

Boost irradiation of breast carcinoma: teletherapy vs. brachytherapy

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Abstract

Background: The results of adjuvant radiotherapy including a boost dose after breast-conserving surgery of mamma carcinoma were retrospectively analysed to relate local tumor control, survival, and cosmetic results to the boost technique. **Material and methods:** The study included 229 female patients who were treated in the period 1986–1997. Group A consisted of patients where the primary irradiation was hyperfractionated (two fractions per day) and the boost was applied by reduced portals, also at two fractions per day. In group B the ‘boost’ was applied interstitially intraoperatively and the ‘primary’ irradiation followed at one fraction per day. The cosmetic results and the late changes to the mamma were the subjects of follow-up examinations and were assessed using the EORTC score. **Results:** 129 patients formed group A, median follow-up 4.2 years, and 100 patients with median follow-up of 9.4 years formed group B. 59% of group A and 60% of group B were in stage pT1, 38% and 39% were in pT2, and 25% and 39% were in stage N1 or N2 (no significant differences). Tumors were mostly poorly to moderately differentiated. The upper outer quadrant was most afflicted. Local recurrence occurred in two and five cases, lymph-node recurrence in two cases each, while there were ten and 12 cases of distant metastases. There were no deaths in group A and in group B six with obvious distant metastases and eight with other causes of death. The cosmetic results and late side-effects (induration, teleangiectasis, ulcers) were significantly worse in the interstitial group B. Multivariate analysis revealed that only the total applied dose significantly affected the severity of late radiation side-effects. The cosmetic results worsened with time, the tendency for lymph edemas in the irradiated side increased. Induration decreased continuously after pure teletherapy but increased continuously after interstitial therapy. These trends did not change in either group. **Conclusions:** Both therapy schemes resulted in successful local tumor control with good cosmetic results and few side effects, but the interstitial boost therapy was clearly less favourable. Longer-term follow-up is required to compare the late side-effects even further. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Breast cancer; Breast-conserving therapy; Cosmetic outcome; Boost irradiation; Fractionation; Interstitial irradiation

1. Introduction

There is no doubt that the breast-conserving approach of limited surgery followed by radiotherapy is as good as mastectomy as regards overall and recurrence-free survival [4–6,17,20]. Many women can be offered the non-radical treatment, where in recent years the cosmetic result has

become an increasingly more important criterion. The mode of the adjuvant radiotherapy affects this result.

2. Material and methods

In the period 1986 to 1997, 229 female patients underwent adjuvant radiotherapy in our institutions after breast-conserving surgery. In group A ($n=129$) the remaining breast tissue was irradiated with 4 or 6 MV photons at

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Table 1
Patients' characteristics

	Group A (Teletherapy)		Group B (Brachytherapy)		
Number of patients	129 women		100 women		
Age	55±11 years	(23–79 years)	52±11 years	(27–78 years)	n.s.
Body weight	68±14 kg	(47–163 kg)	70±13 kg	(45–110)	n.s.
Karnofsky performance status	Median 90%	(50–100%)	Median 100%	(60–100%)	<i>P</i> <.001
First malignancy	124		98		n.s.
Secondary	5		2		n.s.
Side localisation	re: li=1:1.2		re: li=1: 1		n.s.
Upper outer quadrant	74 (59%)		69 (69%)		n.s.
<i>T-Stage</i>					n.s.
T1	77 (59%)		60 (60%)		
T2	48 (38%)		39 (39%)		
T3	4 (3%)		1(1%)		
<i>N-Stage</i>					n.s.
N0	97 (75%)		61 (61%)		
N1	30 (23%)		36 (36%)		
N2	2 (2%)		3 (3%)		
Involved lymph nodes	Median 0	(0–11)	Median 0	(0–25)	<i>P</i> =.01
Dissected lymph nodes	16±7	(4–36)	20±8	(4–46)	<i>P</i> <.001
M-Stage	M 0		M 0		n.s.
<i>Grading</i>					n.s.
Unknown	5 (4%)		4 (4%)		
G1	3 (2%)		1 (1%)		
G2	70 (54%)		44 (44%)		
G3	51 (40%)		51 (51%)		
<i>Tumor markers</i>					
CA 15–3	17.2±8.4 IU/ml	(0.0–59.0)	16.6±8.0 IU/ml	(2.8–68.0)	n.s.
CEA	1.8±1.3 ng/ml	(0.0–6.9)	2.3±1.6 ng/ml	(0.6–8.8)	<i>P</i> =.001
<i>Histology</i>					
Ductal	71		54		n.s.
Lobular	30		26		
Other	28		20		
<i>Estrogen receptor</i>					n.s.
Unknown	20		2		
Negative	35		36		
Positive	74		62		
<i>Progesterone receptor</i>					n.s.
Unknown	20		3		
Negative	35		46		
Positive	74		51		

two×1.2 Gy per day up to an average total dose of 59 Gy, thereafter the portals were limited to the primary tumor volume for 12 Gy on average as a boost dose. In group B (*n*=100) an initial dose ('boost') of 18 Gy was applied via Ir-192 interstitially intraoperatively to the tumor bed after resection. This was followed by Co-60 irradiation of one×2.4 Gy per day up to an average total teletherapy dose of 43 Gy.

The acute side-effects of the radiotherapy were assessed and documented at the end of treatment using the RTOG score [10]. At the regular follow-ups the cosmetic results were assigned to one of four classes:

- no asymmetry, treated and untreated breasts hardly differ;
- slight asymmetry, recognisable differences in form and size, slight differences in skin color;
- considerable asymmetry, differences can not be overlooked;
- deformation of the breast.

Temperature differences between the breasts were recorded. Side-effects and late results of the therapy were assessed using the EORTC/RTOG score: development of

teleangiectases, mamma induration, hyperpigmentation, ulceration, and presence of lymph edemas.

The Kaplan–Meier method [12] was followed to calculate the survival probabilities (total survival, recurrence- and metastasis-free survivals). Survival rates were compared using the log-rank test [9]. Medians were compared using the Kruskal–Wallis test [2], averages using the simple *t* test [2], and normal distributions were checked with the Kolgomorov–Smirnov test [19]. For univariate analysis of the influence of one or more variables on outcome, nonparametrical correlations were calculated and significance estimates were based on Spearman's ρ and Kendall's τ [2]. For multivariate analysis the Proportional Hazards model of Cox [3] was used. Changes in trends of long-term measurements were investigated using the sign test for trend of Cox and Stuart [2].

3. Results

Median follow-up of patients in group A was 4.2 years (0.5–8.5 years) and in group B was 9.4 years (5.2–12.6 years). The difference in the time ranges is explained by the fact that we stopped interstitial brachytherapy about 5 years ago.

Patient characteristics at the beginning of radiotherapy are given in Table 1.

The groups were well balanced; significant differences were found only in Karnofsky index, the number of excised and positive lymph nodes, and the CEA start value.

There was a normal distribution of age in both groups (Kolgomorov–Smirnov test: $P=0.81$ and $P=0.68$) and the averages did not significantly differ, 55 years in group A and 52 years in group B. The median Karnofsky index was 90% in group A and 100% in group B ($P<0.001$). In almost all patients the disease was the patient's first malignancy. Both body sides were similarly involved, the upper outer quadrant of the breast was most often diseased (59% in group A and 69% in group B). The stage frequencies were pT1 59% in group A and 60% in group B, pT2 38% and 39%, pT3 3% and 1%. Lymph nodes were positive in 25% and 39% of the patients.

Histologically the majority of carcinomas were invasively ductal and invasively lobular. Only in a small proportion of the patients were the tumors well differentiated. Before radiotherapy the tumor markers CA 15-3 and CEA were in the normal range (7–22 IU/ml and 0–5 ng/ml). Evaluation of the hormone receptors showed similar distributions of receptor-positive and receptor-negative tumors.

In most patients of group A (119/129) a segmental or quadrant resection of the breast was carried out (Table 2), in the other ten a tumorectomy (TE). Dissection of the axilla was undertaken in all cases. In all 100 patients of group B, lumpectomy and axilla dissection was carried out

Table 2
Operative and systemic therapy^a

	Group A (Teletherapy)	Group B (Brachytherapy)	
<i>Chemotherapy</i>			n.s.
None	86 patients	67 patients	
CMF	17	21	
NC	23	5	
FAC	3	7	
<i>Application</i>			n.s.
Sandwich	39	27	
Post rad.	4	6	
<i>Hormonal therapy</i>			n.s.
Tamoxifen	27	25	
Goserelin	4	4	
<i>Surgical treatment</i>		LAITT	
TE/axillary dissection	10		
Segmental res./axillary diss.	102		
Quadrantectomy/axillary diss.	17		

^a Abbreviations: CMF, cyclophosphamid, methotrexat, 5-fluorouracil; NC, Novantron, cyclophosphamid; FAC, 5-fluorouracil, adriamycin, cyclophosphamid; TE, tumorectomy; LAITT, lumpectomy, axillary dissection, interstitial and teletherapy.

(LAITT=Lumpectomy, Axillary dissection, Interstitial Therapy, Teletherapy).

Systemic chemotherapy was begun before radiotherapy in 43 and 33 (26% and 33%) patients, mostly continued as a sandwich application. Hormone therapy, mostly using Tamoxifen, was applied in 31 and 29 patients.

In group A, the diseased breast was irradiated with an average dose of 58.5 Gy (54–63.6 Gy) using a technique with isocentric opposing fields. This was followed with a single field boost to the tumor bed of 10.6 Gy (6.0–16.8 Gy). Fractionation was always two×1.2 Gy per day. In group B intraoperative interstitial local irradiation by Ir-192 of 18 Gy (5–20 Gy) was carried out. Postoperatively 42 Gy (36–50 Gy) total reference dose was applied by Co-60 teletherapy, generally including not only the operated breast but also the sternal region and sometimes the axilla (Table 3).

Treatment planning was 2D CT-based.

The 5-year-survival rate was 87.1% in group A and 92.5% in group B (n.s.). The median survival time was 3.5 years (0.1–7.7 years) and 6.3 years (0.1–11.5 years). Fig. 1 shows the overall survival rates.

In group A, local recurrence occurred in two patients, after 1.1 and 4.8 years, and in group B in five, after a mean 3.3 years (0.5–7.6 years). In follow-up positive locoregional lymph nodes were found in two patients of each group, after 0.3 and 5.2 and 0.5 and 7.6 years. Distant metastases were found in the course of follow-up in ten patients of group A, after a mean 1.6 years (0.8–3.6 years), and in 12 of group B, after mean 4.4 years (0.6–7.9 years). They occurred mainly in bones (five patients), lungs (three patients), and liver (three patients). There were no signifi-

Table 3
Radiation therapy

	Group A (Teletherapy)		Group B (Brachytherapy)	
<i>Irradiation technique</i>				
Mamma only	129 patients		14 patients	
Mamma+supraclav. nodes			4	
Mamma+supraclav. nodes + sternal region			49	
Mamma+sternal region			33	
<i>Doses</i>				
Single dose	Two×1.2 Gy		2.5 Gy	
Single dose (boost)	Two×1.2 Gy			
Total dose	58.5 Gy	(54–63.6)	42 Gy	(36–50)
Total dose (boost)	10.6 Gy	(6.0–16.8)	18 Gy	(5–20)

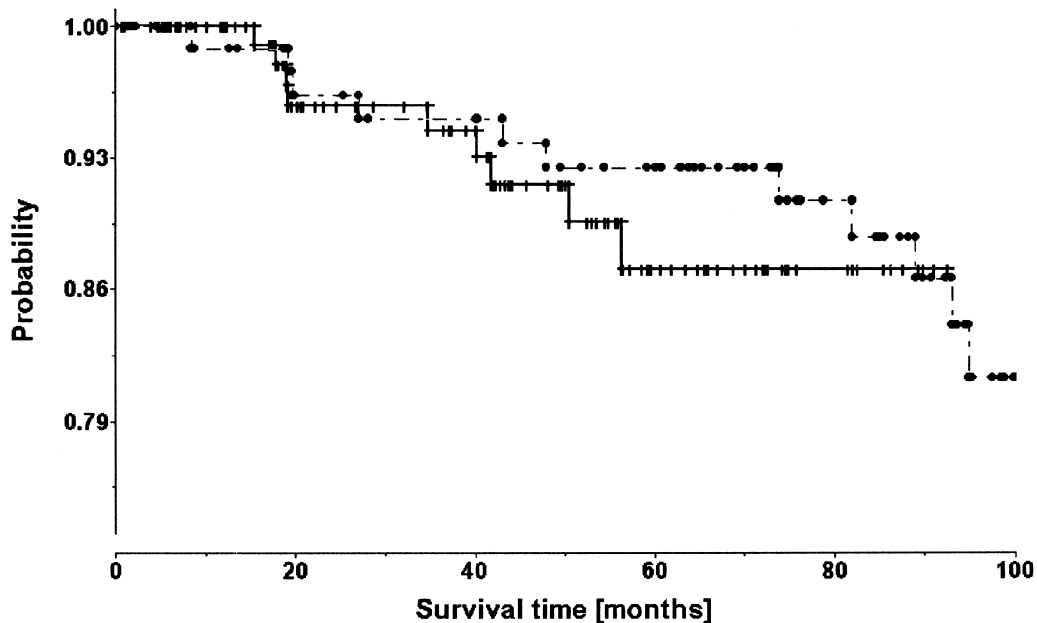


Fig. 1. Overall survival of both (Kaplan–Meier estimate). Teletherapy 129 patients (—), teletherapy plus interstitial boost irradiation 100 patients (- - -). No significant difference between both groups.

cant differences between the groups in numbers or times to recurrence.

The acute side-effects of the radiotherapy did not differ significantly between groups (Table 4). The late side-effects diagnosed in the course of follow-up are summarised in Table 5. As a consequence of the different time behaviour of the late side-effects the maximum degree of severity was reached at different time points.

Symptomatic pneumonitis, pericarditis, or plexus lesions were not found. The interstitial ‘boost’ proved clearly inferior to the percutaneous boost as regards the cosmetic results over all, induration of breast tissue, and development of teleangiectasis and necroses ($P < 0.001$ for each feature). There was no significant difference between

groups in the appearance of hyperpigmentation or development of lymph edema on the irradiated side.

Univariate analysis showed the total dose ($P < 0.04$), the

Table 4
Acute side-effects

	Group A (Teletherapy)		Group B (Brachytherapy)	
None	15	11.6%	11	11%
Erythema	60	46.5%	54	54%
Dry desquamation	43	33.3%	31	31%
Moist desquamation	10	7.8%	4	4%
Ulceration	1	0.8%		

Table 5

Late side-effects: Maximum degree of severity diagnosed during the follow up^a

	Group A (Teletherapy) Number of patients	Group B (Brachytherapy) Number of patients		Group A (Teletherapy) Time	Group B (Brachytherapy) Time
<i>Ulceration</i>			$P<.001$		(4.7±0.2) years
Yes	0	6			
No	129	86			
Unknown	0	8			
<i>Teleangiectasis</i>			$P<.001$	(4.0±0.3)	(4.6±0.1)
Yes	4	50			
No	120	45			
Unknown	5	5			
<i>Induration</i>			$P<.001$	(1.7±0.1)	(1.9±0.2)
None	94	3			
Slight	29	19			
Considerable	0	73			
Unknown	6	5			
<i>Cosmesis</i>			$P<.001$	(1.7±0.1)	(1.9±0.2)
No asymmetry	5	28			
Slight asymmetry	104	39			
Considerable asymmetry	18	21			
Deformation	2	4			
Unknown	0	8			
<i>Lymphedema</i>			n.s.	(1.9±0.1)	(1.9±0.2)
Yes	29	43			
No	94	49			
Unknown	6	8			
<i>Hyperpigmentation</i>			n.s.	(1.3±0.2)	(1.5±0.2)
None	74	49			
Slight	50	34			
Considerable	0	9			
Unknown	5	8			

^a The values in parentheses describe the mean time period between the onset of radiotherapy and the diagnosis of the maximum degree of severity of the respective late side-effect during the follow up.

boost dose ($P<0.001$), and the dose fraction ($P<0.023$), furthermore lymphangiosis ($P<0.001$) and operation type ($P<0.04$) to significantly influence the cosmetic results. Multivariate analysis, however, showed only the applied total doses to be significant, total breast with $P<0.04$ and boost with $P<0.001$. The same approach showed a weak dependence of induration on the boost dose ($P<0.04$) and also of ulceration ($P<0.04$).

The development of teleangiectases in the course of follow-up significantly depended on the applied total breast dose ($P<0.007$) and boost dose ($P<0.002$). The surgical procedure, tumor localisation, radiation type, and irradiation technique had no influence on the cosmetic result or the degree of late changes. The time course of the late results did vary. The general cosmetic result deteriorated with time: after 90 months a slightly worse state ($P<0.02$) in group A, in group B a clear deterioration ($P<0.05$) (Fig. 2). Teleangiectases did not develop in the irradiated volume after teletherapy (group A), but in group B there was a steady increase in the development of new small vessels ($P<0.001$).

Induration in the irradiated breast decreased continuous-

ly with time in group A ($P<0.02$) but did not in group B ($P=0.5$) (Fig. 3).

Lymph edema tended to increase with time in both groups ($P<0.05$ and $P<0.005$).

4. Discussion

Postoperative radiotherapy is a mandatory part of breast-conserving therapy of a mamma carcinoma. Apart from a homogeneous irradiation of the remaining glandular tissue, a boost dose to the tumor bed is theoretically well founded, even though the actual value of the boost is still a subject of discussion [18,22]. Technically the boost can be applied percutaneously (electron or photon fixed field) or interstitially using Ir-192. It has not been proven that any one method is best.

The present study has confirmed reports in the literature that both methods are equally good as far as overall and recurrence- or metastasis-free survival are concerned. Both patient groups were well comparable, with differences in risk profile evident only in the status of lymph nodes and

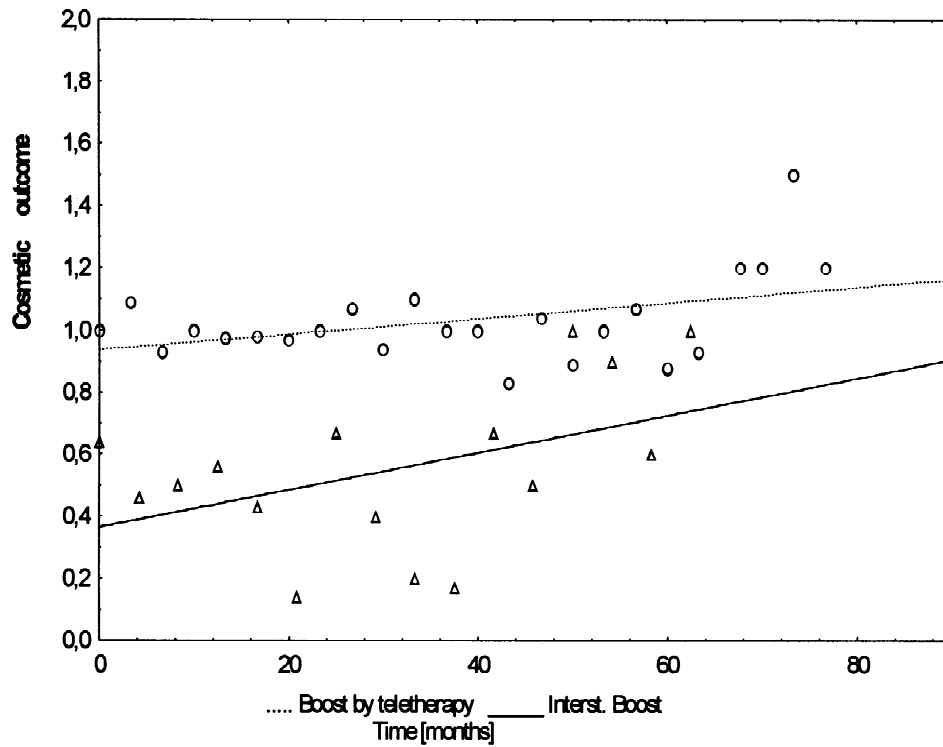


Fig. 2. Time course of the cosmetic outcome. The means are shown at the respective times. The ordinate is scaled from 0 (no asymmetry) to 2 (considerable asymmetry). In both groups we found a significant trend for worsening (Cox–Stuart-test: $P=0.02$ and $P=0.05$ respectively).

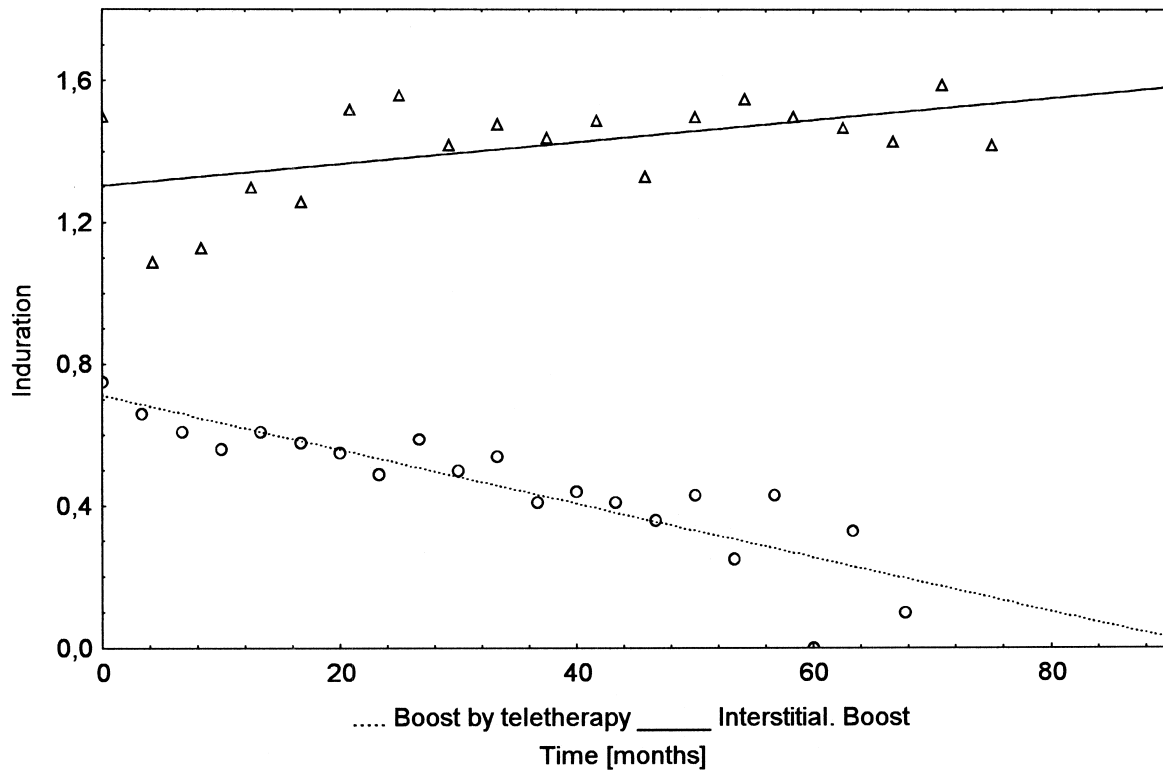


Fig. 3. Time course of the induration of the irradiated mamma. The means are shown at the respective times. The ordinate is scaled from 0 (no induration) to 2 (considerable induration). The observed trend after a pure teletherapy proved to be significant (Cox–Stuart-test: $P=0.02$). In group B (patients with interstitial boost irradiation) there was no significant change ($P=0.5$).

CEA start value. Closer examination, however, shows that differing radicality of the surgeons in the two groups led to different lymph-node status distributions but the median status was the same. The difference in the CEA start value is of questionable significance with respect to its clinical relevance because the means within both groups lie in the normal range.

Investigation of the cosmetic results showed no influence on them by the tumor size or localisation, the previous or perioperative surgical or systemic treatment, or the patient's age [7,8,11,14,15,20,24]. A decline in the cosmetic results from follow-up to follow-up was observed in both groups, in accord with Heidelberg results [13] but in contrast to the findings of Amichetti et al. [1].

The only factors showing prognosis for the cosmetic results were the magnitude of the total dose to the remaining glandular tissue and of the boost dose, as reported by other authors [16,21,23].

In summary, the treatment method followed in group B was the worse one because of the cosmetic results. This is a consequence both of the use of a higher single dose (2.5 Gy vs. two \times 1.2 Gy) and of the biologically more significant total dose of 42 Gy teletherapy+18 Gy interstitial boost (vs. 59 Gy at two \times 1.2 Gy per day+12 Gy boost, all teletherapy).

Interestingly, even after 5 years a trend of continuing changes in the cosmetic appearance and induration of irradiated tissue was observed. That means that a plateau has not been reached, which warrants further long-term follow-up, probably more than 10 years.

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