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Local Control of Operable Breast Cancer after Radiotherapy Alone

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221 patients with operable breast carcinoma stage Tis, T1, T2, T3, N0N1 were treated with radiotherapy alone without tumorectomy. The mean follow-up time was 15.5 years (range 5–22). The annual risk for local recurrence was 3% during the first 5 years and 1% during the following 10 years, resulting in an actuarial local control rate of 75.4% after 15 years. The risk for local recurrence was assessed in multivariate analysis and was significantly related to the size of the tumour measured on mammography ($P = 0.0002$), the radiation dose administered ($P = 0.0018$), the length of the split-course intervals being longer than 75 days ($P = 0.001$) and age ($P = 0.019$). Dose was related to response over a wide range as a function of tumour volume. All 18 patients with minimal tumour load (T0 and Paget's disease) treated with doses above 55 Gy in 6 weeks achieved local control. 5-year local control rates ranged from 40 to 100% for T1 carcinomas treated with 45–110 Gy, and from 0 to 95.3% for T2 carcinomas at the same dose. For T3 carcinomas local control varied between 50 and 83% at 60–110 Gy. The risk for local failure increased by 8% per cm tumour diameter. With exclusive radiotherapy, the doses needed to provide local control rates similar to those obtained after tumorectomy and irradiation are 10 Gy higher for T1 (95% 5 year control) and 35 Gy higher for T2 (90% 5 year control).
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INTRODUCTION

BREAST-CONSERVING surgery with radiotherapy has become a valid alternative to mastectomy in the treatment of operable stage I and II breast cancer [1–3]. Experience in operable breast cancer (UICC stages I, II, IIIA) treated with radiotherapy alone without tumorectomy is less extensive. In the early days of breast-conserving treatment radiotherapy alone was offered as an alternative to patients refusing mastectomy [4–6]. These studies were extended into the megavoltage range, when mainly French institutions treated these patients with radiotherapy alone [7–9]. High radiation doses are required for control of breast cancer with radiotherapy alone [9–11]. These high doses result in excessive fibrosis of normal tissues [12, 13]. Therefore most centres now favour the combined treatment with surgery and radiotherapy for small breast tumors.

Several groups [9, 11, 14] have shown that the possibility of breast cancer control with radiotherapy alone is related to tumour size and radiation dose. However, follow-up has been limited [9] or the dose range has been small. And the large study of Arriagada *et al.* [11] mainly concerned patients with locally advanced rather than operable disease. We have updated the Leuven experience with more information on tumour size and dose response in patients with operable stage I, II and IIIA breast cancer treated with radiotherapy alone. The follow-up of the patients previously reported [9] is now longer than 15 years, while additional patients treated up to 1984 have been included.

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PATIENTS AND METHODS

Patients

221 patients treated between 1967 and 1984 at the University Hospital of Leuven with radiotherapy alone for Tis, T1, T2, T3, N0N1 breast cancer have been analysed. Mean follow-up is 15.5 years (range 5–22). Most were treated before 1977 (94%). Age ranges between 28 and 86 years (mean 59.4). All patients had undergone a Vim Silvermann needle biopsy and fine-needle aspiration cytology. The biopsy specimens and cytological slides were reviewed by J.V.W. The diagnosis of breast cancer was confirmed on biopsy in 195 cases and by cytology in 24 patients. In 2 patients both biopsy and cytological examination showed no breast cancer cells, but the clinical presentation, mammography and clinical course with metastases have confirmed the malignant character of the breast tumour. Biopsy samples were classified and graded according to the WHO classification (Table 1). All patients were reclassified according to 1987 UICC Tumour/Node/Metastases staging (Table 2). Tumour size was measured in 185 available mammograms.

Radiation schedules

1967–1984 included the period of early experiences with breast-conserving therapy in Leuven. In the first patients treated, low radiation doses were used (below 50 Gy). Gradually, higher doses were administered, up to 96 Gy in 1976. Later,

Table 1. Operable breast cancer treated with radiotherapy alone (WHO classification)

	Invasive	Non-invasive
Morbus Paget	0	14
Ductular	182	1
GI	32	
GII	70	
GIII	42	
Not graded	38	
Lobular	17	
Medullary	2	
Colloid	1	
Malignant nipple fluid		2
No histological confirmation*	2	
Total	204	17

*Clinical and radiological diagnosis of malignant invasive breast tumour, confirmed by metastatic course.

doses were lowered to 65 Gy. The doses have been recalculated for all patients and specified at midline depth on the central axis of the beam, as is recommended by the ICRU (International Commission on Radiation Units and Measurements) (Table 3). 185 patients received 2 × 6 Gy (n = 182) or 2 × 4 Gy (n = 3) with 13–15 MeV of a Brown Bovery Betatron on limited fields, as a 'prebioptic flash' before biopsy. Total doses to the whole breast range between 36 and 85 Gy. Most patients have received either about 40 Gy in 4 weeks (n = 33), 60–65 Gy in 8–10 weeks (n = 164), with fraction sizes ranging between 200 and 225 cGy per day. 15 patients have received higher total doses to the breast (up to 85 Gy). After the breast irradiation, booster doses on limited fields were administered to the primary tumour area in 146 patients, usually with 15 MeV electrons. In 124 cases booster doses of 10 × 2 Gy were administered. 22 patients were boosted after the breast irradiation with doses of 3 × 3, 5 × 2, 7 × 3 or 10 × 2 Gy. Because of the variation in fraction size, total doses were recalculated for analysis to biological equivalent doses of 2 Gy per fraction, assuming an α/β ratio of 10 Gy. Treatment-free intervals during irradiation occurred in most schedules, except in the low-dose schedules (below 45 Gy in 5 weeks). In patients treated with a prebioptic flash (2 × 6 Gy), 2–7 days usually passed between this flash and the start of radiation to the breast. In most patients an interval of 2–4 weeks was planned after 45–50 Gy. Another rest period of 2 days to 2 weeks occurred before the boost irradiation. In some of the patients, however, treatment-free intervals were longer because of patients' illness, temporary overload of the radiotherapy department, or due to an administrative mistake in the appointments of 1 patient. Total split-times were calculated for each patient by summing all the treatment interruption days.

Table 2. Operable breast cancer treated with radiotherapy alone (UICC staging)

	N0	N1	Total
Tis	17*	0	17
T0	1	1	2†
T1	28	2	30
T2	91	33	124
T3	27	21	48
Total	164	57	221

*2 patients had malignant nipple fluid, 1 ductular carcinoma *in situ* and 14 Paget's disease.
†2 patients had biopsy-proven invasive ductular carcinoma.

Table 3. Fractionation schedules for Tis–T3 breast cancer cases

Prebioptic flash	No. of fractions	Fraction size (cGy)	Total dose (Gy)	No.
0	14–21	210–400	35.6–46.8	4
0	21–25	200–255	52 –57.8	3
2 × 600	19–23	200–210	50.1–58.2	14
0	27–33	200–255	60–69.9	11
2 × 400	27	200–210	62	1
2 × 600	23–27	200–300	63–66	3
2 × 400	23	205–410	73.2	1
0	32–33	224–233	73.9–78.5	4
2 × 600	29–30	200–210	72–75	43
0	39–40	210–250	80.9–86.1	7
2 × 400	34	220–233	84.2	1
2 × 600	32–36	200–300	80.1–89.1	8
0	42–44	200–200	90.5–96.7	5
2 × 600	37–42	200–220	91.1–100.4	64
0	48	200–220	103.1	1
2 × 600	38–47	200–280	100.2–109.2	47
2 × 600	45–47	200–280	112.5–113.5	3

No patient received adjuvant hormonal therapy or chemotherapy.

Analysis

Survival and local control rates have been calculated according to the actuarial life-table method. Significance of differences between subsets of patients was assessed by the log-rank test. Prognostic factors for local control were analysed with a stepwise, proportional hazards, general linear model.

RESULTS

Survival

Overall survival was 67.7% at 5 years, 39.7% at 10 years, 19.5% at 15 years and 6% at 20 years. Disease-free survival was 60.6%, 46.8% and 38% at 5, 10 and 15 years, respectively.

Local recurrences

Local recurrences in the breast and/or on the thoracic wall (within the radiation field) occurred in 38 patients (17.2%). 22 recurrences were at the original tumour site, while in 2 patients the recurrence was located in another quadrant of the breast. The tumour recurred diffusely in the breast with involvement of the skin in 6 patients. In 7 patients the recurrence involved not only the treated breast but also the skin of the thoracic wall. In 1 patient, treated elsewhere for a breast recurrence, the exact location of the recurrent tumour cannot be specified.

The actuarial local recurrence rate at 5, 10 and 15 years was 17%, 19.1% and 24.6%, respectively. The annual risk for recurrence was 3.3% per year during the first 5 years, declining to 1% per year between the 5th and 14th year. After 14 years

Table 4. Actuarial local control rates in patients with operable breast cancer treated with radiotherapy alone

	No.	5 yr (%)	10 yr (%)	15 yr (%)	P*
All	221	83.1	80.1	75.4	—
Premenopausal	67	81.7	81.7	81.7	
Post-menopausal	152	83.1	79.1	72.8	0.07
Age (yr)					
<40	19	65.8	65.8	65.8	0.06
>40	202	84.7	81.6	76.4	
Non-invasive Tis	17	94	94	94	NS
Invasive cancer	204	82.1	79.1	74.2	
Lobular cancer	17	100	86.7	86.7	0.076
Ductular cancer	183	80.4	78.4	72.9	
Differentiation IDA					
GI + GII	102	87.35	85.6	77.8	0.038
GIII	42	70.15	65.1	65.1	
T1	30	86.3	86.4	86.4	
T2	124	85.4	80.5	74.1	0.0357
T3	48	70.1	70.1	60.2	
N0	164	86.6	85.3	79.1	0.005
N1	57	72.5	64.6	64.0	

*Univariate analysis. NS = not significant.

there were no more local recurrences in the survivors (21 patients at risk) up to 20 years after treatment.

Various factors, such as age, menopausal status, histological subtypes, degree of differentiation, tumour size and nodal status as well as radiation dose and total split-time were tested for their impact on local control in univariate (Table 4) and multivariate analyses. In the multivariate analysis, the total dose to the tumour ($P = 0.0018$), treatment-free interval longer than 75 days ($P = 0.001$), tumour size ($P = 0.0002$) and age ($P = 0.0134$) were independent significant prognostic factors for local control.

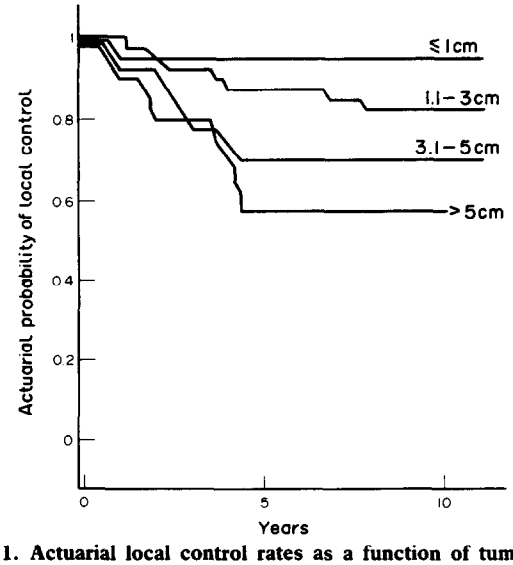

Fig. 1. Actuarial local control rates as a function of tumour size measured on mammography.

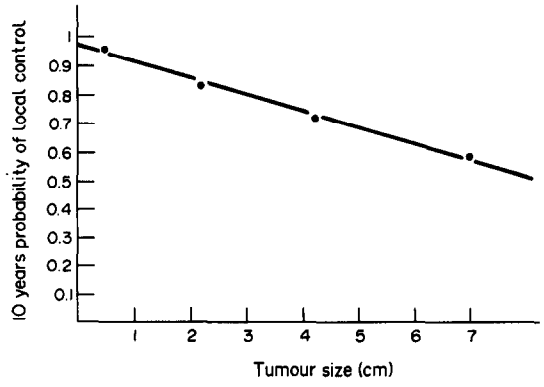

Fig. 2. 10 year probability of local control as a function of tumour size, measured on mammography.

Tumour size

There was a relation between tumour size and probability of local control. Clinical size as well as size measured on mammography were significantly correlated with local control. Actuarial local control rates at 10 years were 100% in 2 patients with T0 carcinoma, 94% for Tis, 86.4% for T1, 80.5% for T2 and 70.1% for T3 tumors (Table 4). Local control rates as a function of tumour size, as measured on mammography in 185 patients, are shown in Fig. 1. Local recurrences at 10 years were seen in 4% of lesions smaller than 1 cm, in 17% of lesions between 1.1 and 3 cm, and in 29.5% of lesions between 3.1 and 5 cm. Tumours measuring more than 5 cm on mammography recurred in 42% of patients followed up for 10 years ($P = 0.037$). This corresponded to an increase of 8% in the 10 year failure rate per cm tumour diameter on mammography (Fig. 2).

Histopathological subtype and differentiation

Better local control rates were noted in 15 patients with invasive lobular (100% at 5 years, 86.7% at 15 years) than in 183 patients with invasive ductular carcinoma (80.4 at 5 years, 72.9% at 15 years) (Table 4). The difference was not, however, significant ($P = 0.076$), possibly due to the small number of patients with lobular carcinoma. Of the 17 patients with invasive lobular carcinoma only 1 has had a local recurrence: a T2 tumour, treated with 72 Gy. However, this patient had a treatment-free interval of 118 days (see further) after 40 Gy because of pneumonia. For ductular carcinoma, local control was related to the degree of differentiation. Significantly worse results were seen in poorly (WHO grade III) differentiated tumours: local control at 10 years was 65.1% compared with 85.6% for grade I and II tumours ($P = 0.038$).

Age

Local control was worse in 19 patients aged below 40 (65.8% vs. 81.6% at 10 years) than for older patients ($P = 0.06$ in univariate and $P = 0.019$ in multivariate analysis) (Table 4).

Radiation dose

There was a significant correlation between the radiation dose administered and probability of local control ($P = 0.0018$, log-rank). The 5 year actuarial local control rates as a function of T stage and radiation dose are shown in Table 5. For T0-Tis tumours, local control was virtually 100% in all patients treated with doses higher than 55 Gy ($P = 0.01$). 3 out of 5 T1 cases treated with doses lower than 60 Gy had recurrences in the breast; this was the case in only 1 out of 26 cases (4%) treated

Table 5. Operable breast cancer—local recurrence as a function of radiation dose (Gy) and T stage

	<50 Gy	51–60	61–70	71–80	81–90	91–100	100–114
T0–Tis	1/2*	0/3	0/4	0/2	0/3	0/2	0/1
	(50%)†	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)
T1	2/2	1/3	—	0/4	0/1	1/11	0/10
	(0%)	(50%)		(100%)	(100%)	(90%)	(100%)
T2	—	2/7	2/7	5/24	4/9	4/45	3/33
	—	(66.7%)	(71.4%)	(83%)	(62.5%)	(92.8%)	(89%)
T3	—	1/6	0/1	7/19	1/3	2/11	2/7
	—	(83.3%)	—	(57.3%)	(50%)	(79.2%)	(83.3%)
All	3/4	4/19	2/12	12/49	5/16	7/69	5/51
	(25%)	(75.7%)	(83.3%)	(74.8%)	(69.4%)	(90.6%)	(90.7%)

*Number of recurrences over number of patients.
†5 year actuarial probability of local control.

with more than 70 Gy (P = 0.03). For T2 tumours, local control rates rose from 66.7% for 51–60 Gy up to more than 90% for doses over 90 Gy (P = 0.04).

For T3 cases no significant correlation was found between total dose and local control. This seems to be related to the high local control rate obtained in a subgroup of 6 T3 cases treated with low total doses (51–60 Gy). 5 of these 6 patients had invasive lobular (n = 4) or medullar carcinoma (n = 1). The only patient with invasive ductular carcinoma in this subgroup had local recurrence before the 5th year after treatment.

When only patients with invasive ductular carcinoma were considered, the 5 year actuarial local control rates for the different subgroups became 0/1 patient (51–60 Gy), 57.3% (71–80 Gy), 50% (3 patients 81–90 Gy), 77% (91–100 Gy) and 83.3% (more than 100 Gy). The dose–response curves for patients with ductular carcinomas are shown in Fig. 3. These curves were drawn by quadratic regression. Because some of the subgroups were small, wide confidence intervals have to be accepted for part of the curve.

Total treatment time

In 18 patients where the total treatment-free split-time became longer than 75 days, the local control rate was significantly poorer. Local failures occurred in 15.3% (31/203) of patients with total split-times less than 75 days, while failures were seen in 39% (7 out of 18) patients with longer total split times (P = 0.035). This split-time effect was seen over the whole dose range, except in patients receiving high doses (more than 90 Gy). In patients treated with doses lower than 90 Gy, recurrences were noted in 21.7% (20/92) of the patients with split-times shorter than 75 days, but in 66% (6/9) in cases with longer treatment-free intervals. In patients treated with doses over 90 Gy, however, recurrences occurred at the same rate, whatever the total split-time: failures were noted in 10% (11/113) for the shorter treatment intervals and in 11% (1/9) for the longer intervals.

Since the abnormally long split-times might have significantly influenced local control rates, local control as a function of total dose was analysed, with the exclusion of patients with split-times longer than 75 days (Fig. 4). As expected, the dose–response curve for patients without a long split-time (75 days) was steeper than that for the whole population.

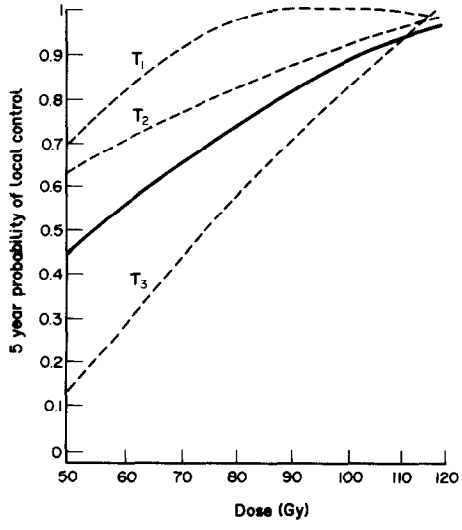

Fig. 3. Actuarial 5 year local control rates according to T stage as a function of total dose administered (IDA patients only).

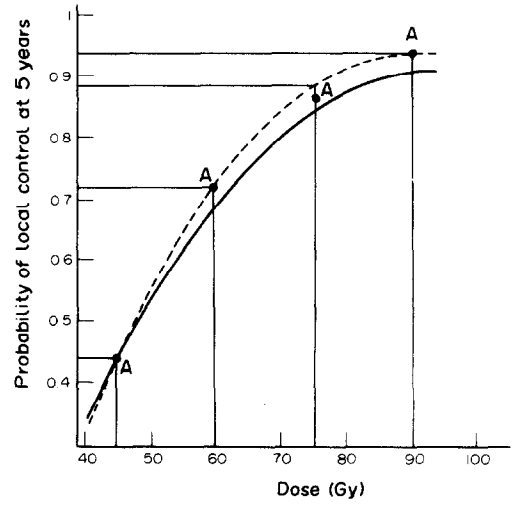

Fig. 4. 5 year local control probability as a function of radiation dose. —— = all patients and - - - - = exclusion of patients with total split-times over 75 days. A: prediction of local recurrence rates, based on the findings of Arriagada *et al.* [11] that the relative risk of local recurrence decreases by a factor 2, for every 15 Gy administered.

DISCUSSION

The local control rates in this series of operable breast cancer, treated with radiation only (without tumour excision) compare favourably with reported data. The average annual risk for recurrence was 3.3% for the first 5 years and 1% for the next 10 years. This risk for late recurrences agrees with the Creteil and Marseille experience and with our studies with patients treated with surgical excision and lower doses of radiation. Leung *et al.* [15] reported a recurrence rate of 7.5% at 5 years and 10% at 10 years, corresponding to an annual risk of 0.5% between the 5th and 10th years. Kurtz *et al.* [16] demonstrated that patients surviving at 10 years were exposed to an annual risk of 1% till the 20th year of follow-up. In our patients treated with combined surgery and radiation [17] the annual risk for local failure was 2% during the first 5 years and less than 0.5% during the next 10 years.

The favourable local control results in our series are probably related to the high radiation doses administered. At 10 years local control was obtained in 96.4% of Tis (mainly Paget's disease), 86.4% of T1, 80.5% of T2 and 70.1% of T3 tumours. In contrast, results from two large French centres showed local failure rates of 27–38.5% at 10 years for T1/T2 tumours treated with radiotherapy alone [10, 18]. For T3 tumours, recurrence rates of 41% at 10 years have been reported [10].

It has been repeatedly shown that the probability of controlling a breast tumour with radiotherapy alone is related to the radiation doses administered [11, 14, 20–22] and to the size of the tumour [10, 11, 19, 22, 23]. Timothy *et al.* [22] suggested that local control rates drop about 10% when clinical tumour size increases from 1 to 5 cm. This would correspond to an increase in risk of recurrence of 2% per cm. In the IGR series [23] the risk for local failures increased 1.8 times for tumours measuring between 4 and 8 cm and 4 times for larger tumours compared with tumours smaller than 4 cm. This corresponds to an estimated increase in risk of 4% per cm tumour diameter. In our series the risk for local failure increased with 8% for every cm increase in tumour diameter measured mammographically.

Excellent local control rates were obtained for small lesions (T0–Tis) with moderate radiation doses. These lesions can be controlled in virtually all cases with doses of at least 55 Gy. For larger lesions, increasing radiation doses are needed to ensure acceptable local control. When local control after tumorectomy and irradiation is compared with that after radiotherapy alone, the doses needed for a 95% local control at 5 years in T1 tumours are about 10 Gy higher (75 Gy) [2, 3, 17, 18]. For T2 tumours an extra 35 Gy is needed to achieve the same result (90% local control at 5 year) as for that after combined treatment [17]. These high doses have sequelae. Only 25–40% of patients treated with doses exceeding 75 Gy have excellent or good cosmetic results [13, 17], compared with 60–80% of patients treated with tumour excision and radiation doses between 60 and 70 Gy [7, 18, 24, 25].

Other dose response data come from retrospective analyses of different patient groups (stages I to III as well as recurrent disease), which may have important differences in prognostic features. On the other hand there may also be important differences in treatment techniques, dose specification and overall treatment time. The first studies that mentioned a dose–response relation for the local control of macroscopic breast cancer came from Cohen in 1952 for recurrent breast cancer [20] and from Ghossein *et al.* [21] for advanced disease. Later, Bataini and his colleagues reported a significant difference in local control rates at 5 years in a series of 122 T2T3, N0N1 breast cancers larger than 3 cm [14]. Local control was obtained in 23% of cases treated with doses under 1950 rets (about 65 Gy in 7 weeks), in 30% at 1950–2150 rets and in 64% over 2150 rets (about 75 Gy in 8 weeks). Timothy *et al.* [22] in stage II and III breast cancer treated with radiotherapy alone, suggested a dose–response relation since local control rose from 45% after 50 Gy in 25 fractions in 5 weeks up to 80% for patients treated with 80 Gy in 40 sessions in 8 weeks.

The best data, since the investigators considered the dose–response relation as a function of tumour size, were from Arriagada and his colleagues [11]. They studied 402 breast cancer patients, most of them suffering from locally advanced, inoperable disease. More than 75% had T4 or T1–3, N2–3 carcinoma. Patients with carcinomatous mastitis, however, were excluded. About 20% had operable T1–3A, N0–1 tumours, and 4% T1–3B, N0–1 tumours. Dose–response of local recurrences was only analysed in patients with a partial tumour response rate higher than 50% or a complete response; this group formed 85% of the population studied. The individual risk for local recurrence was determined by tumour size, the presence or absence of tumour fixation to the pectoral muscles, the presence or absence of fixed lymph nodes in the axilla and radiation dose. According to the shape of the dose–effect curve, it was deduced that an increase of 15 Gy might decrease the relative risk of local recurrence by a factor of 2, independently from the other risk factors. The dose–response relation we obtained was less steep. Various factors, which we have discussed above, may have contributed to this effect. One of the important factors may have been the dose–time distribution.

Local control rates are not only dose dependent, but could possibly also correlate with total treatment time. This hypothesis has gained renewed interest [26, 27]. Theoretically, treatment interruptions during radiotherapy could be disadvantageous because of accelerated tumour cell repopulation during the interval. Some experimental data suggest that accelerated repopulation takes place after an initial course of radiotherapy [28–30]. It has also been suggested that the probability of local control of head and neck cancers decreases with protraction of the overall treatment time [26–27, 31] or after split-course regimens [32]. Clarke *et al.* [33] suggested this was also the case for breast cancer: significantly poorer local control rates were found after radiobiologically equivalent doses lower than 65 Gy (expressed in TDF values). However, the differences in TDF values were largely attributed to differences in overall treatment time and not to differences in total dose or number of fractions. Also our data could be compatible with a negative effect from increasing treatment-free interval times on the local control probability of breast cancer since long treatment-free intervals led to significantly poorer local control.

The effect of total treatment time also modifies the dose–response curves. From Arriagada's study, an increase of 15 Gy diminished the risk for local recurrence by a factor of 2. When we compared our dose–response curve with the data from Arriagada *et al.* [11], the resemblance was striking. The same result was found in our data when patients with long split-intervals were excluded: 56% recurrence rate for 45 Gy, diminishing to 28% at 60 Gy, 12% at 75 Gy and 7% at 90 Gy, giving support to the Villejuif and Toronto data [11] (Fig. 4).

Although the numbers of patients were small, our data also suggested that medullary and lobular breast carcinoma were more radiosensitive than common invasive ductular carcinoma. Favourable local control rates after radiation for medullary carcinoma were also reported by Fourquet *et al.* [34] who found a 6 year local-recurrence-free survival of 86% after 55–60 Gy. For patients treated with tumour excision and irradiation no

significant differences in local control were reported for the different histological subtypes (IDA, ILA, medullary carcinoma) in the large Marseille series [35]. It is possible that the difference in radiosensitivity between IDA and ILA cancers is more difficult to demonstrate after combined treatment. Since multicentric tumour foci are more common in lobular cancer, the amount of microscopic tumour foci left behind after surgical excision may be higher in ILA than in IDA cases. This may cause a higher risk for recurrence, counteracting the higher radiosensitivity. The significantly poorer local control obtained in our patients with poorly differentiated tumours and in our patients under 40 years agree with other data [14, 17, 25, 36].

Our retrospective study stresses the importance of tumour size, radiation dose and possibly overall treatment time in the local control of breast cancer with radiotherapy alone. In the total group local relapse rates were reduced by a factor of 2 per dose increment of 15 Gy. The influence of tumour volume leads to a decrease of 8% in local control rates per cm increase in diameter. For T1 tumours dose can be reduced by 10 Gy after removal of the tumour bulk, while in T2 the difference in dose already amounts to 35 Gy [2, 3, 17, 18]. The combined influence of dose and volume means that small lesions (T0–Tis) can usually be controlled with moderate radiation doses while for larger lesions high doses are necessary. This means that for T0 and Paget's disease radiotherapy alone can be the treatment of choice. For larger lesions, the important late sequelae of exclusive radiotherapy make combined surgery and radiotherapy preferable but, if this proves impossible, irradiation alone should be used as an alternative, accepting a less satisfactory cosmetic outcome.

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