Radiol Oncol 2003; 37(2): 79-88.

Prognostic outcome of local recurrence in breast cancer after conserving surgery and mastectomy

Renata Soumarová[1], Hana Horová[1], Zuzana Šeneklová[1], Ivana Horová[2], Marie Budíková[2]

[1] *Radiation Oncology Department, Memorial Cancer Institute Brno,*
[2] *Department of Applied Mathematics, Masaryk University Brno, Czech Republic*

Background. *In our retrospective study we analysed local recurrences in breast cancer patients treated with conserving surgery (CS) followed by adjuvant radiotherapy (RT) or mastectomy (ME) with or without radiotherapy. We analysed the impact of local recurrence on overall survival.*

Patients and methods. *Between 1980-1995, 306 patients underwent conserving surgery and 1,193 patients were done mastectomy in Masaryk Memorial Cancer Institute. The patients lost to follow-up were excluded. After all, we analysed 236 patients who underwent conserving surgery (Group A), and 1,121 who underwent mastectomy (Group B). All patients with CS received adjuvant RT of the breast with or without regional lymph nodes. In 982 patients (87.6 %) with ME, we performed RT of the chest wall with or without regional lymph nodes. Median age at the time of diagnosis was 48.3 years in Group A and 52.1 years in Group B. In Group A, 149 patients (63.1 %) had T1 tumour, 86 (36.4 %) T2 and 1 (0.5 %) T3. In 24.2 % of patients, axillary node involvement was observed. In Group B, 316 patients (30.4 %) had T1 tumour, 607 (58.3 %) T2, 76 (7.3 %) T3, 33 (3.2 %) T4 and 9 (0.9 %) TX. In 46.2 % of these patients, we found axillary node involvement. Invasive ductal carcinoma was histologically proved in 67.4% in Group A and 84% in Group B. Systemic treatment was given to 133 patients (56.4 %) from Group A and to 857 patients (76.4 %) from Group B.*

Results. *Median follow-up was 100.5 months in Group A and 121 months in Group B. In Group A, we registered 22 (9.3 %) local recurrences, 5-year local control was 96.2% and median time to local recurrence was 50 months. In Group B, we registered 65 (5.8%) local recurrences; 5-year local control was 96.6%. Five-year local control in patients with T1, T2 tumours was 97.2%. In patients with adjuvant RT median time to local recurrence was 48.5 months, and in patients without adjuvant RT 51 months. Thirteen patients (8.7 %) who underwent mastectomy without RT had local recurrence . The impact of local recurrence on overall survival was statistically significant in Group B ($p = 0.002$) and not exactly statistically significant in Group A ($p = 0.062$). Patients who developed local recurrence had lover overall survival. Unambiguous linear dependence was confirmed between the time to local recurrence and overall survival.*

Conclusions. *The impact of local recurrence on overall survival was found statistically significant. Probability of local recurrence and time to local recurrence was the same in the patients treated with CS or ME. The overall survival increased with local disease free interval.*

Key words: breast neoplasms - surgery; mastectomy; neoplasms recurrence, local; prognosis; radiotherapy, adjuvant; survival analysis

Received 12 November 2002
Accepted 18 December 2002

Correspondence to: Renata Soumarová, M.D., Department of Radiation Oncology, Masaryk Memorial Cancer Institute, Žlutý kopec 7, Brno 656 53, Czech Republic; Phone: +420 5 4313 1116-7; Fax: 420 +420 5 4321 1169; E-mail: soumarova@mou.cz

Introduction

Significance of local recurrence after breast conserving surgery (CS) or radical mastectomy (ME) has been discussed. Local recurrence after ME is supposed to have worse prognosis than after CS. The role of postoperative locoregional radiotherapy (RT) (to the chest wall or whole breast and regional lymph nodes) has been evaluated in randomised studies during the last 50 years. The results confirmed the impact of locoregional treatment on reduction of local recurrence, but the impact on overall survival (OS) is still not clear.[1] The impact on OS was proved only in the patients with positive lymph nodes and systemic therapy.[2] Breast cancer is a systemic disease. This new approach favoured breast conserving surgery and application of chemotherapy. The number of mutilating operations thus decreased. Nevertheless, locoregional RT remains an important treatment modality.

However, some questions have remained unsolved. Further studies need to be performed to explain the role of RT and its integration in multimodal therapy of breast cancer. CS followed by postoperative RT has become standard treatment modality. Prospective randomised trials have shown that the number of local recurrences after CS followed with RT is the same as after the mutilating ME.[3-8] OS rate and the risk of distant metastases development are equal in both, ME and CS followed by RT.[9-13] Contraindications for RT are the same as for CS: pregnancy, prior breast or chest irradiation (i.e. mantle technique), collagenosis. Other known contraindications for CS are: multifocal tumour, diffuse microcalcification, breast and tumour size disproportion.[14] Patients' opinion has to be respected.

The meta-analysis of 36 randomised studies compared the results of postoperative RT in early breast cancer patients (17 273 patients.) and ME alone. A treble decrease of risk of local recurrence was shown after adjuvant RT. The difference in 10-year survival was not significant.[15] Fisher's study shows similar results.[4]

The prognosis of local recurrence is still uncertain. The impact of local recurrence on overall survival is not clear.

Patients and methods

Patients with breast conserving surgery (CS)

Between January 1983 and December 1994, a total number of 306 patients underwent adjuvant RT after CS at the Masaryk Memorial Cancer Institute (Figure 1). Our report evaluates the available data of 236 patients. For statistical evaluation, SPSS, Matlab, Gehan-Wilcoxon (for survival analysis) and log-rank tests were used. Local therapy (surgery + RT) was followed by adjuvant chemotherapy or hormonal therapy in 54%. Table 1 shows the characteristic of patients. Figure 2 shows the age range. Tumour size up to 2 cm (63.1%) (Figure 3) and invasive ductal carcinoma

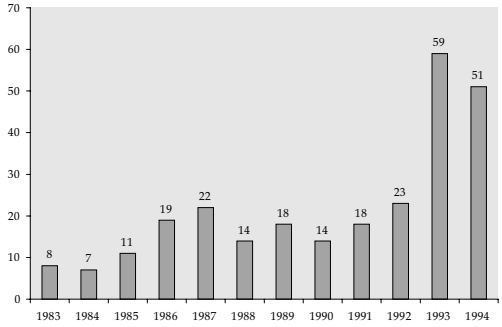

Figure 1. Number of patients treated by conservative surgery and radiotherapy.

Table 1. Characteristics of patients treated by conservative surgery (n = 236)

	Age (years)	
Mean	49.68±0.64	
Median	48.29 (25.3-80.3)	
	Stage of tumour	
T1	149	(63.1%)
T2	86	(36.4%)
T3	1	(0.5%)
	Histology	
Ductal	159	(67.4%)
Lobular	23	(9.7%)
Others	54	(22.9%)
	Margins	
Free	214	(90.7%)
Positive	22	(9.3%)
	Axillary nodes	
Positive	36	(24.2%)
Negative	118	(44.7%)
Unknown	82	(31.1%)
	Side	
Left	124	(52.5%)
Right	112	(47.5%)
	Quadrant	
Outer upper	168	(71.2%)
Outer lower	22	(9.3%)
Inner upper	37	(15.7%)
Inner lower	2	(0.8%)
Central	7	(3.0%)

(67.4%) were found in most cases. The mean follow-up was 110.4 months (median 100.5 months).

Treatment

After the elimination of distant metastases, wide local excision (23.7%) or quadrantectomy (76.3%) was performed. Axillary dissection was not performed and a limited number of axillary lymph nodes were examined in 31.1% of patients. All patients received postoperative RT to the whole breast, with or without irradiation of regional lymph nodes (axillary and supraclavicular). The mean interval between surgery and RT was 23 days (range 10-120, median 28.8 days). The entire

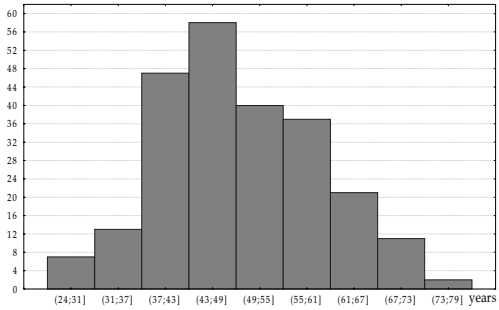

Figure 2. Age distribution of patients after conservative surgery and radiotherapy.

Stage of tumour	Number of pts.	
pT1	149	63, 1%
pT2	86	36, 4%
pT3	1	0, 5%

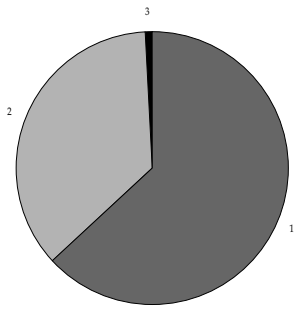

Figure 3. Stage of tumour in patients after conservative surgery and radiotherapy.

breast was included in the target volume. The superior border lay at about the level of the suprasternal notch medially and just bellows the level of the abducted arm laterally. The inferior border lay 1-2 cm below the breast. The medial border was usually in the mid-line, and the lateral border was in the mid-axillary line. Two tangential fields were used for irradiation of breast. Four fields - two tangential and two convergent - were used for irradiation of the breast and regional lymph nodes.

The lymph nodes were irradiated in 169 patients (71.6%). Sixty-two patients (22.7%) were treated with linear accelerator (photons 6MV) and 174 patients (73.7%) with cobalt unit. Electron beam of linear accelerator or caesium unit were used as boosting to tumour bed or axilla. The applied dose was prescribed according to ICRU (International Commission on Radiation Units and Measurements).

Systemic adjuvant therapy was given to 133 patients (56.4%). Hundred and nine patients (46.1%) completed 2-6 cycles of chemotherapy. Eighty-three patients (35.2%) received CMF regimen (cyclophosphamide, methotrexate, and 5-fluorouracil), 11 patients (7.6%) FAC regimen (5-fluorouracil, doxorubicin, and cyclophosphamide), and 8 patients had both regimens, CMF and FAC. Hormonal therapy (tamoxifen 20 mg per day) was given to 68 patients (28.8%). Twenty-nine patients (11%) received chemotherapy and hormonal therapy simultaneously.

All patients were routinely examined every 3-6 months. Once a year, they underwent ultrasonography of the breast or mammography, lung X-ray, ultrasonography of the liver and bone scintigraphy.

Patients with radical mastectomy (ME)

Between 1980 and 1995, a total number of 1,193 patients underwent ME at the Masaryk Memorial Cancer Institute (Figure 4). We evaluated 1,121 patients. The patients lost to follow-up were excluded. Table 2 shows the characteristics of patients. Mean age at the time of diagnosis was 53.1 years (median 52.1) (Figure 5). Tabel 3 and Figure 6 show the size of tumours. Rare occurrence of T3, T4 tumours is due to the exclusion of patients who underwent neoadjuvant RT or chemotherapy. Mean follow-up was 124.6 months (median 121).

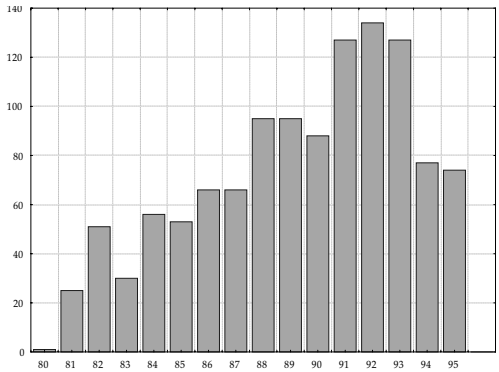

Figure 4. Number of patients treated by radical mastectomy in Masaryk Memorial Cancer Institute.

Table 2. Characteristics of patients treated by radical mastectomy, number of patients 1121

	Age (years)	
Mean	53.1	
Median	52.1	
	Hormonal status	
Premenopausal	488	43.5 %
Postmenopausal	633	56.5 %
	Grade of tumours	
T1	342	30.4 %
T2	647	57.7 %
T3	84	7.5 %
T4	39	3.5 %
TX	9	0.8 %
	Mamma	
Left	548	48.9 %
Right	573	51.1 %
	Histology	
Ductal	942	84 %
Lobular	111	9.9 %
Others	68	6.1 %
	Axillary nodes	
Positive	518	46.2 %
Negative	521	46.5 %
Unknown	82	7.3 %
	Radiotherapy	
Yes	982	87.6 %
Only on chest wall	392	39.9 %
No	139	12.4
	Chemotherapy	
Yes	466	41.6 %
No	655	58.4 %
	Hormonotherapy	
Yes	381	34 %
No	740	66 %

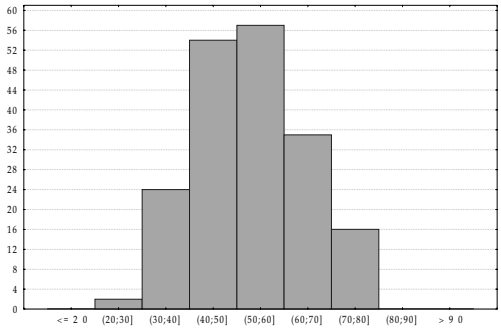

Figure 5. Age of patients after radical mastectomy.

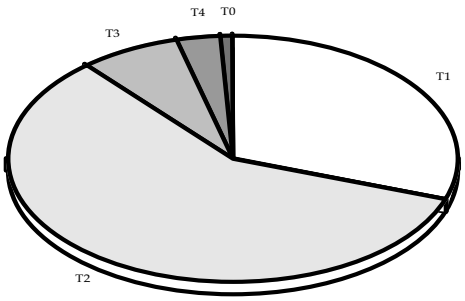

Figure 6. Stages of tumours after radical mastectomy.

Table 3. Patients after conservative surgery and radiotherapy with local recurrence, number of patients 22 (9.3%)

	Age (years)	49.1 (36-69.7)
	Surgery	
Partial mastectomy	12	(54.5 %)
Tumourectomy	10	(45.5 %)
	Histology	
Ductal	15	(68.2 %)
Lobular	1	(4.5 %)
Others	6	(27.3 %)
	Source of RT	
Cobalt Co-60	17	(77.3 %)
Linear accelerator	5	(22.7 %)
	Nodes	
Positive	8	(36.4 %)
Negative	6	(27.3 %)
Unknown	8	(36.4 %)
	Treatment of local recurrence	
Radical mastectomy	11	(35.3 %)
Exstirpation	4	(23.5 %)
Only systemic therapy (CT or HT)	7	(41.2 %)

Treatment

Radiotherapy to the chest wall with or without regional lymph nodes was performed in 982 patients (86.6%) who underwent ME. The patients were treated with linear accelerator (photons 6MV). Two tangential fields were used for the irradiation of the chest wall, two convergent fields for the regional lymph nodes. The lymph nodes were irradiated in 59.5% patients. Median dose of 44 Gy was given to the chest wall, 40 Gy to the regional lymph nodes. Systemic adjuvant therapy (chemotherapy, hormonal therapy or both) was applied to 817 patients (76.9%).

Results

Patients with conservative surgery (CS) and radiotherapy (RT)

Till the date of evaluation (December 2001), 47 patients (19.9%) died, all of them due to the progression of breast cancer.

Local recurrence occurred in 22 patients (9.3%). Table 3 shows the characteristics of patients. The mean time to local recurrence was 63.4 months (range 5 - 168, median 50 months). The mean survival of patients with local recurrence was 41.4 months (range 5 - 122). From 22 patients with local recurrence, 9 developed distant metastases (40.9%). Distant metastases occurred simultaneously or after local recurrence. The mean of follow-up of patients with local recurrence was 101.8 months (range 41 - 187). Till the date of evaluation, 8 patients (36.4%) died. Local recurrence in the primary involved quadrant occurred in 18 cases. Diffuse breast involvement was described in 4 cases. Three patients had lymphangioinvasion described in prime histology; two of them developed diffuse local recurrence. Five-year local control in the whole group of patients was 96.2%. Nine patients (3.8%) had local recurrence within 5 years. Ten-year local control was 91.9%; in 217 patients, local treatment failure was not

observed within 10 years. The histology of local recurrence corresponded to the histology of primary tumour. Among 22 patients with local recurrence, 6 patients were younger than 40 years at the time of diagnosis. Local recurrence had negative impact on survival, p = 0.06 (Figure 7).

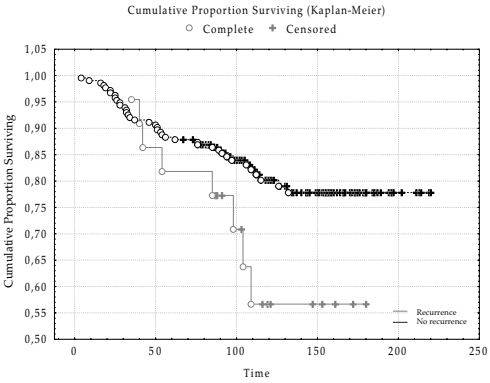

Figure 7. Influence of local recurrence on overall survival in patients after conservative surgery.

Patients with radical mastectomy (ME)

Till the date of evaluation, 65 patients (5.8%) developed local recurrence (Table 4). Five-year local control was 96.6%; in the patients with T1, T2 tumours it was 97.2%. There was no difference in the time to local progression in the irradiated patients (48.5 months) and in the patients without RT (51 months). Local recurrence developed in 13 patients (8.7%) with ME without RT, 44.6% of them had lymph nodes involvement. Lymph node involvement and local recurrence developed independently. Higher number of local recurrences associated with lobular carcinoma was not statistically significant. Patients with local recurrence developed distant metastases more frequently. The impact of local recurrence on OS was statistically significant (p=0.002) (Figure 8). Of patients without local recurrence, 12.9% died, and in the group that locally relapsed 39.1% died. Significant linear correlation between the time to local progression and OS was observed.

Table 4. Characteristic of patients with local recurrence after radical mastectomy, number of patients 65 (5.8%)

	Histology	
Ductal	56	86.15 %
Lobular	4	6.15 %
Others	5	7.7 %
	Nodes	
Positive	29	44.6 %
Negative	36	55.4%

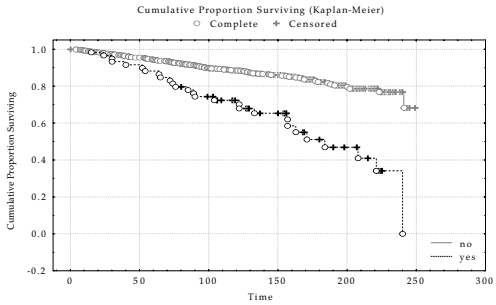

Figure 8. The Influence of local recurrence on overall survival in patients after radical mastectomy.

Discussion

In a French retrospective study of 528 patients with breast cancer, stages I and II, an attempt was made to determine predictive factors for local recurrence.[16] A multivariante analysis of this study showed 4 independent factors most important for local control: young age (up to 40 years), premenopause, bifocality and extensive intraductal component (≥25%).

The impact of local recurrence on OS is not clear. Our study showed negative impact of local recurrence on OS. The difference was on the border of statistic significance in the patients with CS (p=0.06) and significant in the patients with ME (p=0.002). The analysis of 4 prospective studies comprising more than 2000 breast cancer patients tried to evaluate the role of isolated local recurrence.[17] The impact on OS and dissemination was

proved. Elkhuizen reported similar conclusion.[18]

A very important prognostic factor is the interval between the time of diagnosis and local recurrence.[19] In our group of patients (with CS and ME), the time to local progression was equal - 50 months. The patients with longer time to local progression had longer survival. The impact of histologic type of tumour on local recurrence was not proved. Lobular carcinoma, often multifocal and multicentric, was considered not to be convenient for breast conserving surgery. The studies comparing the results of both carcinomas, ductal and lobular, did not show any difference in local control or other parameters.[20,21] The patients with local recurrent ductal carcinoma in situ had significantly better prognosis. Patients with lobular carcinoma in situ have significantly higher risk of unilateral recurrence.[22] Tamoxifen seems to decrease this risk. Histologic type of tumour did not have any impact on local recurrence in our groups of patients. Lobular carcinoma should not be a contraindication for CS.

Till the end of 1970's, postoperative RT was given to all patients with ME. As the knowledge about dissemination of tumour cells advanced, the treatment strategy changed accordingly. Positive outcome of RT after ME must be compared to potential acute and late effects of RT. Modern techniques of RT reduce the doses to the heart and the large vessels.

RT after ME is a standard in patients with high risk of local recurrence: locally advanced tumours - pT3, pT4, 4 or more axillary lymph node involvement, extracapsular invasion.[23,24] The role of postoperative RT is not clear in pT1, pT2, pN0 tumours and 1 - 3 axillary lymph node involvement. A Danish study evaluated the role of postoperative RT.[2] Combined systemic treatment with RT and chemotherapy alone (CMF regimen) were compared. OS and disease-free interval significantly increased in combined therapy. Janni's retrospective analysis evaluated the impact of RT given to the chest wall on local recurrence rate and OS.[25] The decrease of local recurrence and positive impact on OS was statistically significant in the group of patients with RT.

Meta-analysis of 36 randomised studies (Early breast cancer trialist's collaboration group EBCTCG) compared postoperative RT and surgery alone in early breast cancer patients (17,273 patients with mastectomy). The risk of local recurrence after adjuvant RT was treble lower, but the difference in 10-year survival was not significant.[15] No difference was found between the patients with ME and the patients with CS and RT. Fisher's study reported similar results.[4]

The above negative results do not correlate with the results of other randomised studies: Danish 82b and 82c trials, British Columbia study.[2,24.26] Van de Steene tried to solve this contradiction. He confirmed the impact of postoperative RT on survival if modern techniques and standard fractionation of RT were used.[27] Levitt's study showed the impact of RT on OS in the patients with negative resection margin and negative lymph nodes.[28] Another meta-analysis of 6,367 patients verified that locoregional therapy of breast cancer increases disease-free interval and OS.[1]

In our study, the impact of local recurrence on OS was found statistically significant. We did not see any benefit of postoperative RT. Among 65 patients with local recurrence, 51 (78.4%) underwent irradiation of the chest wall.

In primary operated part of the breast, 65 - 80% of local recurrences occurred.[29] In selected group of patients, only tumour bed could be postoperativelly irradiated. Brachytherapy as a separate method of adjuvant treatment of breast carcinoma was described in few reports.[30-34] The studies showed that this treatment was well tolerated and had good cosmetic effect. Good cosmetic effect and reduction of treatment time are the main aim of this method.

Conclusions

There was no difference in the time to local progression found between our two groups of patients. Median time to local progression was equal - 50 months. Five-year probability of local recurrence was equal for the patients with CS (and RT) and patients with ME (without RT) - 9.3%, 8.7% respectively.

Patients with CS who developed local recurrence had equal over-all survival compared to the patients with ME due to T1, T2 tumours with local recurrence (Figure 9). Prognostic outcome of local recurrence after CS or ME does not differ.

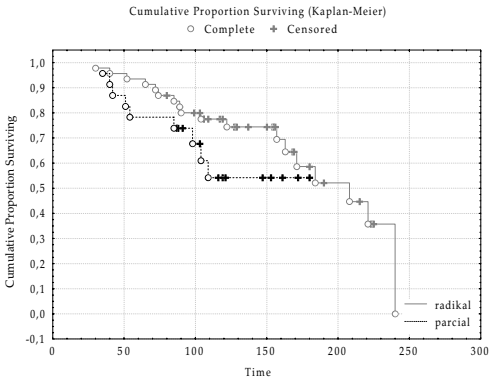

Figure 9. The overall survival of patients with local recurrence treated by conservative surgery or radical mastectomy.

References

1. Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. *Clin Oncol* 2000; **18(6):** 1220-9.

2. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Postoperative radiotherapy in high-risk premenopausal woman with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 1997; **337:** 949-55.

3. Clark RM, Whelan T, Levine M, Roberts R, Willan A, McCulloch P, 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:** 1659-64.

4. Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1995; **333:** 1456-61.

5. Forrest AP, Stewart HJ, Everington D, Prescott RJ, McArdle CS, Harnett AN, et al. Randomized controlled trial of conservation therapy for breast cancer: 6-year analysis of Scottish trial. Scottish Cancer Trials Breast Group. *Lancet* 1996; **348:** 708-13.

6. 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 Monogr* 1994; **86:** 717-22.

7. Veronesi U, Luini A, Del Vecchio M, Greco M, Galimberti V, Merson M, et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Engl J Med* 1993; **328:** 1587-91.

8. Blichert-Toft M, Rose C, Andersen JA, Overgaard M, Axelsson CK, Andersen KW, et al. Danish randomized trial comparing breast-preserving therapy with mastectomy: six years of life table analysis. Danish Breast Cancer Cooperative Group. *J Natl Cancer Inst Monogr* 1992; **11:** 19-25.

9. Fisher B, Redmond C, Poisson R, Margolese R, Wolmark N, Wickerham L, et al. Eight year results of randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1989; **320:** 822-8.

10. Jacobson JA, Danforth DN, Cowan KH, d'Angelo T, Steinberg SM, Pierce L, et al. Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. *N Engl J Med* 1995; **332:** 907-11.

11. Sarrazin D, Le MG, Arriagada R, Contesso G, Fontaine F, Spielmann, et al. Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. *Radiother Oncol* 1989; **14:** 177-84.

12. van Dongen JA, Bartelink H, Fentiman IS, Lerut T, Mignolet F, Olthuis G, et al. Randomized clinical trial to assess the value of breast cancer , EORTC 10801 trial. *J Natl Cancer Inst Monogr* 1992; **11:** 15-8.

13. Veronesi U, Banfi A, Salvadori B, Luini A, Saccozzi R, Zucali R, et al. Breast conservation is the treat-

ment of choice in small breast cancer: Long-term results randomized trial. *Eur J Cancer* 1990; **26:**668-70.

14. Konopásek B, Petruželka *L. Karcinom prsu.* Prague: Galén; 1997.

15. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group. *N Engl J Med* 1995; **333:** 1444-55.

16. Touboul E, Buffat L, Belkacemi Y, Lefranc JP, Uzan S, Lhuillier P, et al. Local recurrences and distant metastases after breast conserving surgery and radiation therapy for early breast cancer. *Int J Radiat Oncol Biol Phys* 1999; **43(1):** 25-38.

17. Schmoor C, Sauerbrei W, Bastert G, Schumacher M. Role of isolated locoregional recurrence of breast cancer: results of four prospective studies. *J Clin Oncol 2000*; **18(8):** 1696-708.

18. Elkhuizen PH, Hermans J, Leer JW, van dE Vijver MJ. Isolated late local recurrence with high mitotic count and early local recurrences following breast-conserving therapy are associated with increased risk on distant metastasis. *Int J Radiat Oncol Biol Phys* 2001; **50(2):** 387-96.

19. Doyle T, Schultz DJ, Peters C, Harris E, Solin LJ. Long-term results of local recurrence after breast conservation treatment for invasive breast cancer. *Int J Radiat Oncol Biol Phys* 2001; **51(1):** 74-80.

20. Peiro G, Bornstein BA, Connolly JL, Gelman R, Hetelekidis S, Nixon AJ, et al. The influence of infiltrating lobular carcinoma on the outcome of patients treated with breast-conserving surgery and radiation therapy. *Breast Cancer Res Treat* 2000; **59(1):** 49-54.

21. Silverstein MJ, Lewinsky BS, Waisman JR, Gierson ED, Colburn WJ, Senofsky GM, et al. Infiltrating lobular carcinoma: Is it different from infiltrating duct carcinoma? *Cancer* 1994; **73:** 1673-7.

22. Sasson AR, Fowble B, Hanlon AL, Torosian MH, Freedman G, Boraas M, et al. Lobular carcinoma in situ increases the risk of local recurrence in selected patients with stages I and II breast carcinoma treated with conservative surgery and radiation. *Cancer* 2001; **91(10):** 1862-9.

23. Fowble B, Gray R, Gilchrist K, Goodman RL, Taylor S, Tormey DC. Identification of a subgroup of patients with breast cancer and histologically positive axillary nodes receiving adjuvant chemotherapy who may benefit from postoperative radiotherapy. *J Clin Oncol* 1988; **6(7):** 1107-17.

24. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group 82c Trial. *Lancet* 1999; **353:** 1641-8.

25. Janni W, Dimpfl T, Braun S, Knobbe A, Peschers U, Rjosk D, et al. Radiotherapy of the chest wall following mastectomy for early-stage breast cancer: impact on local recurrence and overall survival. *Int J Radiat Oncol Biol Phys* 2000, **48 (4):** 967-75.

26. Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997; **337:** 956-62.

27. Van de Steene J, Soete G, Storme G. Adjuvant radiotherapy for breast cancer significantly improves overall survival: the missing link. *Radiother Oncol* 2000; **55:** 263-72.

28. Levitt SH, Aeppli DM, Nierengarten ME. The impact of radiation on early breast carcinoma survival. A Bayesian analysis. *Cancer* 1996; **78:** 1035-42.

29. Liljegren G, Lindgren A, Bergh J, Nordgren H, Tabar L, Holmberg L. Risk factors for local recurrence after conservative treatment in stage I breast cancer. Definition of a subgroup not requiring radiotherapy. *Ann Oncol* 1997; **8:** 235-41.

30. Vicini FA, Chen PY, Fraile M, Gustafson GS, Edmundson GK, Jaffray DA, et al. Low-Dose-Rate brachytherapy as the sole radiation modality in the management of patients with early-stage breast cancer treated with breast-conserving therapy: preliminary results of a pilot trial. *Int J Radiat Oncol Biol Phys* 1997; **38(2):** 301-10.

31. Polgar C, Major T, Somogyi A, Fodor J, Sulyok Z, Toth J, et al. [Brachytherapy of the tumor bed after breast conserving surgery: new radiotherapeutic option in the management of early breast cancer]. [Hungarian]. *Orv Hetil* 1999; **140(26):** 1461-6.

32. Polgar C, Major T, Somogyi A, Fodor J, Toth J, Sulyok Z, et al. Sole brachytherapy of the tumor bed after breast conserving surgery: a new radiotherapeutic strategy for patients at low risk of local relapse. *Neoplasma* 1999; **46(3):** 182-9.

33. Kuske R, Bolton J, Wilenzick R, McKinnon W, Pullen B, Scroggins T, et al. Brachytherapy as the sole method of breast irradiation in TIS, T1, T2, N0-1 breast cancer. [Abstract]. *Int J Radiat Oncol Biol Phys* 1994; **30(1):** 245.

34. Fentiman IS, Poole C, Tong D, Winter PJ, Mayles HM, Turner P, et al. Iridium implant treatment without external radiotherapy for operable breast cancer: a pilot study. *Eur J Cancer* 1991; **27(4):** 447-50.