

LOCAL RECURRENCE FOLLOWING CONSERVATIVE SURGERY FOR BREAST CANCER – TRUE RECURRENCE OR A NEW PRIMARY TUMOR

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Summary

In the group of 1,161 patients submitted to conservative surgery for breast cancer in the period from 1992 to 2002, 95 (8.2%) were found to have locoregional recurrence. The most frequent localization of the recurrent disease was the site of prior excision; in 39% of the patients recurrence developed early, i.e. within the first two years after initial treatment. As a secondary surgical procedure, mastectomy was the most frequent, after which 5 patients presented with repeated recurrence.

KEY WORDS: *breast cancer, conservation surgery, local recurrence*

LOKALNIRECIDIVI RAKA DOJKE POSLIJE POŠTEDNE OPERACIJE - PRAVI RECIDIVI ILI NOVI PRIMARNI TUMOR

Sažetak

U skupini od 1.161 pacijentice u kojih je u razdoblju od 1992. do 2002. godine učinjen pošteđni kirurški zahvat zbog karcinoma dojke, u njih 95 otkriven je lokoregionalni recidiv (8,2%). Najčešća lokalizacija recidivnog tumora bila je na mjestu prijašnje ekscizije, a u 39% pacijentica recidiv se pojavio rano, to jest u prve dvije godine nakon inicijalnog liječenja. Kao sekundarni kirurški zahvat najčešće je učinjena mastektomija, a ponovni razvoj recidiva otkriven je u 5 pacijentica.

KLJUČNE RIJEČI: *karcinom dojke, pošteđna operacija, lokalni recidiv*

INTRODUCTION

The majority of studies show no significant difference in the survival pattern of breast cancer patients submitted to modified radical mastectomy or breast-conserving surgery with postoperative irradiation, but an increased risk of developing local recurrence in conservatively treated patients (1-5). Local recurrence can result from inadequate primary tumor removal, residual noninvasive cancer foci, homing of circulating tumor cells or genetically altered but histologically normal breast tissue (6). In nonirradiated

patients, local recurrences accounted for 30-40%; considering patients submitted to breast-conserving surgery and irradiation, local recurrence is anticipated to develop in 5-20% within a 10-year period following the initial treatment (4, 5, 7-9). Radiation therapy significantly decreases the number of local recurrences and delays their development (2, 8, 10).

From 1992 to 2002, 1,161 breast cancer patients were treated with breast-conserving surgery at the University Hospital for Tumors, Zagreb, Croatia. In the ten-year period, 100 recurrences were discovered and treated in 95 pa-

tients following breast-conserving surgery. The study was aimed at discriminating between true breast cancer recurrences and new primary tumors, and their effect on treatment.

PATIENTS AND METHODS

From 1992 to 2002 at the University Hospital for Tumors, Zagreb, Croatia, 1,161 patients underwent conservative surgery for breast cancer and were followed up till the end of 2003. In this period, 95 patients developed locoregional recurrence, or redeveloped invasive or *in situ* carcinoma in the residual breast tissue or skin, and/or metastases in regional lymph nodes. Recurrence redeveloped in 5 of 95 patients with locoregional recurrence.

2.1 Initial treatment for breast cancer

Patients underwent breast-conserving surgery, i.e. removal of a tumor-bearing segment or quadrant adjacent to the tumor bed. The tumor-bearing breast tissue segment was removed by the dissection of the breast parenchyma extended to the pectoral muscles and pectoral fascia excision. During quadrantectomy, a breast skin segment above the tumor bed was also removed. Axillary dissection involved routine removal of lymph nodes at all three levels.

Postoperative radiation therapy and systemic therapy (chemotherapy and/or hormone therapy) were performed in 77% and 60% of the 95 patients with locoregional recurrence, respectively.

2.2 Patient follow-up

The follow-up of patients submitted to breast-conserving surgery was primarily aimed at early detection and treatment of a local recurrence, as well as an ipsilateral and contralateral tumor. Actually, the recurrence rate after breast-conserving surgery is constant 1-2% at 1 year (16), and the risk of developing a contralateral tumor is 1% at 1 year (17). At the University Hospital for Tumors, the following scheme meeting the breast cancer protocol is applied: during the first year after surgery, follow-up visits are scheduled every three months; during the second and third postoperative year,

there is a 4-month interval between the follow-up visits; then, the visits are scheduled every six months. In addition to physical examination, the following laboratory tests are made: complete blood picture, alkaline phosphatase level and liver tests. According to the protocol, operated patients have mammograms once a year, and breast ultrasound if indicated. For early detection of dissemination, a chest x-ray is regularly done twice a year during the first postoperative year, and then if indicated. Gynecological examination is first scheduled 6 months after the operation, and then, once a year. Laboratory test results indicate x-ray imaging and bone scintigraphy, and abdominal echosonography, if any. Levels of the tumor marker CA 15-3 are measured twice.

After pathohistologic verification of cancer recurrence, further diagnostic tests are indicated for breast cancer patients (chest x-ray, bone x-ray or scintigraphy, US and abdominal CT), aimed at detecting distant metastases which may be anticipated in 5-10% of patients with local recurrence (12-15, 32).

RESULTS

From 1992 to 2002 at the University Hospital for Tumors, 1,161 patients underwent conservative surgery for breast cancer. In the same period, 95 patients (8.2%) developed a locoregional recurrence, of whom 5 patients redeveloped a recurrence. The mean age of the breast cancer patients with a redeveloped recurrence was 52 years, with the youngest of them being 25 at the time of diagnosis and primary tumor treatment, and the oldest 81. The mean interval between initial treatment and the development of locoregional recurrence was 4.3 years (the shortest interval between primary cancer operation and locoregional recurrence was 3 months).

A. Initial treatment

Conservative surgical procedure (segmentectomy, quadrantectomy) with axillary dissection was performed in 77 patients (81%), while 18 patients underwent surgery for breast cancer alone (19%). In 13 or 16.8% of patients in whom axillary dissection was performed, lymph nodes

were involved with tumor tissue. Of 95 patients, 73 (77%) underwent radiation therapy after initial surgery, and 57 patients (60%) received systemic therapy - 34 chemotherapy and 23 hormone therapy. The NSABP B-06 (National Surgical Adjuvant Breast and Bowel Project) results show that local recurrence develop in 12% of patients undergoing lumpectomy with adjuvant radiation and lumpectomy, or in 43% of patients undergoing lumpectomy alone (5). Whelan et al. (8) evaluated disease outcome comparing lumpectomy with and without radiation therapy. In patients who received radiotherapy, the 5-year local recurrence rate was 8%, compared to 30% in the group without postoperative irradiation. The 5-year survival rate was 88% and 86%, respectively.

Of 13 patients with positive axillary lymph nodes, 9 (69%) received postoperative radiotherapy. In this group, 77% of the patients received systemic therapy, which exceeds 60% reported for all the patients receiving systemic therapy. In 8/13 chemotherapy was indicated, and 2/13 received hormone therapy. In this group, the mean interval between initial surgery and the development of local recurrence was 3.2 years, or one year less than in patients not undergoing axillary dissection or patients with negative axillary lymph nodes.

In the group of 18 patients not undergoing axillary dissection, 7 had noninvasive carcinoma. The percent of irradiated patients in this group was 44% (8 patients), while 16% (3 patients) received systemic therapy.

B. Localization of recurrence

The most common localization of recurrence was at the site of prior excision (54 patients - 54%). In 37 patients, local recurrence developed elsewhere within the breast, remote from the primary tumor site. Five patients developed disease recurrence in the regional lymph nodes, while in 4 patients the recurrence presented either with an ulceration or signs of inflammatory cancer. In the first 5-10 years, the localization of a recurrent tumor is at the site of or adjacent to the site of prior excision (14, 19, 20). After that period, recurrences increasingly develop elsewhere within the breast suggesting the existence of two processes: the growth of a «true» recurrence and

the development of a new primary tumor in the same breast. Studies show that patients with late recurrences and recurrences localized in other breast quadrants (the majority of which might be new primary tumors) have a better prognosis (21). The analysis of 73/973 patients with a local recurrence developed after breast-conserving surgery and radiation therapy treated at the Yale-New Haven Hospital (9) showed distant metastases developed in 50% of the patients with local recurrence developed within 4 years from the primary tumor diagnosis, and in 17% of patients with later developed local recurrence. According to the Fredriksson's study (21), the risk of death from breast cancer was the highest in women with an early recurrence located in the same breast quadrant as their primary tumor. The Joint Center for Radiation Therapy analyzed the localization and 5-year survival rate following the treatment for operable local recurrences in the group of patients with local recurrence developed within 5 years after primary therapy, and in the group with local recurrences developed later (19). In the first group, 14% of patients developed recurrence at a site remote from the primary tumor bed with the 5-year survival rate after local recurrence accounting for 61%; in the second group, the rate of recurrences developed elsewhere in the breast and the survival rate were 31% and 84%, respectively. Fredriksson et al. studied a lead-time bias in early and late recurrences and set the time limit for developing an early recurrence to two years (21). Although patients with a new primary tumor have significantly higher survival rates than patients with a true recurrence, these patients are at increased risk of developing contralateral disease (22). As regards our patients, 95 (9.5%) developed also contralateral breast cancer. The prognosis following the development of contralateral disease is similar to that following the development of late recurrence, with 5- and 10-year specific survival accounting for 89% and 77%, respectively (23).

C. Multicentric breast recurrence

The risk of death from breast cancer is almost the same in early recurrences and multicentric carcinoma (21). Two of our patients had a multicentric breast recurrence and in both,

the recurrence developed at a site remote to the primary tumor bed. In one of them, pathohistology showed invasive lobular carcinoma, and in the other papillary carcinoma *in situ*. In the first case, the recurrent tumor was diagnosed as multicentric invasive ductal carcinoma, and invasive papillary carcinoma in the second. In both cases, secondary surgery included modified radical mastectomy with axillary dissection (no axillary lymph node metastases were found in either of the patients).

D. Early development of local recurrence

In 37 (39%) patients, locoregional recurrences developed within 2 years (early recurrence) after primary treatment for breast cancer (two patients had noninvasive carcinoma). Nine (19%) patients underwent breast-conserving surgery, 28 or 75% breast-conserving surgery with axillary dissection, with 9 (24%) of them having metastases in axillary lymph nodes. Postoperatively, 20 (54%) patients received radiation therapy, and 29% were submitted to systemic therapy (8 received chemotherapy and 3 hormone therapy). In addition to local recurrence, 4 (11%) patients also developed distant dissemination. The majority of recurrences were localized in the region of the primary tumor bed (27 patients or 73%). Seven patients had a recurrence localized in other breast segments, two were diagnosed with Mb Paget, and one had a recurrence in the axillary lymph nodes. Comparing the data of recurrent tumor localization in the early recurrence group with the early and late recurrence group, the rate of recurrences localized at the site of prior excision was significantly higher - 73% vs. 54%. Likewise, the positive axillary lymph node rate was higher in the early recurrence group (24% / 17%), but the number of patients undergoing postoperative radiotherapy was smaller (54% / 77%). Percentage of patients with distant dissemination at the time of developing local recurrence was relatively lower in patients with early recurrence (11% vs. 15.7%).

E. Local recurrence after treatment for noninvasive breast cancer

Results obtained in the majority of studies show that the success rate of local recurrence

treatment after conservative surgery for noninvasive breast cancer is rather high. The majority of recurrences after surgery for noninvasive cancer, regardless whether radiotherapy was administered or not, are located at the site of prior excision, with approximately a half of them being noninvasive (24, 25). At the University Hospital for Tumors in Zagreb, Croatia, of 95 patients who developed locoregional recurrence after breast-conserving surgery, 10 (9.5%) had noninvasive primary carcinoma. In 9 patients, the histologic finding of the primary tumor showed noninvasive ductal carcinoma, and in 1, papillary carcinoma *in situ*. All of the patients underwent tumorectomy or segmentectomy of the breast, and in three, axillary dissection was done (with no metastases found in the axillary lymph nodes). Adjuvant therapy was not performed in either of these patients. The study performed by the Japanese Gunma University School of Medicine reports the recurrence rate in noninvasive cancer patients undergoing breast-conserving surgery alone of 27.8% with the mean follow-up of 86 months, with the majority of these recurrences occurring after surgical treatment for carcinoma *in situ* located near the mamilla (26). In our patients, in the 1-9-year interval (median 4.1 years) recurrences in three cases developed at the site of prior excision, in 7 patients the recurrence was located at the site remote to the primary tumor bed, with some of them possibly being new primary tumors. Eight patients (80%) developed an invasive recurrence, 7 of them invasive ductal carcinoma and one multicentric papillary carcinoma (in this patient, the histologic finding of the primary tumor was papillary carcinoma *in situ*). In two patients, the local recurrence was also noninvasive, papillary carcinoma *in situ* in one, and lobular carcinoma *in situ* in the other. In both cases, the histologic finding of the primary tumor showed noninvasive ductal carcinoma. In one patient, two years after initial treatment for breast cancer, contralateral carcinoma was detected. After the diagnosis of local recurrence, 9 patients underwent mastectomy with dissection, or redissection of the axilla, and one mastectomy alone. Of 9 patients in whom axillary lymph nodes were removed, lymph node metastases were detected in two. In patients with non-

invasive recurrence, adjuvant therapy after secondary surgical treatment was not indicated. In the group with invasive recurrence, four patients received radiation therapy, four patients received hormone therapy, with chemotherapy being indicated in only one patient with multicentric invasive recurrence.

H. Treatment of locoregional recurrence after breast-conserving surgery and radiotherapy

Treatment of breast cancer local recurrence is rarely curative, although patients with a recurrence localized in the breast or the thoracic wall can have a long-term survival with adequate therapy. The relapse-free 5-year survival rate in patients with an operable recurrence and without dissemination is nearly 60-75%, with the specific survival rate of 80-85% (12, 15). When the study also includes patients with an inoperable recurrence and patients with parallel distant metastases, the 5-year survival rate after local recurrence is 35-70% (14, 15, 27, 32), with a long-term disease-free interval in 30-50% of patients. After mastectomy for local recurrence, the majority of patients develop a relapse due to distant dissemination. After mastectomy, 10-25% of patients develop a recurrence in the thoracic wall (12, 19). According to one study (28), the majority of patients with a recurrence in the thoracic wall develop a progressive local disease despite any further treatment.

Prior to the treatment for local recurrence, the staging and spread of the disease should be re-evaluated. Whenever possible, the recurrence diagnosis should be confirmed both histologically and cytologically, while estrogen and progesterone levels as well as the HER2/neu status in the recurrent tumor, and knowledge about previous adjuvant treatment, are important information for deciding about further therapy.

1. Surgical management

Surgical management for operable local recurrence usually includes mastectomy, although some centers also perform secondary conservative surgery with postoperative irradiation. Whether the survival rate in patients undergoing mastectomy after the development of local recurrence is higher than in patients undergoing sec-

ondary breast-conserving surgery with radiation therapy remains unclear. Nevertheless, patients undergoing secondary breast-conserving surgery followed by irradiation run a significant risk of developing further recurrences. Actually, the study of Fowble et al. (15) which reports the 5-year disease-free survival in 59% of patients treated with secondary mastectomy. The study of the Women's College Hospital, Toronto, Canada showed the 5-year rate of developing secondary local recurrence of 69% for patients treated with secondary breast-conserving surgery alone, and 11% for patients in whom radiation therapy was performed, too (29). According to a Milan study, 11% of patients redevelop a recurrence after secondary breast-conserving surgery and irradiation (30). On the other hand, results of the study carried out in the Marseille Cancer Institute showed the same rate of repeated recurrence (9%) after conservative surgery with irradiation and mastectomy as a secondary surgical procedure. Some patients with unsuccessful secondary conservation treatment followed by irradiation were additionally treated with wide excision and interstitial implantation, or external irradiation of a small breast portion. After the mean follow-up of 4 years, the recurrence developed in 23% of the patients (31).

At the University Hospital for Tumors, the most common surgical procedure after diagnosis of locoregional recurrence was mastectomy which was performed in 48 patients (48%). Surgical treatment for locoregional recurrence was followed by irradiation in 37 patients. In 28 cases, in addition to mastectomy, axillary lymph nodes were removed. Twelve patients underwent extirpation of their recurrence alone. Due to recurrence in their regional lymph nodes, axillary lymph nodes were removed in 7 patients, and in 1 patient, secondary surgery included quadrantectomy with axillary dissection. In 36 patients in total, dissection or redissection of the axilla was done, with metastatic axillary lymph nodes detected in 20 or 55.5%. On the other hand, the initial treatment showed positive regional lymph nodes in 16.8% of the patients. Six patients had a noninvasive recurrence. Of them 2 developed noninvasive recurrent ductal cancer, 2 developed Mib Paget, and 2 developed carcinoma *in situ* - 1 lobular and 1 papillary. All of them underwent mastectomy, in 5 with axillary dissection. Four pa-

tients with a cytologically verified recurrence did not undergo surgical treatment, of them one for inoperable recurrent tumor, and three for dissemination of the disease (two patients had multiple pulmonary metastases, and one had pulmonary and hepatal metastases). These patients were candidates for systemic therapy.

2. Systemic treatment

Systemic therapy was administered in 74 patients in total (74%). Chemotherapy was indicated in 47 (47%) in distinction from 36% of the patients receiving chemotherapy as initial treatment for primary breast cancer. Hormone therapy was administered to 27 patients (after the primary surgical procedure, 23 patients received hormone therapy).

Administration of systemic therapy to patients with local recurrence appears reasonable due to an increased risk of distant dissemination and possibly a higher mortality rate. However, there are few convincing data that support the indication and success of systemic therapy for local recurrence. If the patient does not receive systemic therapy after primary surgical treatment, treatment options for local recurrence may be similar to those for a newly detected breast carcinoma, but if the patient has already been on systemic therapy, then there are several questions to be considered at indicating second-line systemic therapy. Actually, the majority of patients receive several chemotherapy drugs within their initial treatment, so the detection of drug resistance can be difficult. On the other hand, as these patients can be at an increased risk of developing toxicity, the potential benefit of chemotherapy should be weighed against its long-term toxicity (11).

3. Redevelopment of local recurrence

Five patients redeveloped locoregional recurrence in the interval of 2 to 3 years following the secondary surgical procedure. In 4 patients, secondary surgery included mastectomy with dissection, or redissection of the axilla, and 1 underwent axillary redissection alone for recurrence in the regional lymph nodes. In two patients, repeated recurrence was located in post-operative scar tissue, while the remaining three patients redeveloped recurrence in axillary

lymph nodes. In our patients, surgical treatment included either wide excision or extirpation of axillary lymph nodes. Four patients received radiotherapy for a secondary recurrence, and in all 5 chemotherapy or hormone therapy was indicated, depending on the type of prior systemic therapy. The study of the Joint Center for Radiation Therapy (12) shows that subsequent recurrences occur about 16.5 months after the first relapse on the average. According to this study, patient age, initial tumor stage, relapse location and disease-free interval do not have any prognostic value for the redevelopment of recurrence after secondary surgical treatment, unlike histology of the recurrence.

DISCUSSION

According to our study, locoregional recurrence following breast-conserving surgery was found in 8.6% of the studied patients, which complies with the results of other cancer centers. It should be taken into consideration that our result includes also the nonirradiated group and the group with noninvasive primary carcinoma. Following the results of Fredriksson and Abnera (21,12), we have expected a higher rate of recurrent tumors located at the site of prior excision (70- 85%). In more than a half of our patients, the recurrence was located at the site of the primary tumor bed (54%). The higher rate of this localization was found in patients with early recurrence (occurring within 2 years after primary treatment) – 73%, which complies with the judgement that early recurrences developed at the site of prior excision are true recurrences, resulting from incomplete removal of the primary tumor, unlike late recurrences and recurrences in other breast quadrants which may be new primary tumors. Although some centers use salvage therapy even after the development of local recurrence, and although studies to date have not yet reached a unanimous decision on the surgical treatment of choice for recurrences (29, 30, 31), in the University Hospital for Tumors, Zagreb, Croatia, the majority of patients, i.e. 66% of them, underwent mastectomy following the diagnosis of local recurrence in the breast. Unlike some other cancer centers (9, 12, 15, 32), where 30–50% of patients received systemic therapy for local recurrence,

74% of our patients received either chemotherapy or hormone therapy. As mentioned above, thoracic wall recurrence after secondary mastectomy occurs in 10–25% of breast cancer patients (12, 19). In the University Hospital for tumors, Zagreb, Croatia, cancer recurred in only 5.3% of the patients, with the mean lead time being 2.6 years.

CONCLUSION

The increasing number of breast cancer patients undergoing breast-conserving surgery and radiotherapy, and the increasing number of locoregional recurrences thereof, requires the definition of adequate follow-up and treatment protocols aimed at as early as possible relapse detection and reduction of breast cancer mortality rate in these patients. The only prevention of true local recurrences is the radical removal of primary cancer, even so it does not apply to local recurrences located in other breast quadrants some of which are usually new primary tumors with a better prognosis.

What are the risk factors for the development of local recurrence, what is an adequate surgical treatment for true recurrences and for new primary tumors, how do we distinguish them, and finally, what type of systemic therapy should be used and in which patients, are the questions that still require the final answer.

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