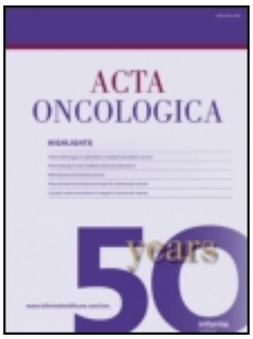

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POSTMASTECTOMY IRRADIATION IN HIGH-RISK BREAST CANCER PATIENTS

Present status of the Danish Breast Cancer Cooperative Group trials

M. OVERGAARD, J. JUUL CHRISTENSEN, H. JOHANSEN, A. NYBO-RASMUSSEN, H. BRINCKER, P. VAN DER KOOY, P. L. FREDERIKSEN, F. LAURSEN, J. PANDURO, N. E. SØRENSEN, C. C. GADEBERG, M. HJELM-HANSEN, J. OVERGAARD, K. WEST ANDERSEN and K. ZEDELER

Abstract

All pre- and postmenopausal high-risk breast cancer patients in the protocols DBCG 77 of the Danish Breast Cancer Cooperative Group received postmastectomy irradiation before randomization to either adjuvant systemic therapy or no such treatment. The actuarial loco-regional recurrence rate at 9 years was 6–17%, with the lowest rate in patients who also received additional adjuvant chemotherapy or tamoxifen. In a subsequent study (DBCG 82) the role of postmastectomy irradiation together with systemic treatment was evaluated in high-risk patients. Pre- and menopausal patients were randomized to postmastectomy irradiation+CMF (cyclophosphamide, methotrexate, 5-fluorouracil), CMF alone or CMF+TAM (tamoxifen). Postmenopausal patients were randomized to postmastectomy irradiation+TAM, TAM or CMF+TAM. At 4 years the loco-regional recurrence rate was significantly lower in the irradiated patients (5–7% vs. 23–33%). Further, disease-free survival was significantly improved in both pre- and postmenopausal irradiated patients compared with those who had only systemic treatment. At present, there are no significant differences between survival in the treatment groups. Thus, adjuvant systemic treatment alone (chemotherapy and/or tamoxifen) did not prevent loco-regional recurrences in high-risk patients after mastectomy and axillary lymph node sampling. However, a longer observation time is necessary to evaluate the consequence of primary optimal loco-regional tumour control in high-risk breast cancer patients with respect to survival.

Key words: Breast cancer, postmastectomy irradiation, loco-regional recurrence, adjuvant treatment.

The treatment of operable breast cancer comprises 2 major components—management of local and regional disease and eradication of occult systemic metastases.

During the past century surgery has varied from extensive radical mastectomy to simple mastectomy. In the same period of time postmastectomy radiotherapy has been evaluated in several randomized studies. In principle, these studies can be divided into 2 main groups on the basis of the extent of the surgical procedure. In the first group adjuvant radiotherapy was evaluated in patients treated with radical mastectomy including axillary node dissection (4, 9, 12, 16–18, 25, 26, 29). The results from these studies have shown a reduction in loco-regional recurrences in patients treated with postoperative irradiation, but no improvement of long-term survival, except in 2 more recent studies in which irradiation was more optimal concerning target volume and total dose (17, 28, 29). However, in an overview of mature randomized trials concerning postoperative adjuvant radiotherapy (6) an excess of deaths was observed among patients given radio-

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therapy, after 10 years of observation. In the other main group of studies radical mastectomy without radiotherapy was compared with simple mastectomy and postoperative radiotherapy (4, 5, 7, 11, 13, 19, 20, 22). In general, the results from these trials showed equal loco-regional tumour control as well as long-term survival in both treatment groups leading to the conclusion in many centres that less mutilating surgery followed by radiotherapy was the treatment of choice and further, these results were the foundation for even more conservative surgical procedures, namely quadrantectomy or tumourectomy, combined with subsequent radiotherapy (15, 21, 27, 28).

With the use of adjuvant systemic therapy during the past 20 years, a re-assessment of the role of radiotherapy of loco-regional disease may be necessary. Firstly, node sampling from the axilla was introduced for staging prior to further therapy and, secondly, the efficacy of systemic therapy with respect to loco-regional tumour control after non-radical mastectomy (i.e. axillary sampling instead of axillary dissection) has not been sufficiently evaluated (1, 14). The aim of the present analysis was to evaluate the status of radiotherapy after non-radical mastectomy in high-risk patients in 2 consecutive randomized trials.

In the first trial (DBCG 77) all high-risk patients received postmastectomy irradiation as a standard component of the loco-regional treatment. The aim of this trial was to evaluate the effect of adjuvant systemic therapy in pre- and postmenopausal women on disease-free and overall survival. The second trial (DBCG 82) was designed to evaluate the efficacy of postmastectomy radiotherapy combined with adjuvant systemic therapy against adjuvant systemic therapy alone with respect to loco-regional tumour control, disease-free survival, survival, and toxicity.

Material and Methods

Patients. In the consecutive studies, DBCG 77 b+c and DBCG 82 b+c, all pre- and postmenopausal high-risk breast cancer patients were included. The definitions of high-risk status and menopausal status are given elsewhere (2, 8, 23).

In DBCG 77 there was no upper age limit, but in DBCG 82 only patients less than 70 years of age were eligible. For illustration of the baseline surgical efficacy the low-risk DBCG 77 and 82 patients were included as well. In both studies the criteria for entry were as follows: no evidence of advanced disease as estimated by physical examination, biochemical tests, chest radiography, bone scintigraphy or radiography and no previous or concomitant other malignant disease. Orally informed consent was mandatory (2).

Protocol design. Protocol DBCG 77 b+c recruited patients from August 1977 to November 1982. After mastectomy premenopausal and menopausal high-risk patients (77 b) were randomized to postoperative radiotherapy (RT) alone, or to RT plus 3 different regimens of adjuvant systemic therapy for 12 months (2, 8, 23). Similarly, postmenopausal women (77 c) were randomized to RT alone versus RT plus 2 different regimens of systemic therapy for 12 months (2, 8, 23).

Protocol DBCG 82 (b and c) recruited patients from November 1982 and is still open for patient entry. After mastectomy pre- and menopausal women (82 b) were randomized to RT+CMF (cyclophosphamide, methotrexate, 5-fluorouracil) versus CMF alone versus CMF+TAM (tamoxifen) for 9 months (8). Similarly postmenopausal women (82 c) were randomized to RT plus TAM versus TAM alone or CMF+TAM (23). CMF was given for 9 months and TAM for 12 months.

Surgery. The primary surgical treatment was total mastectomy and axillary sampling (2). A mean of 5.4 and 6.3 lymph nodes were available for examination in DBCG 77 and in DBCG 82 respectively. These numbers were significantly different ($p<0.001$). The mean values variated from 1.9–8.9 among the different surgical departments. The aim of the surgery was to make a macro-radical removal of the primary tumour and grossly involved axillary lymph nodes and at the same time obtain a pathological staging.

Radiotherapy. The aim of the radiation therapy was to deliver a tumour dose sufficient for eradication of subclinical disease in peripheral lymph nodes and chestwall, including the surgical scar.

In the DBCG 77 protocol the intended total dose corresponded to 1345 ret (NSD) calculated as minimum target dose with reference points at the midplane of the axilla and at the pleural surface below the anterior chestwall. Two different fractionation schedules were used, namely a minimum dose of 36.60 Gy in 12 fractions with 2 fractions per week or a minimum dose of 40.92 in 22 fractions with 5 fractions per week. The 2 schedules were equated by the Ellis' Nominal Standard Dose formalism as described in detail elsewhere (24). The maximum doses in both schedules reached levels 30–40% higher than the minimum doses due to different anterior-posterior diameters in the patients. The treatment technique also varied in the different centres. Four larger centres used an anterior photon field against supraclavicular/infraclavicular and axillary regions combined with anterior electron field against the chestwall, while one centre used tangential photon fields against the chestwall. In 8 small centres the patients were treated with 250 kV x-rays using the McWhirther technique. Here the minimum intended dose was 36.00 Gy/20 fractions in 4 weeks.

Due to an unacceptable complication rate in patients treated with 2 fractions per week in the previous DBCG 77 study it was decided to give 4 or 5 fractions per week instead in the DBCG 82 study. Further a major revision of the postmastectomy guidelines was made to optimize and standardize the treatment in all centres. On the basis of CT-scans in patients lying in treatment position a thor-

Table 1

Incidence of local control as a function of protocol and treatment

Protocol	No. patients	No. of local recurrences			Actuarial local control rate %*
		Alone	With DM	All	
DBCG 77a					
Premeno.	1 158	200	14	214	79
Postmeno.	1 968	277	33	310	80
Total	3 126	477	47	524	79
DBCG 77b					
RT	187	8	8	16	88
RT+Leva.	112	5	7	12	86
RT+C	424	20	2	22	94
RT+CMF	423	16	4	20	92
DBCG 77c					
RT	848	56	36	92	83
RT+Leva.	221	17	6	23	85
RT+TAM	868	47	24	71	88
DBCG 82a					
Premeno	1 171	105	11	116	86
Postmeno	1 348	93	5	98	87
Total	2 519	198	16	214	86
DBCG 82b					
RT+CMF	497	8	8	16	93
CMF	492	49	12	61	76
CMF+TAM	319	57	16	73	67
DBCG 82c					
RT+TAM	457	10	5	15	95
TAM	458	59	10	69	70
TAM+CMF	432	49	12	61	77

DM=Distant metastases, RT=Radiotherapy, Leva=Levamisole, C=Cyclophosphamide, CMF=Cyclophosphamide, metotrexate, 5-fluorouracil, TAM=Tamoxifen.
* DBCG 77: 9 years' observation; DBCG 82: 4 years' observation.

ough definition of standard target volume was worked out. Besides the supraclavicular/infraclavicular and axillary nodes the target volume now also included the internal mammary nodes. From the CT-information it was possible to give guidelines for field arrangements which could be placed individually for each patient using a simulator. In addition, simple measurements, such as anterior-posterior diameter and chestwall thickness measured by ultrasound, made it possible to make individual dose calculations. The intended dose in DBCG 82 was either a median absorbed dose in the target volume ($D_{T\text{-median}}$)= 50.00 Gy in 25 fractions in 5 weeks, or $D_{T\text{-median}}$=48.00 Gy in 22 fractions in 5 1/2 weeks, according to ICRU-29. In principle the field arrangement was similar to that used in DBCG 77, where most patients were treated with anterior photon and electron fields. However, 10–15° angling of the photon field was now advised, both to avoid the spinal cord and to optimize the junction of the photon and electron fields. Posterior axillary fields were advised in patients with large anterior-posterior diameter to reduce the maximum absorbed target dose to 55.00 Gy/25 fractions or 52.80 Gy/22 fractions.

Adjuvant systemic treatment. In DBCG 77 the systemic treatment as well as the irradiation was started 2–4 weeks after mastectomy and these treatments were given simultaneously (8, 23), which meant that patients who were treated with chemotherapy received 2 cycles of C (cyclophosphamide) or CMF during the radiotherapy course. In case of major skin reactions the patients either had a break in the radiation or the chemotherapy was postponed. The systemic therapy lasted for one year.

In DBCG 82, CMF and radiotherapy were given sequentially (8, 23), with an interval of a few days from the first cycle of CMF and the start of RT and an interval of 1–2 weeks after the completion of RT. Thus, patients who were randomized to RT+CMF received only a total of 8 CMF cycles, whereas patients randomized to CMF or CMF+TAM were given a total of 9 CMF cycles.

Follow-up. The patients were followed at regular intervals up to 10 years as previously described (2). In DBCG

Table 2

Localization of local recurrence as a function of protocol and treatment

Protocol	Localization of local recurrence							Total
	Chest-wall	Axilla	Sup./inf. clav.	Axil.+ chestw.	Axil.+ sup./inf.	Chestw.+ sup./inf.	Axil.+ chestw.+ sup./inf.	
DBCG 77a								
Premeno.	123	72	11	7	1	0	0	214
Postmeno.	198	86	9	13	4	0	0	310
Total	321	158	20	20	5	0	0	524
DBCG 77b								
RT	8	6	1	1	0	0	0	16
RT+Leva.	7	2	2	1	0	0	0	12
RT+C	11	7	3	0	1	0	0	22
RT+CMF	11	8	1	0	0	0	0	20
DBCG 77c								
RT	48	28	7	5	2	2	0	92
RT+Leva.	8	12	2	1	0	0	0	23
RT+TAM	39	19	8	4	1	0	0	71
DBCG 82a								
Premeno.	64	39	6	5	1	1	0	116
Postmeno.	63	24	7	4	0	0	0	98
Total	127	63	13	9	1	1	0	214
DBCG 82b								
RT+CMF	8	3	1	2	1	1	0	16
CMF	28	23	5	3	1	1	0	61
CMF+TAM	25	28	13	3	2	1	1	73
DBCG 82c								
RT+TAM	6	5	3	1	0	0	0	15
TAM	35	28	2	1	1	1	0	69
TAM+CMF	30	17	8	4	1	1	0	61

Abbreviations as for Table 1.

82, however, repeated blood tests and bone surveys were not required. In addition to the recording of recurrences and survival data an attempt was made in DBCG 82 to record treatment complications, such as arm oedema and impaired shoulder movement in all patients irrespective of radiotherapy and systemic adjuvant treatment. Due to a revision of this registration in October 1986, these data are at present incomplete.

Statistical methods. All diagnostic, therapeutic and follow-up data were validated and processed by the DBCG data centre. In DBCG 77b and c the levamisole treatment was terminated in December 1979 due to toxicity and an increased relapse rate (10). Further in DBCG 77b the control arm with postoperative radiotherapy alone was closed in January 1981. DBCG 82b and c are still open for patient entry except for the CMF+TAM group in pre- and menopausal patients. This treatment was stopped in June 1986 due to a significantly higher mortality in this group compared to that of the other treatment groups.

The frequency of loco-regional recurrences with and without distant metastases were evaluated by the life-table method and compared using the log-rank test. Similarly, disease-free survival and survival were evaluated and compared. The p-values given are those for a 2-tailed test. A Cox's regression analysis was performed in the DBCG 82 data to find subgroups especially at risk for loco-regional recurrences.

Results

The definition of the endpoint loco-regional recurrence was first site of recurrence either alone or together with distant metastases. Loco-regional recurrences occurring after first relapse are not included, thus the data in Table 1 and 2 represent minimum values. The loco-regional region includes the homolateral supra- and infraclavicular region, the axilla and the chestwall.

Protocol 77b and 77c. A total of 3083 patients entered the trial, and the number of patients in each treatment group are given in Table 1. A minor proportion, i.e. 15% of all patients, were treated with orthovoltage radiation. Fig. 1 shows the loco-regional tumour control in all high-

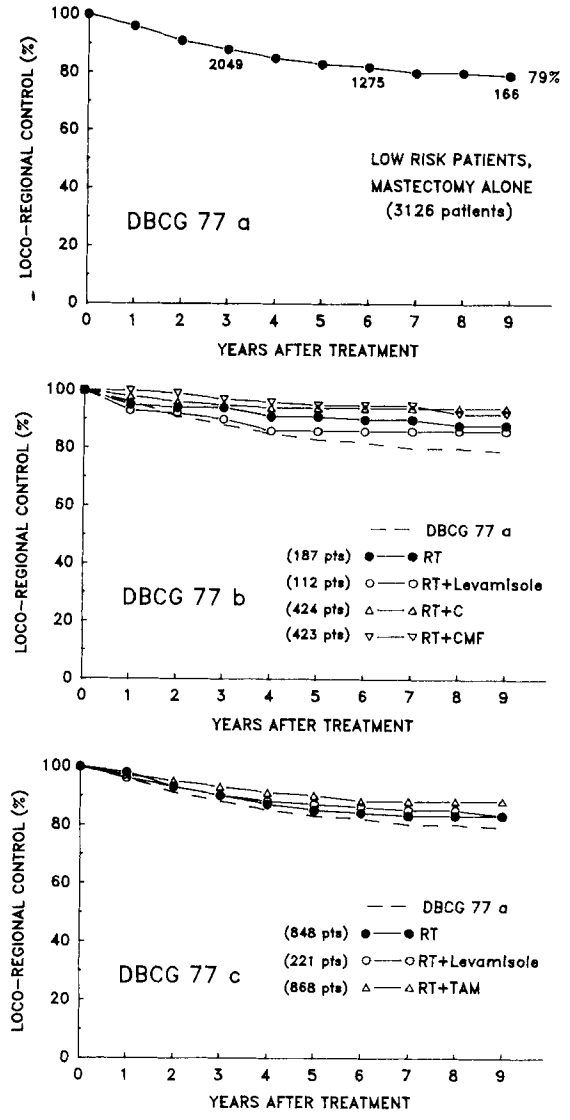

Fig. 1. Loco-regional control in DBCG 77 protocols. The dashed line in the 2 lower panels indicates the loco-regional control probability of low-risk patients (DBCG 77a, upper panel).

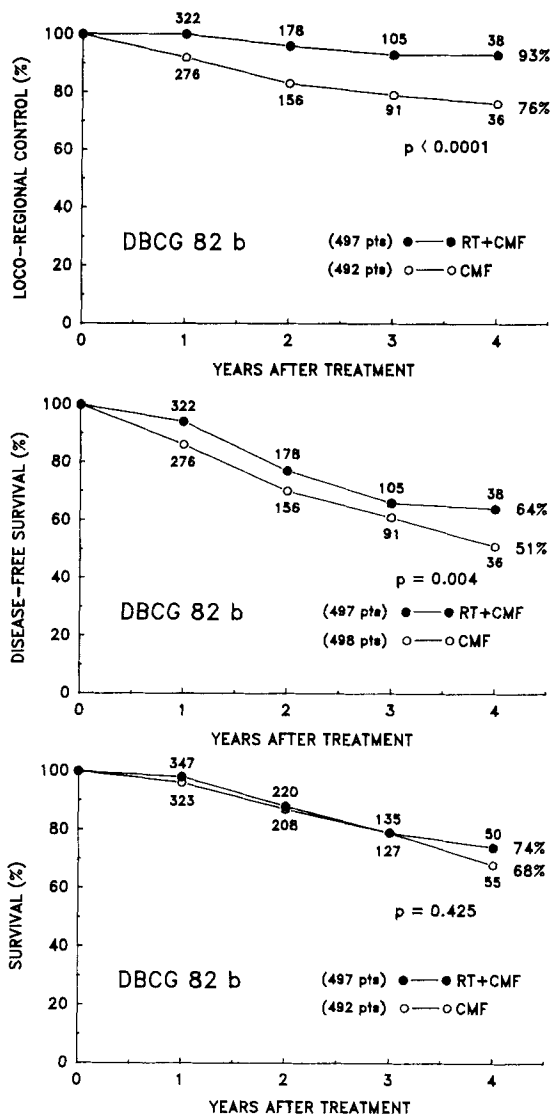

Fig. 2. Loco-regional control (upper panel), disease-free survival (middle panel) and survival (lower panel) in high-risk, pre- and menopausal patients (DBCG 82b) given adjuvant treatment with RT+CMF or CMF alone.

risk pre- and postmenopausal patients. For comparison the loco-regional tumour control in all low-risk DBCG 77 patients (77a) has been shown as well. It should be noted that the low-risk patients had surgery only as the primary treatment. The loco-regional control rate in 77b and c group ranged between 83–94% which was even better than the 79% observed in the low-risk patients. Loco-regional tumour control was highest (but not significantly so) in patients who also received adjuvant chemotherapy or tamoxifen compared with those who had only postoperative radiotherapy. Disease-free survival and survival in DBCG 77b and 77c are analysed specifically with respect to efficacy of adjuvant systemic treatment elsewhere in this issue (8, 23).

Protocol 82b and 82c. At present a total of 2655 patients have entered this trial, as given in Table 1. The total number of patients receiving orthovoltage treatment has been reduced to 8% of irradiated patients.

The loco-regional tumour control in DBCG 82b is analysed in Table 1 and Fig. 2. A statistically significant improvement in loco-regional tumour control was found in irradiated patients (93% actuarial rate) compared to high-risk patients who were only given systemic adjuvant therapy (76% and 67% in the CMF and CMF+TAM groups respectively, $p<0.0001$). Among patients with loco-regional recurrences 49% had recurrences in the chestwall, 17% in the supraclavicular/infraclavicular region and 45% in the axilla (Table 2).

From the data in Table 1 it was estimated that 79% of loco-regional recurrences occurred as the only first relapse in non-irradiated patients, whereas 50% of patients in the irradiated group with loco-regional failure had also concomitant distant metastases ($p<0.05$). The disease-free survival is seen in Fig. 2. This shows a significant difference in favour of the group which received both radiotherapy and CMF (64%) compared to CMF alone (51%, $p=0.004$). However, this difference has not been found to influence survival (74% versus 68%, $p=0.425$) (Fig. 2). A multivariate analysis suggested that irradiated patients younger than 45 years of age and with 4 or more positive nodes in the axilla had an improved disease-free survival compared to the non-irradiated group (data not shown).

In the postmenopausal group, DBCG 82c, a similar improvement in loco-regional tumour control was observed in all irradiated patients (95% vs 70% and 77%, $p=0.0001$) (Table 1, Fig. 3). In the non-irradiated group 83% of the loco-regional recurrences occurred as first relapse without concomitant distant metastases, whereas this was only 67% in patients given radiotherapy (not significant) (Table 1). The reduced loco-regional failure rate resulted in a significant difference in disease-free survival between the RT+TAM group and TAM alone group (60% and 49% respectively, $p=0.047$) (Fig. 3). Nevertheless, survival is not different at present (Fig. 3). The site of loco-regional recurrences in the postmenopausal patients reveals a similar pattern as in the former group with 54% in the chestwall, 12% in the supra-infraclavicular region and 40% in the axilla.

Complications. The acute and late complications due to postmastectomy irradiation with and without systemic treatment were not evaluated prospectively in DBCG 77. The acute complications, especially in patients who also received adjuvant chemotherapy, were acceptable and caused only occasionally modification of the treatments. However, a higher incidence of late complications, such as skin fibrosis, telangiectasia, lung fibrosis, arm oedema and impairment of shoulder movement were noted in departments using the 2-fraction-per-week schedule. A detailed analysis of this fractionation effect has been described previously (24) and formed the basis of the subsequent trial with respect to optimization of field technique, fractionation and proposal of prospective follow-up of acute and late complications in irradiated normal tissues. As mentioned before, the prospective registration of complications in DBCG 82 cannot be evaluated at present, but the overall conclusion is a reduction of complications after the change of fractionation schedule from 2 fractions per week to 4 or 5 fractions per week (24).

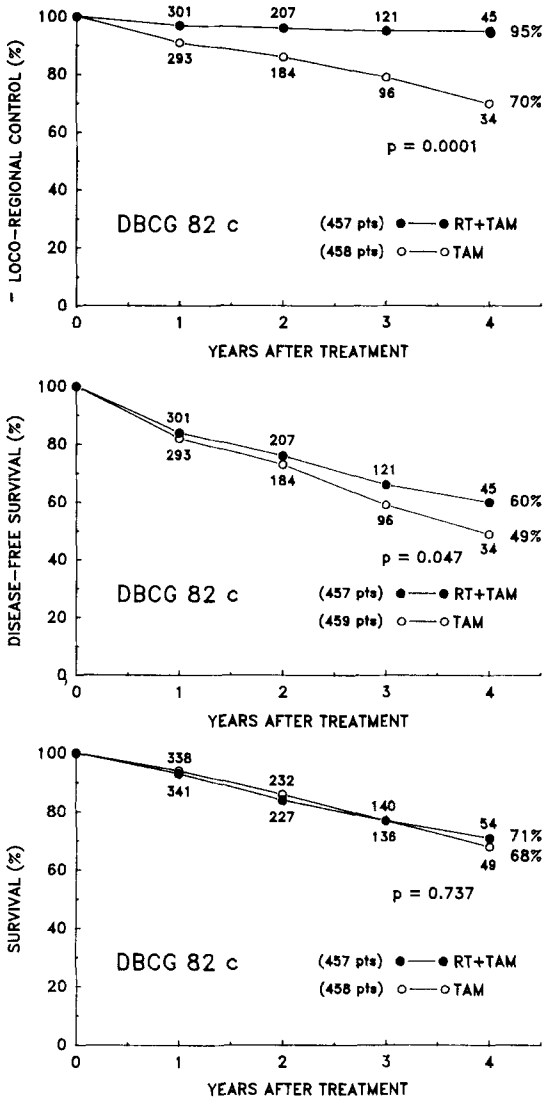

Fig. 3. Loco-regional control (upper panel), disease-free survival (middle panel) and survival (lower panel) in high-risk, postmenopausal patients (DBCG 82c) given adjuvant treatment with RT+TAM or TAM alone.

Discussion

The maximum and minimum doses administered in DBCG 82 patients are within the same range as the doses in the 5-fraction-per-week schedule in DBCG 77. Therefore, a similar complication rate would be expected unless other factors in the total treatment, such as changes in the surgical procedure and the timing of chemotherapy, have interfered. Registration of the long-term complications in DBCG 82a, b, and c is still in progress in 3 of the largest centres and has to be completed before further analysis.

With respect to tumour control no difference could be found according to the fractionation schedule used (24). Neither the use of orthovoltage radiation treatment showed any statistical difference in loco-regional tumour control compared to the results in patients treated by megavoltage radiation.

In DBCG 77 all the high-risk breast cancer patients received postmastectomy irradiation routinely before ran-

domization to adjuvant systemic treatment or no such therapy. This resulted in a satisfactory loco-regional tumour control in all high-risk patients, especially in those who also received adjuvant chemotherapy or tamoxifen. The relatively poor loco-regional control in low-risk patients treated with surgery alone (DBCG 77a) indicates the limitation of the mastectomy procedure with respect to tumour control both in the chestwall and in the axilla. This suggests that further loco-regional treatment in low-risk patients may be considered.

Bearing in mind that the same surgery has been used in all high-risk patients it is not surprising that the subsequent DBCG 82 study showed a significant reduction in loco-regional recurrences and thereby improvement of disease-free survival in all irradiated patients compared to those who received chemotherapy and/or tamoxifen only. The efficacy of radiation after non-radical mastectomy is in agreement with several other studies (4, 5, 7, 11, 13, 19, 20, 22). Whether this has any impact on survival cannot yet be evaluated in this preliminary analysis due to a median observation time of only 2 years.

How to obtain optimal loco-regional tumour control in patients who are also treated with adjuvant chemotherapy or hormonal therapy has only been studied in a few recent trials (1, 14). The basic surgical procedures and the design of these trials are not immediately comparable. However, the main conclusion in these studies as well as in the present study is that systemic adjuvant therapy after non-radical mastectomy does not prevent loco-regional recurrences. Unfortunately, in these trials the observation time is too short to allow an evaluation of any long-term benefit on survival. There is, however, some data which indicate that insufficient loco-regional tumour control may have had an influence on survival (3, 11, 15). Thus, one of the early randomized trials comparing tumourectomy and mastectomy from Guy's Hospital, described by Atkins et al. (3) revealed a significant reduction in overall survival in stage II patients treated insufficiently to the axilla by low-dose radiotherapy, compared to stage II patients who had radical node dissection in the axilla. A more recent trial, the NSABP (11), showed a similar statistically significant increase in distant recurrences in patients who were not optimally treated at the loco-regional site. Furthermore, there is an indication that patients with inner quadrant breast tumours show significant improvement in survival by additional treatment of internal mammary nodes either by surgery or radiotherapy (28). Thus, some evidence points at the fact that loco-regional tumour control is of importance in the treatment of breast cancer with respect to disease-free survival and possibly also to survival for subgroups.

However, the temporary and persistent toxicity following each treatment modality (local or systemic) and the possible interaction by combining 2 or 3 modalities have to be weighed against the outcome of obtaining an optimum quality of life. A further search to identify favourable prognostic subgroups is important to avoid unnecessary adjuvant systemic or local treatments.

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