients treated by conservation surgery.

Breast conservation surgery was introduced in our Institute in 1980, and put into procedure as of 1983. In the beginning these operations were performed in small percentage in relation to the total number of sick with breast cancer, as well as on the number of sick with radical mastectomy.

The number of operations was growing in all conformity to the world trend, as well as personal experiences in this field of surgery. In the previously published works we have presented results of the breast CS curing over the period between 1989 and 2000. Our experience is based on 958 patients operated by conservation surgery in the above-mentioned period of 12 years, patients aged (Rank 22-62). In the beginning the small tumours up to 15 mm were treated, but later, this limit is moved to 25 mm (T1,T2 small).

Firstly, pathologists were asked to give their opinion on the type of tumour on the frozen-section biopsy, and primarily we performed CS in ductal CA, both DCIS and invasive CA.

Lately, we have been performing operations in other types (lobular, tubular, mixed), but only if mammograph finding is a solitary knot. As for nodal axillary status, the attitude is that, when decision is made for CS, it is always necessary to perform dissection of axilla and this attitude is being respected up to the present moment.

With N1, clinically palpable lymphatic knots we are managing frozen-section biopsy and if removed knot is negative, the same will be performed. Depending on surgeon and technique applied, one or two breast incisions are applied, i.e. in axilla. In the beginning only quadrantectomies were performed, even biquadrantectomy, but it was abandoned due to bad cosmetic results. Analysis showed that volume of the resection of the glandular tissue does not provide bigger protection against appearance of the local recidivism (N=958, 7%). Over the last years, the lumpectomy was performed in invasive CA, and extended tumourectomy in DCIS, other than in comedo CA. Percentage of CS in relation to the radical mastectomies is undergoing changes, and now, it amounts to 16% (Rang 5-25), annually.

In comparison to the series as presented by Veronesi, at the latest symposium in September 2001, in Naples, the percentage of CS varies from 35 to 65%, in relation to the number of operated patients, differing from centre to centre in Europe.

Our percentage of CS can not be satisfactory one, but there exist some objective reasons for that. First of all, with us, breast cancer is being detected most frequently, in the second stadium (T2, No-1) which is the consequence of non-existence of screening, low level of health consciousness in population, and limited possibilities for diagnostics. The lack of satisfactory number of mammomats or amortization of old machines, the possibility for detection of early carcinoma is decreased (To and T1 small under 10 mm).

Unfortunately, here, there are paramedical reasons, damages and lack of machines for postoperative radiation. Another factor should be taken into account: man (surgeon - patient) who chooses method in the primary breast cancer treatment.

CONCLUSION

Breast CS has its place in the primary curing of early breast carcinoma and may be equally performed in stage I and in the early stage II. Cosmetic effects and esthetic view in CS, substantially improve the patient's quality of living.

Long distance results and a long, free interval show that performance of these surgeries is justified.

The choice of radical or conservative method should be handed over to the surgeon in agreement with patient, respecting the oncological principles.

Attitude that know -how on CS with us , is being changed, will enable progress in this field of surgical oncology.

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Archive of Oncology 2001;9(Suppl 2):78-80.

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Adjuvant systemic treatment of early breast cancer - review article

KEYWORDS: Breast Neoplasms; Adjuvant therapy; Drug therapy; Antineoplastic agents, Hormonal

Before concentrating on the modalities of specific adjuvant therapy, it is essential to discuss the need for any kind of adjuvant systemic therapy.

There are two groups of breast cancer (BC) patients for which adjuvant therapy is not appropriate: those with favorable prognosis without any adjuvant treatment - where adjuvant treatment offers no additional effect, and those for which specific adjuvant therapy is not useful. In all other patient groups the decision on systemic adjuvant treatment, as well as on the type of therapy, relies on the evaluation of positive effects and potential risks.

Is there any group of patients with invasive BC and enough good prognoses in which systemic therapy does not yield any additional benefit? It is recently postulated that women with node-negative breast cancer <1 cm in diameter and/or 1-2 cm in diameter and histologic grade 1 have the same survival probability as the age-matched women without breast cancer (1). If adjuvant systemic treatment is possible with some non-toxic agent, there is the possibility of adjuvant treatment of these patients too, in order to reduce the risk (although very small) of later disease progression. Tamoxifen is commonly considered to be such an agent, especially in premenopausal women (2,3), while cytostatic therapy is not.

In the T1a, b N0 or T1c grade 1 N0 patient subpopulations tamoxifen should be prescribed only within controlled clinical trials, with written detailed informed consent (4). An example of the patients for which adjuvant therapy should not be applied due to ineffectiveness is hormonal therapy in the absence of steroid receptors (3), or Herceptin therapy for tumors with low HER2 expression (still an investigational adjuvant therapy, at the moment) (5). The data obtained by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) also indicate that the contribution of cytostatic therapy is reduced with advanced age, thus toxic effects may predominate in women aged 60-70 (4,6,7).

OPTIMAL ADJUVANT ENDOCRINE THERAPY

Tamoxifen, as the first tested selective estrogen receptor modulator (SERM), is most extensively studied. Without doubt, based on a large amount of data, 5-year daily tamoxifen administration reduces the risk of breast cancer progression in women with receptor positive tumors by 47%. This reduction of risk is higher than with any other systemic therapy. Five-year tamoxifen administration is recommended since its contribution is greater than that obtained with 2-year administration (greater, again, compared to 1-year treatment). It was indicated so far that 10-year tamoxifen treatment is not superior to 5-year treatment (8). A large international trial, ATLAS (with 20.000 examinees) should provide more accurate information on this problem. Besides prevention of metastatic breast cancer, 5-year adjuvant tamoxifen significantly improves local disease control and prevents the contralateral cancer. Negative tamoxifen effects are related to a certain degree of bone density loss in premenopausal. Tamoxifen may also have estrogen-like effects on endometrial cancer (increased incidence), it may cause thromboembolism, as well as menopausal symptoms. However, its systemic adjuvant contribution as well as its effect regarding prevention of contralateral breast malignancy, is more than sufficient compensation for its negative effect. Although there is a correlation between the receptor expression level and response to tamoxifen, this agent exerts its positive effects even in women with low levels of receptor expression. The efficacy of tamoxifen in women with receptor positive tumors with HER2 overexpression is still controversial and these patients should not be deprived of tamoxifen therapy.

Other SERMs (e.g. raloxifen) probably have the effects similar to tamoxifen, but they are insufficiently tested in adjuvant settings. Investigations of the specially adjusted SERMs, which retain only the positive effects, are in progress. However, for the time being, tamoxifen is the only SERM used outside investigational trials - it is a drug of choice for adjuvant treatment of receptor positive BC.

Surgical ovarian ablation (laparoscopic oophorectomy) or pelvic irradiation is a one-occasion treatment for premenopausal women. In the Oxford review from 1995 the reduction was found of the year chance for lethal outcome of 24% for women aged <50, with positive receptor status. In women with negative receptor status ovarian ablation produces no response (10).

OPTIMAL ADJUVANT CYTOTOXIC THERAPY

Among the first regimens of polychemotherapy with proven contribution regarding DFS and OS, as adjuvant treatment for early breast cancer, was CMF - "Bonadonna regimen". CMF has been extensively tested in clinical trials (with survival improvement as the endpoint) now for 30 years. It remains a most popular regimen throughout the world, though the tendency of use gradually declines.

The Oxford review from 2000 confirms that polychemotherapy based on anthracyclines offers better results compared to CMF. There are, however, long-term anthracycline-related sequels - risk of cardiac toxicity, secondary leukemia. Though the overall risk at cumulative doses usually administered in most adjuvant regimens is relatively low, certain circumstances make this risk too high and unacceptable. In older patient populations, as well as in those with concomitant cardiac dysfunction or hypertension, the non-anthracycline regimens are desirable. Moreover, CMF may be applied also in those who had already received anthracyclines for previous malignancy (11). Studies indicate non-cross-resistance with anthracyclines, which make CMF a complementary regimen for sequential treatment after anthracyclines (in many European centers, several courses of CMF are administered after four AC cycles) (12).

There is no sufficient evidence suggesting positive effect of addition of taxanes to AC regimens in node-negative disease, regardless of tumor and other factors. Addition of paclitaxel (T) to an adjuvant treatment of node-positive disease has been approved in the USA but not in Europe (13). Despite the initial enthusiasm, there is no convincing evidence that sequential AC/T approach is superior to appropriate anthracycline regimens. The final answer about the value of adjuvant taxanes in high-risk disease awaits completion of current clinical trials (with 24.000 enrolled patients).

The very frequently asked question is whether the advantage of anthracyclines reported by the Oxford 2000 review is actually realized in regimens such

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The manuscript was received: 12. 10. 2001.

Accepted for publication: 19. 10. 2001.

as 4 cycles AC with only 240 mg/m^2 total cumulative doxorubicin dose. If we accept the postulate that 4AC is perhaps suboptimal, its use should probably be restricted to low-risk cancers (with small number of involved lymph nodes, lower invasive potential, without HER2 expression). In high risk BC patients, especially in those with >3 involved nodes and HER2 expression, naturally, the regimens containing higher cumulative anthracycline doses compared to 4AC, are more desirable. The following regimens are recommended: CAF; Canadian CEF; French FEC (14). Large randomized trials with dose escalation (in relation to standard doses of cytostatics) have not been proven superior to higher doses. Even the doses requiring autologous stem-cell transplantation support are not superior to conventional doses. It remains on investigators to identify the group of patients that require the above-mentioned approach (15).

In order to take a complete insight into the absolute positive contribution of adjuvant therapy, we may compare the effects of this treatment in two patient groups: one with positive lymph nodes and 35% probability of lethal outcome at 10 years; other with unaffected lymph nodes and 10% probability of lethal outcome at 10 years. Proportional reduction of mortality as a result of adjuvant chemotherapy would be around 25% in both groups, since chemotherapeutic regimens developed by now are equally effective in all nodal subgroups. However, this means that 26.25% of node-positive patients die from breast cancer (absolute difference, 8.75%), while that proportion would be only 8% for node-negative cases (absolute contribution of 2%). If chemotherapy were toxic, many of the node-negative patients would refuse it due to its modest absolute contribution, while those with high-risk disease would consider it a good option (16).

According to the results published by the EBCTCG, chemotherapy is more effective in younger patients (14). Since most women below 50 are premenopausal, at least a part of the total chemotherapeutic contribution is probably the result of its effect upon ovaries. In 12 out of 15 groups of premenopausal patients treated with adjuvant chemotherapy, those with amenorrhea have longer disease-free interval compared to those without amenorrhea. In 8 out of these 12 groups the difference is statistically significant. Overall survival was evaluated in only 5 of those groups, but still is better in patients with amenorrhea. Amenorrhea occurs more frequently in older than in younger premenopausal women (14).

Recent report of the International Breast Cancer Study Group (IBCSG) shows that adjuvant chemotherapy, as a single modality, is markedly less effective in women aged <35, than in pre- and perimenopausal women aged >35. It is interesting that the difference was observed among cases aged <35 with ER+ tumors. This patient group is characterized by a lesser frequency of amenorrhea (around 30%) after 6-12 months of classical CMF therapy, compared to older women. It is most likely that the difference in the frequency of amenorrhea caused the difference in response rates between these two age groups. The authors concluded that chemotherapy only is the insufficient adjuvant treatment for women younger than 35 with ER+ tumors. However, it has not yet been demonstrated that this effect could be overcome by adding ovarian ablation, especially in this age-group, which warrants organizing a prospective randomized trial (17).

In one ovarian ablation trial (ECOG 5188/Intergoup 0101) there were 1537 enrolled subjects, randomized to receive 6 CAF courses, CAF + Zoladex for 5 years or CAF + Zoladex + tamoxifen for 5 years. After 7 years, DFI in these 3 groups was 58%, 64% and 73%, respectively. Comparison of DFI in the CAFZT group and CAFZ group was statistically significant. Overall survival in these groups was 77%, 78% and 80%, respectively. The results still cannot provide a final answer regarding the addition of ovarian ablation. Still, ovarian ablation is more important for younger than for older premenopausal women.

The effects of adjuvant tamoxifen may be more pronounced in women with cessation of ovarian function as a consequence of chemotherapy or chemotherapy plus Zoladex. Since ovaries do not produce estrogen after menopause, it may well be said that the discussion about amenorrhea and ovarian ablation is relevant only regarding chemotherapeutic effects in premenopausal women.

There are a few studies dealing with the adjuvant chemotherapy effect on postmenopausal ovary. Many women have estrogen levels above the usual postmenopausal values in the period of 2 years after the last menstrual cycle. The average duration of menopause is about 4 years. The main product of postmenopausal ovary is androgens, the production of which continues during lifetime. Postmenopausal women who undergo oophorectomy have 40% less testosterone and 15% less androstenedione, and a tendency towards lower levels of estradiol (p=0.095). These androgens, as well as those produced by the adrenals, are converted in peripheral tissues into estrogens by the enzyme called aromatase. Aromatase levels rise during the life of a woman: in those aged 60 the levels are twice as high as in women aged 20. In a normal breast, aromatase is produced primarily within the fat tissue fibroblasts; breast cancer cells demonstrate elevated aromatase activity and may produce estrogens, which may function as autocrine or paracrine growth factors. Adrenal androgens (to a lesser extent ovarian androgens as well) are the source of circulating estrogens in postmenopausal women. LH-RH agonists reduce circulating androgens; as evidence suggests, chemotherapy may exert similar effects. Some trials demonstrate that the combination chemotherapy + tamoxifen is superior to tamoxifen monotherapy in postmenopausal women. This is perhaps the result of reduced androgens and/or estrogens during chemotherapy and the consequence of increased sensitivity to tamoxifen. There are reports too demonstrating that postmenopausal women respond to oophorectomy. Interestingly, women in the menopause lasting >10 years have the best response, which perhaps may be related to the elevated levels of circulating testosterone in older postmenopausal women.

The most effective way to inhibit aromatase is the third generation aromatase inhibitors (anastrazol, letrozol and exemestan). Trials have been initiated to evaluate the role of these new aromatase inhibitors in adjuvant setting (ASCO 2001).

It is quite certain that the HER2 expression is associated with poor prognosis and a more aggressive disease course, independent of other tumor prognostic factors. It seems appropriate to treat women with HER2 expression with anthracycline-based regimens (not 4AC) rather than with CMF regimen.

A large number of prospective studies examine various adjuvant regimens, with or without Herceptin, for tumors with HER2 overexpression. The IBCSG compared carboplatin + docetaxel + Herceptin with AC, and then docetaxel with or without Herceptin. The trial of adjuvant Herceptin (HERA), starting in 2001, should provide the answer to the question whether 1 or 2 years are superior to the approach without Herceptin for HER2 3+ breast cancer, regardless of the proscribed adjuvant chemotherapy regimen (18).

Numerous other proteins and genes are involved in transcription, cell cycle control, growth, proliferation and invasion - processes deregulated within breast cancer cells. Amplification of topoisomerase II gene, frequently encountered in association with HER2 expression, is investigated as a possible explanation of HER2 + tumors' sensitivity to anthracyclines.

Alteration of p27 gene, suppressor gene involved in transition control from G1 to S phase of the cell cycle, is in correlation with poor prognosis of node-negative breast cancer and represents a predictive factor of response to chemotherapy. Tumors with p53 mutations may be particularly sensitive to taxanes and relatively resistant to anthracyclines. Changes of Ki67, a marker of proliferation, may be useful in monitoring response to neoadjuvant chemotherapy and hormonal therapy in locally advanced disease. Nonetheless, there is no clinical, level 1 evidence, which would definitely suggest the predictive role of any tumor or patient characteristic regarding response to polychemotherapy.

Adjuvant treatment of breast cancer is still a matter of controversy. Investigations aimed to define predictive factors, as well as an ever-increas-

ing number of options of adjuvant cytostatic therapy, will result in appropriate, strictly targeted adjuvant therapy with high probability of tumor response.

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Radiotherapy after breast conserving surgery and breast reconstruction

KEYWORDS: Breast-conserving surgery; Breast Reconstruction; Radiotherapy; Mastectomy

Radiotherapy to the breast is an integral part of the management of early breast cancer. In combination with wide local excision of the primary tumor local control rates can be achieved that are equivalent to mastectomy. There is also mounting evidence that this local effect translates into an overall survival advantage for some groups of women.

It is therefore clearly essential to identify those patients at high risk of cardiac toxicity and develop techniques that allow them to maintain improved local disease control with RT without the possibility of serious side effects (1).

Adjuvant breast radiotherapy is now part of routine care of patients with early breast cancer. However analysis of the Early Breast Cancer Trialists Collaborative group suggests that patients with the lowest risk of dying from breast cancer are at significant risk of cardiac mortality due to longer relapse free survival. Patients with a significant amount of heart in the high dose volume have been shown to be at risk of fatal cardiac events.

The goal in radiotherapy is to achieve local tumor control without exceeding tolerance doses of the surrounding radiosensitive normal tissue. New conformal techniques in radiotherapy try to adapt dose distribution as closely as possible to the target volume. This could be realised using multiple portals with individual beam shaping. However, there are cases of complex shaped tumors in close relationship to organs at risk where no sufficient dose distribution could be achieved with conventional technique. This could be seen especially in concave shaped targets enclosing organs at risk. An improvement in dose distribution could be achieved using divers intensities within each portal. Thus, dose escalation to the tumor without increased complication rate seems possible in several cases.

Different techniques are available for delivery of intensity modulated beams. The first clinical application was carried out with compensators. The beam intensities are modified due to the 2 dimensional thickness profiles of the metal absorber. Most patients were treated with intensity modulated radiotherapy (IMRT) in step and shoot technique. Here the intensity profiles are divided into multiple subsegments, which are formed by multileaf collimator.

IMRT offers the possibility of shaping dose distributions by varying the dose intensity across each beam.

Due to steep dose gradients between target volume and organs at risk and

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The manuscript was received: 12. 10. 2001.

Accepted for publication: 19. 10. 2001.

the application of a set of small portals special attention is given to reproducibility of patient set up and verification of the calculated dose distribution.

There is special focus of interest in implementation of IMRT into clinical routine of breast cancer.

Additionally IMRT enables to introduce new principles into radiotherapy. An integrated boost as a new treated concept. It delivers a high dose to the macroscopic tumor site and simultaneously a homogenous dose to the surrounding tissue of microscopic spread.

Patients who have undergone previous breast conservation surgery with radiation therapy as part of their treatment or patients who require postoperative chest wall radiation following a mastectomy also are not good candidates for tissue expander - implant reconstruction. Radiation injury to the chest wall tissues makes adequate expansion difficult and increases the risks of the expander or implant complications such as infection implant exposure rib fracture or capsular contracture. Alternative, usually autologous reconstructive techniques are chosen for these patients. If one chooses to use tissue expansion in irradiated patients then both patient and surgeon must be prepared to abandon the technique if complications occur.

When a tissue expander has been placed and chest wall radiation is required postoperatively adequate expansion is often difficult to achieve. In these cases the addition of latissimus dorsi flap can obtain a reasonable cosmetic result. Patients who have undergone breast conservation and develop tumor recurrence require total mastectomy. If the TRAM flap donor is not available the latissimus dorsi flap is good choice.

In recent years, changes in definitive surgical procedures and improvement in radiation techniques and plastic reconstructive methods make it possible to give adequate therapy for breast cancer and restore the feminine form as well.

Tissue expansion has rapidly become a popular method of breast reconstruction. Techniques for breast reconstruction can be divided loosely into two basic categories: autologous and implant techniques (2).

More and more women undergoing mastectomy for early breast carcinoma are consulting plastic surgeons regarding reconstruction of the breast. Some general surgeons perform immediate reconstruction at the time of mastectomy.

Often the patients refereed to the plastic surgeon immediately following the diagnosis of breast cancer and recommendations for mastectomy. This initial consultation at which the patient is provided with information that will help make an educated informed decision, is very important. The patient is often under great psychological stress and must absorb tremendous amount of information in a very short period of time. The plastic surgeon must make the breast reconstruction information concise and complete so that the patient can make an informed decision.

If the best choice for reconstruction is to be made several key questions must be answered prior to the mastectomy. What is the risk of the developing of cancer in the contralateral breast? Does the contralateral breast require the biopsy to resolve the pathologic issues that would determine the need for contralateral mastectomy? These issues are important because the approach to bilateral reconstruction might be quite different from that to unilateral reconstruction. Is it feasible to alter the contralateral breast to obtain symmetry or will the oncology surgeon or mammography object believing it will interfere with future monitoring? This decision may alter the technique of breast reconstruction chosen. Will postoperative radiation be required ? Radiation can significantly compromise the likelihood of success with an implant reconstruction. Has the patient definitely decided upon mastectomy or is breast conservation an alternative?

When the reconstructive process is perceived as very complicated the patient can choose the conservation. At the initial consultation the patient must be given all information about alternatives and expected outcome. Patients undergoing immediate breast reconstruction usually follow the referral guidance of their oncology surgeon and rarely seek second option (3).

Indications for adjuvant RT following mastectomy with or without reconstruction include positive deep surgical margins, four or more involved axillary nodes, extracapsular nodal extension skin involvement and stages T3, T4, N2, N3. Some radiation oncologists recommend radiotherapy (RT) for inner quadrant or central tumours with any number of metastatic axillary nodes. Many of these indications are not known until pathologic staging is complete. Therefore it is important to have some idea of the success rate of immediate reconstruction plus RT when postoperative RT might be recommended.

Detection of chest wall recurrences is not prevented by the presence of a prosthesis under the pectoralis major muscle. Chest wall recurrence is usually in the skin and subcutaneous tissues, which remain readily accessible to examination.

Table 1. Reconstructed breast cosmetic evaluation guidelines (Baker)

Excellent:	Nearly identical to normal breast in size, shape, texture, and pigmentation
Good:	Some asymmetry is present, but there is an acceptable match in clothing; a recognizable inframammary fold exists; Baker I and II in texture; some alteration of pigment may be present
Fair:	A breast mound is present though significant asymmetry exists; does not have a recognizable inframammary fold; Baker III
Poor:	Inadequate breast mound, frank failure, aborted effort; Baker IV.

Radiotherapy and breast reconstruction are not incompatible, but the cosmetic failure rate and grade 2 - 3 complication rate are significant (Table 1).

It should be emphasized that only 10-15% of patients are estimated to require radiotherapy after mastectomy, according to guidelines we have used in this paper. Proper clinical staging prior to mastectomy will reveal a subset of favorable breast cancers unlikely to require radiotherapy and suitable for immediate reconstruction. An example of this would be a T1N0M0 breast cancer, many patients who meet these criteria would also be suitable for breast conservation therapy and may elect not to receive a mastectomy.

Breast reconstruction following mastectomy or "lumpectomy" and breast irradiation represent therapeutic alternatives to many patients.

Following mastectomy and immediate reconstruction external beam radiation might be necessary to provide optimal local control that is, in a patients who undergo augmentation mammoplasty and subsequently develop tumors, primary radiation may be indicated to preserve optimal cosmetic result.

We don't recommend the immediate placement of submuscular tissue expanders when there appears to be a high likelihood that RT will be required (3).

Tumour control is the primary objective in managing these patients. With proper teamwork between oncologists and plastic surgeons, good or excellent cosmetic results with fewer complications are possible. Further studies with greater numbers of patients will be required to identify additional factors influencing optimal results.

Literature contains some information regarding breast reconstruction following postoperative radiation, however, little clinical information exists regarding the use of radiation in patients with prosthesis in place.

When good surgical and radiotherapeutic techniques were applied acceptable cosmetic results could be obtained in those patients with prostheses in place, without compromising optimal cancer therapy(4).

The studies indicates plastic reconstruction in feasible after vigorous cancer therapy without long delays. Although reconstruction does not give the patient a new breast, it does restore her nature. Disease free interval histologic grade and estrogen receptor status is important in identifying those patients who will respond favorably(6).

Additional therapy after salvage mastectomy depends on a variety of factors including the biologic prognosticators of the tumor and the condition of the patient.

A mammary recurrence in the face of long disease-free interval and in a biologically favorable tumor may treated with salvage mastectomy and close observation or hormonal therapy if there is no evidence of metastatic disease (7).

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A review on application of radiotherapy after breast reconstruction: Physics aspect

KEYWORDS: Breast meoplasms; Breast reconstruction; Radiotherapy

INTRODUCTION

Immediate breast reconstruction after surgical intervention in younger patients, suffered from the breast carcinoma, gains in popularity in the FR Yugoslavia. It is not a new approach and predominantly represents demand therapy of women in western world (developed countries). Mammoplasty is applied in millions of women around the world for more than 30 years (1), by a subpectorally placed silicone prosthesis (2), by two-stage saline-filled implant breast reconstruction (3), by myocutaneous flaps (mostly latissimus dorsi with skin island and tram flap) (4), etc. Some of these patients require radiotherapy for prevention of local/regional relapse, and some for post-surgical local/regional recurrence.

Even, applied for 30 years management, morbidity, and oncologic aspects in patients with immediate breast reconstruction are still in the process of investigation. It seems that is well tolerated and does not interfere with oncologic adjuvant treatment, i.e. radiotherapy (5). Reported complication rates after both surgery and radiotherapy (that include: radiation-induced damage, post-surgical infection, wound breakdown and pain), varied from low to relatively high rates (6). On the other hand radiation therapy can decrease angiogenesis, cellularity, and the inflammatory cell response to the implants. Qualitatively, radiation treatment can seemingly improve rather than compromise the connective tissue response to the implant (7).

The aim of this short paper is to review the influence of the prosthesis on dose distribution in an irradiated breast and effects of radiation therapy on the silicon prosthesis, as well as, to advice surgeons, radiation oncologists and medical radiotherapy physicist at the issue. In this paper, clinical outcome in patients receiving specific anti-tumor therapy isn't considered.

OBJECTIVE

Dosimetry Ion chamber results indicated no significant alteration of 150 kV - 15 MV photon depth doses away from the implant with only minor tissue-implant interface perturbations (8-10). Compared to water measurements, at depths smaller than the practical range of the electron beams the

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The manuscript was received: 12. 10. 2001.

Accepted for publication: 19. 10. 2001.

dose distribution using 9-20 MeV electrons showed no significant difference in the dose delivered due to the presence of the prosthesis (the central axis depth dose values below the prosthesis were lower for all energies by as much as 3.5%) (11). According to the measurement (12), silicone gel behaves like tissue i.e. half value thickness for silicone gel and water is almost the same, as well as, linear absorption coefficients for silicone gel and water. A slight decrease in dose of approximately 8% was found only at the interface between the prosthesis and muscle-equivalent material, due to electronic disequilibrium effects that occur at the surface of the prosthesis (13).

Radiation damage Silicone gel breast implants should not be damaged by radiation. Shedbalkar et al. (14) referred to manufacturer's data, which indicates: i) little change in prosthesis with a radiation dose of 2.5 Mrad, and ii) a noticeable change in hardness at about 4.0 Mrad. In the radiotherapy dose range, there was no statistically significant difference in silicone capsule thickness compared to non-irradiated controls. Capsule morphology, can differed markedly (7). Changes following 50 Gy can be in a gel color, and formable capacity (8).

CONCLUSION

There are no specific recommended actions, dosimetry need for corrections for the presence of silicone gel breast implants, but there may be cosmetic effects.

Usage of a shield designed to protect healthy contra-lateral breast tissue from "scatter irradiation" can be considered in younger patients, patients with lower disease stages and women with either a very positive family history, known BRCA1/2 genetic mutations (15).

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Immediate and delayed breast reconstruction after radical mastectomy

KEYWORDS: Mastectomy; Breast reconstruction; Quality control

A breast represents a secondary sexual characteristics and symbol of femininity and maternity. A radical and modified radical mastectomy is a mutilate surgical intervention which causes a number of emotional and social problems. Reconstructive surgery helps to overcome psychosocial problems of a patient and his return to everyday activities. A good choice of type of reconstructive surgery and correctly undergone operation enables a patient with mastectomy to live a normal, good life. The aim of this work is to show number and cases of reconstructive operations performed on the Oncology and Radiology Institute of Serbia, surgical department from 1997 to 2001. Methodology: The aim of the reconstructive surgery is to recover enough skin, reconstruct. The breast shape, reconstruct nipple and areolar complex, symmetrisation of contralateral side. Indication for reconstructive surgery is:

1. A breast amputation
2. Psychooncology (to easier overcome psychotrauma and to delay relapse)

Contraindications for primary and postponed reconstructive surgery are:

1. A general health condition of a patient
2. Technical-operative ability of a surgeon

Eighty three operations were undergone. Average age of patients were 40 years (sd-7.5). There were 36 primary, 27 secondary, 7 mammilla reconstructions, and 13 corrections of a position and shape of the other breast. Endoprosthesis implanting were undergone with 47 patients, 11 musclecutaneous flaps of latissimus dorsi. in combination with endoprosthesis, and 9 cases of TRAM flap. Complications after surgery happened with 4 patients. There were 2 prolapses of endoprosthesis, 1 injury of the implanted substance and one partial necrosis of the flap. Well-chosen type and technically correctly undergone surgery enables a patient with mastectomy to live normally. Primary reconstruction is an imperative.