

Therapeutic Options for Breast Cancer

GEORGESCU MILENA, GEORGESCU E., NEMES R.

Department of Surgery, University of Medicine and Pharmacy of Craiova

ABSTRACT Breast cancer remains a major public health problem, being the second cause of cancer death in women. There is a marked tendency to restrict the extension of surgical gesture, which directly led to the emergence of two different attitudes: radical surgery and conservative surgery, to which, at least in our country there are still some delays. Prospective and retrospective studies have shown that in 20 years, conservative and radical therapy were about the same rate of survival and disease-free interval, at least for breast cancer stage I and II, the only real counterargument against conservative surgery is that it is encumbered by a higher rate of recurrence local constraint can be removed but by postoperative radiotherapy in principle. Finally, the survival rate is the main parameter distance evaluation assessing the effectiveness of treatment in breast cancer, as in all forms of cancer.

KEY WORDS *breast cancer, conservative surgery, chemotherapy, mastectomy.*

Introduction

Breast cancer represents an important issue of public health, having a very high incidence rate (25% of all female cancer cases), with the steep increase in incidence; in 2006 the European age-standardised incidence rate (dates from 25 countries) was de 110/100.000 and mortality rates 25/100000 [1]. Although breast cancer benefits from important discoveries in the field of chemotherapy, surgery remains the main pylon of therapeutic algorithm for breast cancer. But a tendency to restrict the extension of surgery led to appearance of two different therapeutic options: radical mastectomy and breast conserving surgery.

Aim and method

The goal of this comparative retrospective clinical study was the evaluation of two therapeutic options for breast cancer. The study included 377 patients diagnosed with breast cancer and operated in a period of 5 years (2005-2009) in 1st Department of Surgery Craiova and 4th Department of Surgery ("CFR" Hospital), divided in two groups:

Group A -171 patients diagnosed and treated in 1st Department of Surgery Craiova;

Group B – 206 patients diagnosed and treated in 4th Department of Surgery ("CFR" Hospital).

The male patients were not included in study because of extremely low incidence rate which would not lead to any valid conclusion.

Necessary dates for the study were obtained from:

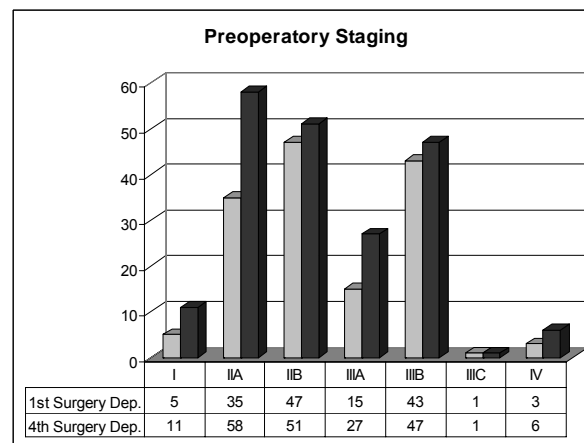
- -patient's clinical history,
- -operator protocols,
- -biological / microbiological probes,
- -pathologic examinations: biopsy punch, extemporaneous pathologic examinations,

paraffin tissue embedded pathologic examination,

- - medical imaging,
- - autopsy results.

Results

Clinical staging was based on: clinical examination, mammography exam, cytology/biopsy exam, lung X-ray, ultrasonography and biological examination.



Graph 1 Preoperative staging

Of 377 patients, 350 were operated (92.83%), 147 (85.96%) from group A and 203 (98,54%) from group B. 27 patients were not operated: 4 refused operation and the rest of the patients being stage III B and C were transferred to the Oncology Department for neoadjuvant radio- chemotherapy (study finished before completing neoadjuvant therapy). Following the goal of the study to evaluate indications, advantages and limits of two different therapeutical approaches, we compared professional experiences of two surgical

departments – 1st Surgery Department (group A) with eclectic attitude and 4th Surgical Department “CFR” Craiova (group B).

In these circumstances, it was natural for the share of breast conserving surgery to vary in the two groups. Thus, if for group A the breast conserving surgery (24 cases) represented only 16.32%, being reserved exclusively for patients in the early stages (5 stage I, 14 stage IIA, 4 stage IIB and 1 stage IIIA), in group B the share of breast conserving surgery (50.97%) was almost equal to that of radical surgery (49.03%), restricted in most cases to the early stages (stage I 11 cases, 48 cases stage IIA), but with the tendency of widening the indications of the breast conserving surgery area towards more advanced stages (IIB 31 cases, 8 cases IIIA, IIIB 2 cases and IIIC 1 case).

Although the standards relating to the indications of radical surgery were met, the share of this type of surgery was different in the two groups. Thus, in group A (1st Surgery Dep.), radical operations with curative goal were performed in 71.92% of cases (117), while in group B (CFR Surgery Dep.), they represented only 49.03% (97) of cases, the remainder being resolved by breast conserving surgery. The modified Madden radical mastectomy was the election process used in both groups: 96 cases for group A and 73 cases for group B. Simple mastectomy was used in few cases (three for group A and one for group B) and only at the patients' express request, referred to specifically and explicitly with their signature in the sheet of observations.

Salvage or "toilet" mastectomy was practiced in 40 cases, 18 cases in group A and 22 cases group B, with the same indications in both groups; it was usually reserved for neglected cases, with bulky tumors, sores, infected, fixed on deep levels, with fixed ipsilateral lymph nodes, which often makes true ganglion blocks, which are difficult or impossible to remove. The operation, though laborious and sometimes burdened by high risks, is still a necessity and cannot meet the criteria of radical surgery, especially in terms of cancer healing. Moreover, it mostly ends with important skin or parietal flaws, which may be covered by plastic processes that are carried out subsequently or during the same surgical session. In group A, the therapeutic approach consisted of performing both mastectomy and skin graft during the same surgical session, in collaboration with the plastic surgeon.

Neoadjuvant (preoperative) chemotherapy aims at reducing tumor volume and reducing the

risk of dissemination of malignant cells during the surgical act; is indicated for the treatment of breast cancer in its early developmental stages and also in some stages of locally advanced disease (IIB and IIIA), stages when surgery is possible with the intention of cancer healing.

In our study, neoadjuvant chemotherapy was used in 85 cases (49.70%) in the patients in group A and in 74 cases (35.92%) in the patients in group B. We noted that in group A, neoadjuvant chemotherapy was used in 67.05% (57) of the cases of patients belonging to stages I, II and IIIA, i.e. those suitable for surgery with cancer healing visa, as opposed to group B, in which neoadjuvant chemotherapy was used only in 40.54% (30) of cases in similar stages. In stage IIIB, stage where surgery is not the first therapeutic sequence, neoadjuvant chemotherapy was used in 26 (30.58%) cases in group A and in 36 (48.64%) cases in group B.

Neoadjuvant (preoperative) radiotherapy has few indications, which vary by stage; it can replace or allow the postponement of surgery at a stage when surgery is the first therapeutic sequence (stages I and II) in the patients with biological imbalance or with comorbidities that do not allow surgery (4 cases in group A and 7 cases in group B) or it can complete neoadjuvant chemotherapy with no answer or uncertain treatment response in the patients with stage III (4 cases in group A and 17 cases in group B). Radiotherapy was performed in all cases operated in group A and in 97 patients (91.50%) in group B.

Chemotherapy preceded radiation therapy in all the 24 cases that underwent breast conserving surgery according to the scheme 6 cycles of Docetaxel + Epirubicin in 14 cases and FEC (5 Fluorouracil + Cyclophosphamide + Epirubicin) in 10 cases. The combination chemo-radiotherapy was performed only in 26 cases in group B.

In all the 24 cases that underwent breast conserving surgery in group A, the molecular profile was determined by immunohistochemical examination, and in 18 cases with positive estrogen receptors (RE+HER-) hormone therapy was associated with anastrozole in 7 cases, with letrozole in 5 cases, with tamoxifen in 5 cases, and with exemestane in 1 case. In group B, the molecular profile was established only in 46% of cases, and hormonal therapy was associated with other means of adjuvant therapy in 32 (30.18%) cases.

Adjuvant postoperative radiotherapy was performed for 87.80% (108) patients in group A

and for only 34.02% (33) of the patients belonging to group B.

Chemotherapy, in accordance with treatment guidelines, preceded radiation in all cases where it was indicated. The chemotherapy performed in 91.05% (112) of cases belonging to group A consisted of six courses of chemotherapy regimens administered sequentially as follows: Docetaxel - Epirubicin 81 cases (72.32%) and FEC 31 cases (27.68%). In group B, adjuvant chemotherapy was associated with radiotherapy only in 72.16% (70) of cases using the same number of courses and the same regimens.

There were a total of 55 such postoperative complications recorded, with a postoperative morbidity rate of 21.42%.

Tabel 1. Complications after breast cancer surgery

Complications	1 st Surgery		4 th CFR Surgery		Total	
	Dep.		Dep.		No	%
Hematoma	4	2.72	4	1.94	8	2.28
Wound infection	5	3.40	7	3.39	12	3.42
Axillary seroma	3	2.04	4	1.94	7	2.00
Skin defect	3	2.04	5	2.42	8	2.28
Breast swelling			13	6.31	13	3.71
Lymphedema	5	3.40	2	0.97	7	2.00
Total	20	13.6	35	16.9	55	21.42%

Local relapse after breast conserving surgery, found in 3 cases in group B (relapse rate = 2.83%) occurred postoperatively in 8, 12 and 15 months respectively in two patients who refused postoperative adjuvant radiotherapy or followed an incomplete treatment.

Local recurrence after radical surgery, also found in three cases belonging to group A (local recurrence rate = 2.29%) occurred after the Madden surgery, performed to pretreatment staged cancer, stage IIIB, in 12, 14 and 15 months respectively postoperatively and it consisted of the appearance of permeation nodules of the postoperative scar (3 cases) and of an axillary lymph block (1 case). Histopathology of the resection piece showed a G3 invasive ductal carcinoma in all cases, which persisted after the local recurrence treatment (excision of permeation lymph nodes = axillary iterative lymphadenectomy).

Regarding the "systemic relapse" or metastatic disease, defined for the purposes of the foregoing, it was found in 15 (10.20%) cases belonging to group A and in 9 cases (9.27%) belonging to group B. This particular type of recurrence occurred after the Madden operation in 19 cases and after toilet mastectomy in 5 cases, with patients staged before treatment IIB (3 cases), IIIA (5 cases) and IIIB (16 cases) after a disease-free interval of between 4 and 25 months. The primary

tumor histology was invasive ductal carcinoma in 20 cases and the invasive lobular carcinoma in 15 cases, 10 cases G2 and G3 in 15 cases. Chemotherapy was the treatment of choice and the survival rate for this type of relapse ranged from 18 to 31 months.

Discussion

Nowadays, the treatment of breast cancer is a pluridisciplinary complex treatment, which underwent an impressive evolution along the time, partly because of the progress made in understanding the biology of the disease, and secondly due to the increasingly frequent detection of the disease in earlier stages, and also due to the diversification of therapeutic methods, including surgery, radiotherapy, chemotherapy, hormone therapy and immunotherapy, the indications and sequence of these therapeutic procedures varying according to the disease stage, the histological type and tumor grading, the patient's age and general condition [2,3,4].

The conservative treatment of breast cancer represents a therapeutic alternative to radical surgery and it comprises at least two treatment sequences: a minimal surgical intervention followed by postoperative adjuvant radiotherapy to eradicate any residual disease, with or without chemotherapy and hormonal therapy [5,6,7].

The conservative treatment of breast cancer has elective indication and curative visa in the early stages (I and II), but it can be used, with limited indications and palliative character also in advanced stages (IIIA and IIIB), especially in the case of elderly, sick patients.

Conserving breast surgery includes:

- Primary tumor surgery - lifting of the primary tumor through a conservative mamectomy, defined as a bloc excision of the primary tumor with 1.5 cm healthy peritumoral breast tissue, by extemporaneously histopathology verification of the absence of tumor invasion into the remaining wall cavity. The term conservative mamectomy replaced the other terms used in the mammary gland cancer breast conserving surgery (tylectomy, lumpectomy, sectorectomy, quadrantectomy), over which there is controversy.

- Surgery of axilliary lymph nodes - axilliary lymphadenectomy, now considered by many authors as having a more prognostic significance and as an important parameter to determine whether adjuvant chemotherapy is appropriate. The radical, axilliary lymphadenectomy visa is questioned by the circumvention of a main lymph node station – the internal breast lymph nodes.

The magnitude of the breast excision depends on: the morphology of the primary tumor (size, location and the histopathological type of the primary tumor), breast size and the associated breast lesions. In determining the indication of breast conserving surgery, in the end there are two important parameters, ensuring the achievement of both objectives proposed by this type of surgery: the local control of the disease and a satisfactory aesthetic result; these are the ratio tumor / breast, and the existence of negative edges in the remaining cavity walls [8,9,10].

We also mention that the contraindications of breast conserving surgery were respected: multicentric tumors, relatively large tumors (> 3-4 cm) in women with small breasts, especially when the patient did not have neoadjuvant chemotherapy, positive margins after resection or recovery, breast cancer inflammatory phenomena, and the patient's choice for radical mastectomy.

Introduced by Halsted in 1894, based on the concept of loco-regional disease that he also postulated, radical mastectomy bearing his name gave the chance for a better local control of the disease and led to a significant reduction in the rate of local recurrence; it became the standard treatment for breast cancer for more than half a century, but despite improvements in the local control of the disease, the curative potential of surgery has remained limited. In addition, the too large scale and its somewhat disfiguring character and also some late complications with disabling character such as lymphedema, have given rise to technical variations of the Halsted operation, which are less extensive, better tolerated by patients, and burdened by fewer disabling complications, but based on the same pathogenic halstedian concept. These processes - the Patey and Madden operations - have completely replaced the Halsted operation and today they make up the standard radical surgery of breast cancer [11,12].

Notable progress made in recent decades in the field of adjuvant and neoadjuvant therapy, and the appearance of the "systemic" pattern in the behavior of breast cancer have led to the gradual restriction of radical surgery indications, as the test of time defeated conservatism and the surgeons' distrust in breast conserving surgery.

The analysis of the material considered in our study revealed several findings on which we believe several comments are needed. Although the standards relating to the indications of radical surgery were met, the weight of this type of surgery was different in the two groups. Thus, in group A (1st Surgery Dep.), radical operations

with curative visa were performed in 71.92% of cases (117), while in group B (4th Surgery CFR Dep.), they represented only 49.03% (97) of cases, the remainder being resolved by breast conserving surgery. Without thinking strictly about another therapeutic design, we believe that the first explanation of this difference lies in the group structure. Thus, starting from the assumption that radical surgery is reserved primarily to locally advanced stages (stage IIB and IIIA), stages when surgery with curative intention is theoretically possible, we found that the percentage of the cases that have been assessed in these stages was significantly higher in group A, especially in stage IIB (31.75% vs. 24.75%), while for stage IIIA the incidence is similar (10.13% group A vs. 13.10% group B); regarding stage IIIB, suitable for radical surgery, the incidence is still higher for the patients from group A (29.05% vs. 22.81%). On the other hand, even for stage IIA, which usually tends to be breast conserving surgery, and IIB to which conservatory surgery tends to expand the indications, the analysis of the semiological characters of tumors belonging to group A showed us that they were within the upper limit of this stage (tumors with a maximum diameter > 3-4 cm), which is rather a contraindication for breast conserving surgery, especially in the case of the patients with small breasts, where the large size of the tumor makes nearly impossible to meet and carry out safe resection margins. Finally, one last argument in favor of radical surgery was the large share of the invasive ductal carcinoma at the histopathological extemporaneous examination.

Conclusions

1. Breast conserving surgery, reserved for early stages in group A (5 - stage I, 14 - stage IIA, 4 - stage IIB and 1 - stage IIIA) was extended to more advanced stages (31- stage IIB, 8 - stage IIIA and 2 - cases in IIIB), as the therapeutic choice for group B (50.97% of cases).

2. Radical surgery, represented by the Madden operation in both groups, reserved for locally advanced stages, was the dominant therapeutic option for group A, particularly imposed by the group structure: the predominance of locally advanced stages IIB, IIIA and IIIB and of invasive histological forms objectified by the extemporaneous histopathological examination.

3. Neoadjuvant therapy, without leading to a true tumor regression has several advantages (it reduces the local recurrence rate, increases the disease-free interval and the percentage of conservative operations) that make it useful both in early stages and in locally advanced stages

where it is possible to perform an intervention with curative visa.

4. Adjuvant therapy significantly increases survival rates after radical surgery

References

1. FI Bădulescu - Patologia malignă a glandei mamare, Ed. Medicală, București, 2007;
2. Recht A, Come SE, Gelman RS, Goldstein M, Tishler S, Gore SM, et al. - Integration of breast conserving surgery, radiotherapy and chemotherapy for the treatment of early-stage, node-positive breast cancer: Sequencing, timing, and outcome. J Clin Oncol. 1991;9:1662–1667;
3. Buchholz TA, Hunt KK, Amoss CM, Tucker SL, Strom EA, McNeese MD, et al. - Sequencing of chemotherapy and radiation in lymph node-negative breast cancer. Cancer J Sci Am. 1999;5:159–164;
4. De Cuyper L, Van Hee R, Sterckx F. - The effect of social factors on diagnosis and treatment of breast cancer. Acta Chir Belg. 2003;103:585–588;
5. Kim SH, Simkovich-Heerd A, Tran KN, et al. - Women 35 years of age or younger have higher locoregional relapse rates after undergoing breast conservation therapy. J Am Coll Surg. 1998;187:1–8;
6. Coulombe G, Tyldesley S, Speers C, et al. - Is mastectomy superior to breast-conserving treatment for young women? Int J Radiat Oncol Biol Phys. 2007;67:1282–1290;
7. Kurtz JM, Spitalier JM, Amalric R, et al. - Mammary recurrences in women younger than forty. Int J Radiat Oncol Biol Phys. 1988;15:271–276;
8. Clark RM, Whelan T, Levine M, et al. - Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: An update. Ontario Clinical Oncology Group. J Natl Cancer Inst. 1996;88:1659–1664;
9. Liljegren G, Holmberg L, Adami HO, Westman G, Graffman S, Bergh J. - Sector resection with or without postoperative radiotherapy for stage I breast cancer: five-year results of a randomized trial. Uppsala-Orebro Breast Cancer Study Group. J Natl Cancer Inst. 1994;86:717–22
10. Hiotis K, Ye W, Sposto R, Skinner KA. - Predictors of breast conservation therapy: size is not all that matters. Cancer. 2005;103:892–9;
11. Voogd AC, Nielsen M, Peterse JL, et al. - Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: Pooled results of two large European randomized trials. J Clin Oncol. 2001;19:1688–1697;
12. Ward S, Heidrick S, Wolberg W. - Factors women take into account when deciding upon type of surgery for breast cancer. Cancer Nurs. 1989;12:344–51;

Correspondence Address: Georgescu Milena, MD, PhD student, Department of Surgery, University of Medicine and Pharmacy of Craiova, Str Petru Rares nr. 4, 200456, Craiova, Dolj, România email: mikimihajlovic@yahoo.com
