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Randomized Studies of Breast-conserving Therapy

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INTRODUCTION

Progress in two areas of clinical research provided us with arguments to start a multi-center randomized trial 1982 in breast-conserving therapy in the Uppsala/Örebro health care region, Sweden. On one hand, the early outcomes of screening showed a marked shift towards detection of small tumours without nodal metastases (15). On the other, empirical evidence (6) and two randomized trials (4, 17) strongly supported the hypothesis that breast-conserving therapy - at least in breast cancer stage I - give the same survival rates as procedures implying a mastectomy.

THE CW-1 TRIAL

When the trial on breast-conserving therapy was planned, it was known that at least three other studies (8, 12, 16) was under way to produce more data on the comparability between mastectomy and different breast preserving techniques. The trial was therefore designed as an explanatory experiment to study if a standardized surgical sector resection (3) with meticoulus control of tumour radicality and axillary dissection can bring the local recurrence rate down to an acceptable level even without postoperarive radiotherapy (Fig. 1). Only women with tumours $\leq$ 20 mm without axillary metastases are eligible for the study. Local tumour radicality is controlled with peroperative radiography of the specimen and with histopathological examination of the margins. Statistical power calculations with 90% study power and 5% significance level (two-tailed test) resulted in a total sample size of 360 patients to be able to detect a local recurrence rate of 15% in the non-irradiated women, assuming that women the control group have a local recurrence rate of about 5% (1). In November 1987 altogether 307 women were randomized into the trial.

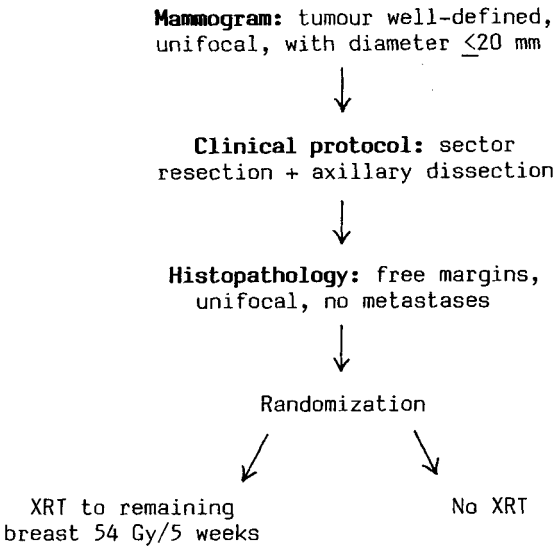

Figure 1. The CW-1 protocol for $T_{0-1a}{}^{pN}{}_0{}^{M}{}_0$ cancer. XRT=radiation therapy.

Evaluation of the cosmetic result

Evaluations of the cosmetic result and of the psycho-social adjustment after breast-conserving therapy were coupled to the CW-1 trial. The cosmetic result was assessed by a mailed questionnaire to 285 women treated with sector resection for benign and malignant breast disease (9). The investigation has two special features as compared to other studies in the literature: Firstly, the result was evaluated on the basis of the women's own opinion, which presumably is the important one if the cosmetic result has any importance for the quality of life. Secondly, women treated for lesions that mammographically strongly suggested a breast cancer, but postoperatively was proved to be benign histopathologically were included. We wanted to know if a sector resection gave cosmetic results that were acceptable also to women where the surgery was only diagnostic.

The overall result was favourable: 96.5% of the patients found the new appearance of the breast very good (30.7%), good (44.0%) or acceptable (21.8%). The rate of reported side effects was so low that the importance of single explanatory variables must be interpreted cautiously. The influence of variables such as demographic background data and variations in the treatment on the satisfaction with the cosmetic result was investigated with multivariate statistical analysis. The outcome for three of the main result variables are displayed as odds ratios in Table 1, where an odds ratio significantly

>1.0 for a certain background factor means a risk to have a more unfavourable result when the background factor was present. The main finding was that it is possible to perform a local radical operation that is highly acceptable to the woman from a cosmetic point of view.

Table 1. Odds ratios and 95% confidence intervals for having a less favourable cosmetic result (OR>1), when a certain background factor was present.

Result variable	Background factor	OR	C.I. 95%
What do you think of the appearance of the treated breast?	Gainfully employed	2.3	(1.4 - 3.7)
	Benign or ca in situ (vs malignant)	2.1	(1.3 - 3.4)
	Curvilinear incision (vs radial)	1.8	(1.1 - 3.2)
Has the changed appearance of the breast been a psychological strain for you?	Preop. anxiousness about the cosmetic result	3.3	(1.5 - 7.1)
	Tumour in medial part of the breast	2.2	(1.1 - 3.9)
Have your sexual relations changed since the operation?	Tumour in medial part of the breast	4.0	(1.5 - 10.6)

Psycho-social adjustment

The psycho-social adjustment was measured in an interview study designed to compare the outcome after breast-conserving treatment and after modified radical mastectomy (10). 99 women participated and the interviews were scheduled 4 and 13 months postoperatively. The interviews were semi-structured and based on the Social Adjustment Scale (SAS) and two additional scales on anxiety, depression and adjustment to a normal sexual relationship.

The SAS inventory revealed no statistically significant differences between the groups concerning adjustment to work, family and social life, sexual relationship, and parental role. The SAS interview also implies that the interviewer at the end of the meeting with the women rates for his/her opinion of the women's adjustment. In the interviewer's rating there was a trend for the conservatively treated women to do better, as is shown in Table 2. The same trend was discerned in the scales for anxiety, depression and adjustment to a normal sexual relationship. The differences were small, however, and the main conclusion is that larger studies with longer follow-up

are needed to reveal if there are any clinically important differences between the groups. These findings agrees with the similar studies published so far (5, 7, 11, 13, 14, 18), which have found a less damaged body image and better appraisal of the cosmetic result among women with a preserved breast, but not any striking differences in other aspects of psycho-social adjustment.

Table 2. Mean scores in the interviewer's rating in the SAS protocol of the psychosocial adjustment 13 months postoperatively for women treated with mastectomy or breast-conserving therapy. The scale ranges from 1 to 7, where 1 and 2 are normal or near normal, and 5 or more is a disturbance which the women is unable to manage on her own.

Adjustment to	Mastectomy		Breast-conserv.		
	n	*mean score* (SD)	*n*	*mean score* (SD)	t-test p value (two-tailed)
Work	59	1.73(0.57)	37	1.62(0.51)	0.32
Social and leisure activities	59	1.74(0.63)	37	1.67(0.50)	0.58
Marriage	43	1.40(0.65)	25	1.31(0.39)	0.49
Sexual relationship	43	2.34(1.65)	23	2.71(1.75)	0.41

Rationale for new studies

Several factors encouraged us to continue our investigations in breast conserving therapy: The publication of the NSABP protocol B-06 (8) strengthened our hypotheses in the CW-1 protocol. The NSABP study showed that mastectomy and conservative procedures combined with systemic adjuvant treatment when nodes were positive produced equal results concerning survival in tumours up to 4 cm in diameter with or without axillary involvment. The postoperative irradiation in breast-conserving therapy lowered the rate of local recurrences, but did not influence over all survival. The results of the NSABP study show that the local recurrecne rate after breast-conserving operation is high without radiotherapy - but a non-standardized surgical technique was used. It might be argued that the method required in the CW-1 protocol - using well-defined anatomical landmarks and meticolous control of the local radicality (3) - can prevent local recurrences more efficiently. Furthermore, the early results on cosmetic outcome from our study were encouraging and the findings in the study of psycho-social adjustment discussed above raised new interesting questions to be studied. Finally, the

randomization into the CW-1 study was steady over time (Fig. 2) and control of patient-log in the participating centers was good, 74% of all eligible patients were randomized up to October 1986 as is shown in Table 3. Thus, a new protocol have been introduced under 1987: the CW-2 protocol.

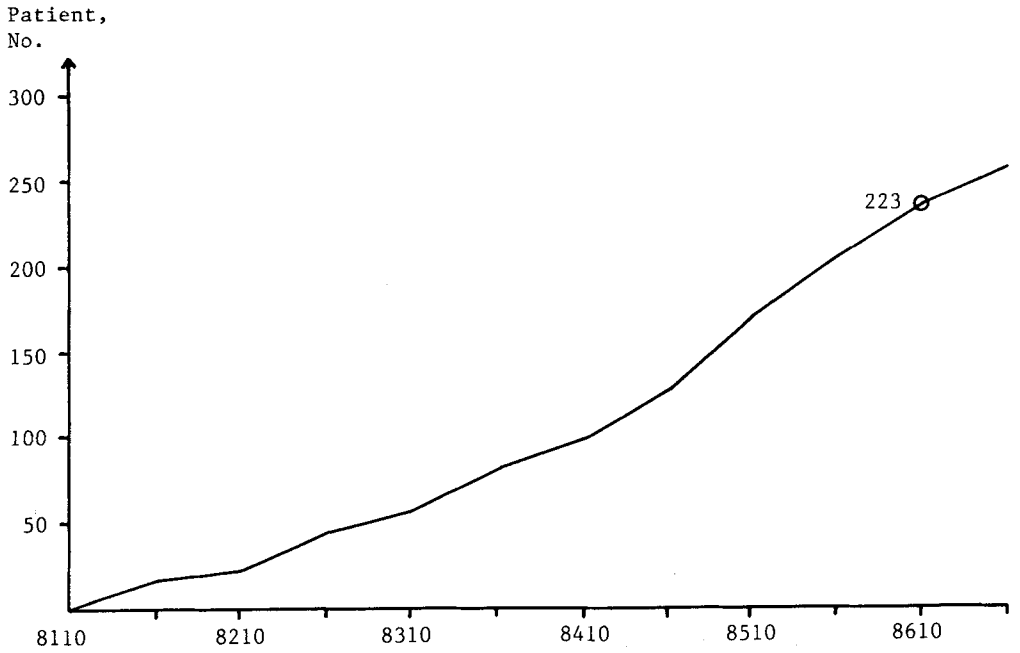

Figure 2. Randomization into the CW-1 trial.

Table 3. Inclusion of patients in breast cancer stage I into the CW-1 trial up to 1986-10-01.

Eligible, randomized	223
" not randomized	76
Not eligible	306
Total, pTNM, stage I	605

THE CW-2 PROTOCOL

The protocol (2) is parallel to the CW-1 study, with the only principal difference that women with breast cancers 21-30 mm in diameter are randomized into the trial. Still, only women with histopathologically negative nodes are

included. Power calculations were made on the same assumptions as for the CW-1 trial, but a one-tailed test of significance was now accepted, since data from the literature unequivocally points to the conclusion that post-operative radiotherapy cannot increase the rate of local recurrences during the first five years of follow-up. A total of 200 evaluable patients is needed.

The CW-1 and CW-2 protocols will in the future give us a range of data to evaluate many important aspects of breast-conserving therapy: We will be able to investigate the local recurrence rate in relation to surgical margins in the specimen, to histopathological characteristics of the primary tumour, and to the radiotherapy. It will help us to reveal the natural history of the multicentric lesions that inevitably will be left behind in the breast in a proportion of cases. Cosmetic and psycho-social viewpoints can be further studied. In the long run, late effects of the radiotherapy can be studied in the two protocols combined.

REFERENCES

1. Adami HO, Graffman S, Holmberg L. Bröstbevarande behandling av cancer mammae i stadium I (TO-1a, pNO, MO). En multicenterstudie. Regionalt onkologiskt centrum i Uppsala/Örebrogregionen. Uppsala 1983 (ISBN 91-506-0368-X).

2. Adami HO, Graffman S, Holmberg L. Bröstbevararande behandling av cancer mammae i stadium II (T2(21-30 mm), pNO, MO). En multicenterstudie. Regionalt onkologiskt centrum i Uppsala/Örebroregionen. Uppsala 1987 (ISBN 91-506-0639-5).

3. Aspegren K, Holmberg L, Adami HO. Standardization of the surgical technique in breast-conserving treatment of mammary cancer. Submitted.

4. Atkins H, Hayward JL, Klugman DJ, Wayte AB. Treatment of early breast cancer: A report after ten years of a clinical trial. Br Med J ii:423-9, 1972.

5. Beckmann J, Johansen L, Richardt C, Blichert-Toft M. Psychological reactions in younger women operated on for breast cancer. Dan Med Bull 30(Suppl):10-13, 1983

6. Bluming AZ, Dosik G, Lowitz B et al. Treatment of primary breast cancer without mastectomy. Ann Surg 204:136-47, 1986

7. Fallowfield LJ, Baum M, Maguire GP. Effects of breast conservation on psychological morbidity associated with diagnosis and treatment of early breast cancer. Br Med J 293:1331-34, 1986

8. 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 in the treatment of breast cancer. N Engl J Med 312: 665-73, 1985.

9. Holmberg L, Zarén E, Adami HO, Bergström R, Burns T. Patient's appraisal of the cosmetic result of segmental mastectomy in benign and malignant disease. Ann Surg, in press.

10. Holmberg L, Omne-Pontén M, Burns T, Adami HO, Bergström T. Psycho-social adjustment after mastectomy and breast-conserving treatment. Submitted.

11. Sanger CK, Reznikoff M. A comparison of the psychological effects of breast-saving procedures with the modified radical mastectomy. Cancer 48:2341-46, 1981.

12. Sarrazin D, Le M, Rouéssé J et al. Conservative treatment versus mastectomy in breast cancer tumours with macroscopic diameter of 20 millimeters or less. Cancer 53:1209-13, 1984.

13. Schain W, Edwards K, Gorrell CR, de Moss EV, Lippman ME, Gerber LH, Lichter AS. Psychosocial and physical outcomes of primary breast cancer therapy: mastectomy vs excisional biopsy and irradiation. Breast Cancer Research and Treatment 3:377-82, 1983.

14. Steinberg MD, Juliano MA, Wise L. Psychological outcome of lumpectomy versus mastectomy in the treatment of breast cancer. Am J Psychiatry 142(1):34-39, 1985.

15. Tabár L, Gad A, Åkerlund E, Holmberg L. Screening for breast cancer in Sweden. In: Feig SA, McLelland R, eds. Breast carcinoma: current diagnosis and treatment, pp. 315-26. Masson Publishing InC, USA, 1983.

16. van Dongen JA, Bartelink H, Aaronson N et al. Randomized clinical trial to assess the value of breast conserving therapy in stage I and II breast cancer (trial 10801). 4th EORTC breast cancer working conference, London, 1987. (Abstract).

17. Veronesi U, Saccozzi R, Del Vecchio M et al. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. N Engl J Med 305:6-11, 1981.

18. Weissmann MM, Sholomskas D, John K. The assessment of social adjustment. Arch Gen Psychiatry 38:1250-58, 1981.

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