ACTA FAC. MED. NAISS. UDK 618.19-006

Original article

ACTA FAC. MED. NAISS. 2005; 22 (1): 15-20

Lidija Đorđević, Miroslav Jeremić, Nebojša Đorđević, Zoran Rančić, Goran Stanojević, Slavica Jeremić, Ljiljana Jeremić, Vanja Pecić

Surgery Clinic,
Clinical Center of Niš

TEN-YEAR RESULTS OF THE COMPARATIVE STUDY OF THE BREAST CANCER PATIENTS IN CLINICAL STAGE I AND II AFTER CONSERVATIVE SURGICAL AND MODIFIED RADICAL MASTECTOMY

SUMMARY

Conservative approach in early breast cancer surgery is nowadays a widely accepted treatment option, though there are still controversies when compared to mastectomy.

In the period from 1993 to 2003 a prospective study was performed at the Departement of Chest Surgery, Surgical Clinic, Clinical Center Niš, comparing the results of tumorectomy with axillary dissection and radiotherapy with mastectomy plus axillary resection for breast cancer stages I and II.

Here we present the results of the 10-year-long follow- up.

Sixty patients with breast cancer stage I and II, treated with modified radical mastectomy or conservative treatment were monitored for 10 years and one month for immediate and remote results/effects, overall survival and disease free period. Ten-year survival of mastectomy treated cases was 70%, i.e. 21 women, and 73.34%, i.e. 22 women after conservative treatment ($p<0.01$).

Local recurrence was observed in 23% both after mastectomy and conservative approach ($p<0.01$).

Conservative treatment (tumorectomy, axillary dissection, radiotherapy) demonstrated 10-year results almost identical to those achieved with modified radical mastectomy.

***Key words*: breast cancer, conservative surgery, modified radical mastectomy, ten-year survival**

INTRODUCTION

The surgical treatment of breast cancer, for the most part, concerns the treatment of potentially curable cancer confined to the breast and regional lymph nodes (1). For early stages of breast cancer, surgical removal provides a reasonable chance for curing. The approach to operable breast cancer changed dramatically over the past century, and so did the clinical presentation of breast tumors (2). In 1894 Halsted presented his first 50 patients treated by the "complete operation", which became the radical mastectomy (3). Over the next 75 years, radical mastetectomy was used to treat virtually every breast malignancy in the United States (4).

The gradual shift away from radical surgery and preservation of the breast and soft tissues was influenced by the results of several large trials of lesser surgical procedures.

Currently , there are many surgical procedures used in the treatment of breast cancer.

1. Radical and extended radical mastectomy.
2. Modified radical mastectomy.

3. Radical versus modified radical mastectomy.

4. Wide local excision and primary radiation therapy (5).

Conservative procedures (breast preserving surgery, breast conservation) refers to various treatment strategies that leave the breast largerly intact with or without postsurgical radiation therapy and with or without axillary dissection (6).

Conservative surgery in breast cancer treatment, though controversial in the beginning, is now widely accepted alternative to mastectomy (7).

Several randomized European and North American studies compared various aspects of conservative surgery and modified radical mastectomy over 10 or more years (8).

They all confirmed almost identical survival after these two treatment options (9).

Here we present the results obtained from the patients treated at the Surgical Clinic in Niš and monitored by the Council for Breast Diseases, Clinic of Oncology Niš.

The patients were prospectively studied and monitored for 10 years for immediate and remote effects.

METHODS

Patients

Between January 1993 and 2003 out of all surgically treated patients, a group of 60 patients was selected with clinical stage I and II breast cancer (T_1 and T_2, diameter up to 5 cm, N_0 and N_1, M_0).

Invasive carcinoma was included, too.

In patients, we registered neither metastatic disease, concomitant or previous ipsilateral or controlled breast cancer nor signs of Paget's disease; also, none of them was pregnant or lactating. They had individual lesions without multiple palpable or mammographically suspected areas.

Comparison of patients' features in those treated conservatively and those treated with modified radical mastectomy revealed no differences. The women were treated either with radical mastectomy plus total axillary dissection or conservatively (excision biopsy all the way into the healthy tissue), complete axillary dissection and radiation therapy. Out of 60 patients included, 30 belonged to the mastectomy and 30 to the conservative treatment group.

The analysis was conducted in January 2003, with the average follow-up (January 1993 – January 2003).

Techniques

The first group included patients treated either with radical mastectomy operation of Madden or Patey with total axillary dissection (I, II, III floor lymph nodes).

The chest was not irradiated postoperatively (except for the scar itself).

The second group included patients treated conservatively. It was necessary to remove the tumor all the way into the healthy tissue (verified microscopically ex tempore). In case of positive margins, a reexcision was done. Margins were considered healthy if cancer cells were present on one or more sides of the tissue surrounding the tumor. Those with positive margins were further divided into two groups: 1) focally positive and 2) more than focally positive. Margins were considered negative if the distance between the labeled margin and malignant cells was over 1 mm. If malignant cells were found within 1 mm distance from the margin, this was termed "almost positive" (close margins). In most of the patients tumorectomy was performed all the way to the healthy tissue (18 cases) while excision margins were invaded in 8 cases (where reexcision was done). Total axillary dissection was performed. Postoperative radiotherapy was instituted with 5.000 cGy in 22 fractions to the whole breast, and for higher grades (II-III) 1.500-2.000 cGy dose was added directly to the tumor site.

In case of positive axillary findings, axillary field irradiation was performed with 4.800 cGy. If the II or III floor nodes were positive, one supraclavicular field with the same dose in 22 fractions (5 a week) was added, too.

In both groups with centromedial tumor localization parasternal field irradiation was performed within the area of a. mammaria interna (the same dose and fractionation).

All involved lymph nodes received adjuvant chemotherapy including cyclophosphamide (cytoxan) and doxorubicin (Adriamycin). Initially, chemotherapy was applied for 6 months in 21-day cycles. Hormonotherapy was administered for estrogen and/or progesterone dependent tumors.

STATISTICAL ANALYSIS

Total survival was measured from the randomization day to the death or last control. Disease free period and local/regional recurrence were calculated from the randomization day to local recurrence or last control.

Contralateral breast carcinoma did not influence survival, but any local or regional recurrence after the initial treatment of the contralateral breast was accounted for as the event related to the primary cancer.

Statistical significance was assessed through polichotomic logistic model with p value based on Vald's test.

RESULTS

After 10-year follow-up (5.2–14.3 years) without disease, the total survival was similar in both studied groups.

Total survival after 10 years in patients treated with modified radical mastectomy was 70% (21 women), in conservative treatment group 73.34% (22 women) $p<0.01$.

Local relapse was classified depending on its place in relation to the primary site and radiation field: 1) true relapse – at the surgery site; 2) relapse at some other site in the ipsilateral breast, and 3) regional lymphatic.

In 7 patients out of 30 treated conservatively, a local relapse occurred: in 5 at the excision site (6.66%), in 1 at some other breast site (3.33%) and in 1 in regional lymph nodes (3.33%).

The result about involvement of excisional surfaces with malignant cells in patients treated with conservative interventions after surgical intervention are shown in Table 1.

Local relapse in those treated with modified radical mastectomy was observed regarding the site of true local relapse at the excision site and in regional lymph nodes.

In 7 patients (23%) out of 30 treated with modified radical mastectomy by Madden-Patey, the local relapse occurred in 3 cases at the excision site (10%) and in 4 (13%) in regional lymphatic.

Comparing the frequency of local relapse after modified radical mastectomy with relapses after conservative surgery, statistically significant difference was not found. Using the polichotomic logistic model with p value based on Vald's test, local relapses were more frequent in patients with malignant cells on excision surfaces.

Total frequency of distant metastases after the treatment was 16.7%, i.e. in 5 out of 30 conservatively treated patients.

Most common metastatic sites were lungs (3 women), skull bones (1 woman), spine (2 women), pelvis (1 case), proximal tibias terminus (1 case), and ribs (2 cases).

Out of 30 patients treated with modified radical mastectomy distant metastases were detected in 4 of them (13.33%).

Salvage therapy included surgery, radiotherapy, chemotherapy and hormonotherapy for distant metastases or treatment failure.

Frequency of ipsilateral local relapse was not associated with any risk factor: age, disease stage, positive nodal status, and positive margins after surgical excision.

Local relapse risk within the breast was not higher in those with incomplete initial excision or those who required secondary reexcision compared to those who did not require secondary reexcision.

The number of patients we could analyze for possible local relapse was small.

Initially, salvage mastectomy was possible in 4 out of 30 women with local ipsilateral relapse. Except for mastectomy in 23 out of 30, further local or regional metastases were absent during the follow-up of 3 months up to 9 years and 9 months.

In 3 out of 18 cases local or regional relapse preceded distant metastases. In the 19th case with inflammatory disease at the time of local relapse and chemo- and hormonal treatment soon after those distant metastases appeared.

In 3 cases distant metastases were registered after salvage mastectomy without further local or regional metastases (the patients were monitored for 50, 69 and 72 months).

One of the three patients also had positive lymph nodes (24/24) secondary to contralateral breast cancer (8 months after salvage mastectomy and 32 months before distant metastases).

DISCUSSION

Conservative therapy in the management of early-stage carcinoma of the breast, once controversial, is now an established alternative to mastectomy (10). Several randomized studies in Europe and North America that address various aspects of

Table 1. Involvement of excisional surfaces with malignant cells in patients treated with conservative interventions after surgical intervention

Primary surgery	Number of patients	Marginal status	Number	%
Conservative surgery	30	Negative	18	60%
		Close positive	4	13,33%
		Positive	8	26,66%
		a) Focally positive b) More than focally positive	4 2	16,66% 10%

conservative treatment of breast cancer have accumulated an experience of 10 or more years of follow-up. All of them confirm that breast conserving local therapies and more radical surgical therapies yield similar rates of survival i.e. the largest of the randomized clinical trials, the National Surgical Adjuvant Breast Project (NSABP) B-06 trial (11).

Furthermore, the National Cancer Institute's early breast cancer trial comparing lumpectomy axillary's dissection, and radiation with modified radical mastectomy has accumulated a median potential 10-year follow-up (median potential follow-up is defined here as the median follow-up if all patients had survived) (12).

During 10 years, the overall survival was 75% for the patients assigned to mastectomy and 77 % for those assigned to lumpectomy plus radiation (p=0.89).

10-year disease free survival was 69% for the patients assigned to mastectomy and 72% for those assigned to lumpectomy plus radiation (p=0.93). The rate of local regional recurrence during10- year follow-up was 10% after mastectomy and 5% after lumpectomy plus radiation (p=0.17). Recurrences after lumpectomy or other conservative surgery were successfully treated by mastectomy.

In the management of stage I and II breast cancer breast conservation with lumpectomy and radiation offers the 10- year results that are equivalent to those with mastectomy.

The results after the average survival of 10 years did not demonstrate any difference in breast cancer treatment either conservatively or with mastectomy. The results of our investigation are in accordance with the results of National Cancer Institute and other studies shown in Table 2.

The follow-up period in these 6 trials was 6–13 years.

Inclusion criteria were variable, as well as special treatment details, including surgery, radiotherapy and protective chemotherapy.

However, the results indicate that the effectiveness of conservative breast cancer treatment plus radiotherapy was similar to mastectomy.

Inclusion criteria were different.

In our study all patients in stage T1 and T2 (tumor sized up to 5 cm) were potentially eligible.

Table 2. Result of National Cancer Institute and other studies

Study	Follow up	Inclusion criteria	Number of patients	Disease free period	OS	Local or regional relapse	Relapse within breast (ipsi- or contralateral)
NSABP B-06 Mastectomy Breast cons.	8	StageI orII;T<4cm	 590 629	 58 59	 71 71	 8 8	 NA 10
Gustave-Roosy Mastectomy Breast cons.	10	Stage I; T<2cm	 91 88	 58 66	 80 79	 10 5	 NA -
Milan MastectomyBreast cons.	13	StageI;T<2 cm	 349 352		 69 71	 2 3	 NA -
EORTC Mastectomy Breast cons.	8	Stage I or II	 426 456		 63 58	 9 13	 NA -
Danish Breast Cancer Group Mastectomy Breast cons.	6	Stage I or II	 429 430	 66 70	 82 79	 6 5	 NA 3
Present study Mastectomy Breast cons.	10	Stage I or II	 116 121	 69 72	 75 77	 10 5	 NA 18

In contrast to NSABP (National Surgical Adjuvant Breast Project) B-06 trial, which excluded women with tumors over 4 cm, the English trial excluded those with lesions larger than 2 cm (13).

Eight percent (10 out of 116 mastectomy treated women and 8 out of 21 conservatively treated) had tumors larger than 4 cm; macroscopic resection was necessary in National Cancer Institute trial where secondary reexcision was allowed, too. In 1 woman reexcision attempt was not successful.

In NSABP B-06 it was necessary that excision margins should be negative, so that 10 patients previously planned for conservative treatment were further treated with modified radical mastectomy due to histological positive margins (14).

It has been recently postulated that remote results in patients treated with salvage mastectomy for local relapse in the breast have an increased risk for distant metastases.

Frequency of breast cancer recurrence in those treated conservatively in NSABP B-06 was 12% for 9 years (range 8-20% for 10-15 years in other studies) (15).

In our study, the ipsilateral breast cancer recurrence was 23.33% for 10 years. Distant metastases did not occur in 12 out of 19 patients three months to 9 years and 9 months after the salvage mastectomy.

The risk of local/regional metastases after 10 years in patients treated with radical mastectomy was 10%. All 10 patients in this group with local or regional metastases had simultaneous or distant metastasis later on, and in none of them the salvage treatment was successful. Distant metastases, which occurred in 5 out of 30 patients with cancer relapse, were observed after conservative surgery.

The ten-year follow-up in our paper confirmed that remote results of clinical stage I and II breast cancer treatment do not depend on the local therapeutic approach for primary disease, of course, if surgery was adequately performed (16).

Modified radical mastectomy and conservative surgery are excellent local treatment methods for clinical stage I and II breast cancer, with similar survival. Even some novel biomarkers or some more sensitive diagnostic method will not influence surgical decision making in breast cancer treatment, influencing the risk of distant metastases or survival. (17).

After careful investigation and analysis by the surgeon and clinical radiologist, the patient should be the ultimate decision-maker regarding her own treatment.

We believe that the improvement of survival and disease free period is possible only in the case of early breast cancer detection, in the absence of disease dissemination, and with adjuvant treatment improvements.

CONCLUSION

Conservative approach in early breast cancer surgery is nowadays a widely accepted treatment option, though there are still controversies when compared to mastectomy.

In our paper, we analyzed early and late outcome of different surgical approaches in early breast cancer.

There is now statistically significant difference between patients underwent conservative surgery, and modified radical mastectomy concerning local recurrence appearance, disease free period and ten-year survival.

In some circumstances conservative surgery is first choice in breast carcinoma treatment.

REFERENCES

1. Fovble BL, Soli LJ, Schultz DJ, et al. Ten-year results of conservative surgery and irradiation for stage I and II breast cancer. Int J Radiat Oncol Biol Phys 1991; 21: 269–77.

2. Abner AL, Recht A, Eberlein T, et al. Prognosis following salvage mastectomy for recurrence in the breast after conservative surgery and radiation therapy for early stage breast cancer. J Clin Oncol 1993; 11: 44–8.

3. Schnitt SJ, Abner A, Gelman R, et al. The Relationship between microscopic margins of resection and the risk of local recurrence in breast cancer patients treated with breast conserving surgery and radiation therapy. Cancer 1994; 74: 1746–51.

4. Amichetti M, Caffo O, Richetti A, et al. Ten-year results of treatment of ductal carcinoma in situ of the breast with conservative surgery and radiotherapy. Eur J Cancer 1997; 33: 1559–65.

5. Danforth DN Jr, Findlay PA, Mc Donald HD, et al. Complete axillary lymph node dissection for stage I-II carcinoma of the breast. J Clin Oncol 1986; 4: 655–62

6. Santoro G, Nacchia F, Rocco P. Local recurrence of breast cancer. G Chir. 1999; 20: 378–80.

7. Fisher B, Bauer M, Margolese R et al. Five-year results of a randomized trial comparing total mastectomy and segmental mastectomy with or without radiation treatment of breast cancer. N Engl J Med 1985; 312: 665–73.

8. Hallahan DE, Michel AG, Halpern HJ, Awan AM, Desser R, Bitran J, et al. Breast conserving surgery and definitive irradiation for early stage breast cancer. Int J Radiat Oncol Biol Phys 1989; 17: 1211–6.

9. Kestin LL, Goldstein NS, Martinez AA, et al. Mammographically detected ductal carcinoma in situ treated with conservative surgery with or without radiation therapy: patterns of failure and 10-year results. Ann Surg 2000; 231: 236–45.

10. Lichter AS, Lippman ME, Danforth DN Jr, et al. Mastectomy versus breast conserving therapy in the treatment of stage I and II carcinoma of the breast: a randomized trial at the National Cancer Institute. J Clin Oncol 1992; 10: 976–83.

11. Saibiston. Text book of surgery. The byological basis of Modern Surgical Practice, XV Edition, 568–71.

12. Marret H, Bougnoux P, Fignou A, et al. Locoregional recurrence prognosis after conservative treatment of breast cancer. J Gynecol Obstet Biol Reprod (Paris) 1997; 26 (Suppl 3): 144–7.

13. Sarrazin D, Le MG, Arriagada R, et al. Ten-year results of randomized trial comparing a conservative treatement to mastectomy in early breast cancer. Radiother Oncol 1989; 14: 177–84.

14. Veronesi U. Optimal surgical treatment of breast cancer. Oncologist 1996; 1: 340–346.

15. Veronesi U, Banfi A, Salvadori B, et al. Breast conservation is the treatment of choice in small breast cancer: long-term results of randomized trial. Eur J Cancer 1990; 26: 668–70.

16. Veronesi U, Luini A, Vecchio MD, et al. Radiotherapy after breast conserving surgery in women with localized cancer of the breast. N Eng J Med 1993; 328: 1587–1591.

17. Veronesi U, Volterrani F, Luini A, Saccozzi R, Del Vecchio M, Zucali R, et al. Quandratectomy versus lumpectomy for small size breast cancer. Eur J Cancer 1990; 26: 671–694.

DESETOGODIŠNJI REZULTATI KOMPARATIVNE STUDIJE BOLESNIKA SA KARCINOMOM DOJKE KLINIČKOG STADIJUMA I I II NAKON POŠTEDNE OPERACIJE I MODIFIKOVANE RADIKALNE MASTEKTOMIJE

Lidija Đorđević, Miroslav Jeremić, Nebojša Đorđević, Zoran Rančić, Goran Stanojević, Slavica Jeremić, Ljiljana Jeremić, Vanja Pecić

Klinika za hirurgiju, Klinički centar Niš

SAŽETAK

Poštedna operacija u hirurgiji ranog karcinoma dojke je sada prihvaćen način lečenja, mada i dalje postoje kontraverze kada se poredi sa mastektomijom.

Između 1993. i 2003. god. na Odeljenju za grudnu hirurgiju Hirurške klinike KC u Nišu sprovedena je prospektivna studija koja je u jednom centru poredila tumorektomiju sa aksilarnom disekcijom i radioterapijom sa mastektomijom uz resekciju aksile kod karcinoma dojke u I i II stadijumu.

Prikazujemo rezultate nakon praćenja bolesnica od 10.1 god.

Šezdeset bolesnica sa karcinomom dojke u I i II stadijumu lečene su modifikovanom radikalnom mastekomijom ili poštednom operacijom. Šezdeset bolesnica koje su podvrgnute prospektivnoj studiji praćene su tokom 10.1 god. Praćeni su rani i udaljeni rezultati, ukupno preživljavanje i period bez bolesti ("disease free" period). Desetogodišnje preživljavanje bolesnica nakon mastektomije iznosilo je 70% odnosno 21 bolesnica, a 73.34%, odnosno 22 bolesnice nakon poštedne operacije p<0,01.

Lokalni recidiv je 23% u oba slučaja i nakon radikalne mastektomije i nakon poštedne operacije p<0.01.

U lečenju karcinoma dojke u I i II stadijumu, poštedna operacija (tumorektomija, akselarna disekcija i radio terapija) pokazuje desetogodišnje rezultate koji su identični onima nakon modifikovane radikalne mastektomije.

***Ključne reči*: karcinom dojke, poštedna operacija, modifikovana radikalna mastektomija, desetogodišnje preživljavanje**