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The Salzburg concept of intraoperative radiotherapy for breast cancer: Results and considerations

Roland Reitsamer[1]*, Felix Sedlmayer[2], Michael Kopp[2], Gerhard Kametriser[2], Christian Menzel[1], Heinz Deutschmann[2], Olaf Nairz[2], Wolfgang Hitzl[3] and Florentia Peintinger[4]

[1]*Breast Center Salzburg, University Hospital Salzburg, Paracelsus Private Medical School Salzburg, Salzburg, Austria*
[2]*Department of Radiotherapy and Radiooncology, University Hospital Salzburg, Paracelsus Private Medical School Salzburg, Salzburg, Austria*
[3]*Research Office, Biostatistics, Paracelsus Private Medical School Salzburg, Salzburg, Austria*
[4]*Department of Gynecology, General Hospital Leoben, Leoben, Austria*

Aim of this study is to show that ipsilateral breast tumor recurrence (IBTR) after breast conserving surgery can be reduced by proper surgery and modern radiotherapy techniques. Three hundred and seventy eight women with stage I or II breast cancer had breast conserving surgery and received 51–56.1 Gy of postoperative radiation to the whole breast in 1.7 Gy fractions, but patients received different boost strategies. Group 1 ($n = 188$) received electron boost radiation of 12 Gy subsequent to the irradiation to the whole breast, group 2 ($n = 190$) received intraoperative electron boost radiation of 9 Gy directly to the tumor bed, followed by whole breast irradiation. After a median follow up period of 81.0 months in group 1 and a median follow up period of 51.1 months in group 2, 12 IBTRs (6.4%) could be observed in group 1 and no IBTR could be observed in group 2 (0.0%). The 5-year actuarial rates of IBTR were 4.3% (95% CI, 1.9–8.3%) and 0.0% (95% CI, 0.0–1.9%), respectively ($p = 0.0018$). The 5-year actuarial rates of distant recurrence were 8.6% (95% CI, 4.9–13.5%) and 4.2% (95% CI, 1.8–8.2%), respectively ($p = 0.08$). The 5 year disease-free survival rates were 90.9% (95% CI, 85.8–94.7%) in group 1 and 95.8% (95% CI, 91.8–98.2%) in group 2 ($p = 0.064$). Immediate IORT-boost and whole breast irradiation yields excellent local control at 5 years, and was associated with a statistically significant decreased rate of IBTR compared with a similar cohort of patients treated with whole breast irradiation and conventional electron boost.
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Key words: intraoperative radiotherapy; breast cancer; breast conserving surgery; boost radiation

Ipsilateral breast tumor recurrence (IBTR) after breast conserving surgery followed by radiation therapy is reported in about 4–7% after 5 years and in about 10–15% in the long term follow up in the literature. Recent data from long term follow up from the MD Anderson Cancer Center report on improving local control rates of 2% in the last years.[1] Many factors contribute to this decline in IBTR rates, as modern surgical techniques, the extensive pathologic evaluation of specimen and margins, the increasing use of adjuvant systemic therapies and the extensive use of radiation therapy. On the basis of low IBTR rates, the concept of whole breast irradiation comes up for discussion and partial breast irradiation increasingly is under consideration. Different methods for partial breast irradiation are under investigation, but short and long term results are not available. The standard of care for patients with breast conservation is the postoperative radiotherapy to the whole breast with 50–55 Gy. With this therapy, an excellent local tumor control can be achieved. The additional application of an external boost radiation of 10–16 Gy to the tumor bed can reduce the failure rate by 40%.[2–4] The exact knowledge of the tumor bed is essential to apply the boost precisely to the target volume. Several methods are used to localize the tumor bed exactly. Tumor bed clipping with titanium clips, perioperative brachytherapy or intraoperative radiotherapy (IORT) are used to localize the target volume. A partial topographic miss of the target volume could be a reason for local recurrence after boost radiation.[5] Intraoperative radiotherapy is referred to the delivery of a single high dose of irradiation directly to the tumor bed during surgery. This single high dose radiation is delivered to a surgically defined target volume, while uninvolved or dose limiting tissues are displaced, with the goal of enhanced locoregional tumor control. The surgeon and the radiotherapist precisely define the target volume by direct visualization and intraoperative ultrasound, and the high precision boost can be delivered and anticipated into the surgical procedure. The Salzburg concept of IORT in breast cancer patients applies electrons from a linear accelerator in a decicated unit directly to the tumor bed in boost modality during surgery. Postoperative whole breast irradiation is a part of this concept. We reported on this concept earlier[6] with excellent short term results. Now we reanalysed our data after a median follow up of 51 months.

Patients and methods

Between 1996 and 2001, 378 patients were treated with breast conserving surgery for stage I and II invasive breast cancer at the Breast Center Salzburg. From January 1996 to October 1998, 188 patients were treated with breast conserving surgery and postoperative irradiation to the whole breast followed by postoperative external beam boost irradiation to the tumor bed (group 1). From November 1998 to March 2001, 190 patients were treated with breast conserving surgery, intraoperative electron boost directly to the tumor bed and postoperative irradiation to the whole breast (group 2). The groups are comparable with regard to age, menopausal status, tumor size, histological type, grading and axillary lymph node status (Table I). Included were patients with invasive breast cancers pT1/pT2/pN0/pN1/M0, who were eligible for breast conserving surgery with histologically clear margins of at least 3–5 mm. Exclusion criteria were neoadjuvant chemotherapy, tumors >pT2, multicentricity and ductal carcinoma *in situ*.

In group 1, 128 patients presented with T1 tumors (68.1%) and 60 patients with T2 tumors (31.9%). In all patients, wide excision of the tumor was performed with clear margins of 3–5 mm minimally. The tumor bed was clipped with titanium clips to mark the excision cavity for postoperative radiation treatment planning and for the tumor bed control. Axillary dissection of levels I and II was performed in all patients of group 1. Postoperative radiation treatment consisted of external beam radiation therapy (EBRT) of 51 Gy/6 weeks (30 × 1.7 Gy equivalent to 52.2 – 54 Gy ICRU) for patients with invasive ductal breast cancer and 56 Gy (33 × 1.7 Gy equivalent to 57 – 58.8 Gy ICRU) for patients with inva-

***Correspondence to:** Breast Center Salzburg, University Hospital Salzburg, Paracelsus Private Medical School Salzburg, Muellner Hauptstrasse 48, 5020 Salzburg, Austria. Fax: +43-662-4482-2572.
E-mail: r.reitsamer@salk.at
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TABLE I – CHARACTERISTICS OF PATIENTS

	Group 1	Postop boost (%)	Group 2	IORT boost (%)	*p*-value
Number of patients	$n = 188$	100.0	$n = 190$	100.0	
Age					
Median age	57.07		59.03		0.78
Min age	32		31		
Max age	84		83		
Range	52		52		
Menopausal status					
Premenopausal	55	29.3	50	26.3	0.475
Postmenopausal	133	70.7	140	73.7	0.524
Tumor size					
T1a	6	3.2	3	1.6	0.316
T1b	20	10.6	15	7.9	0.365
T1c	102	54.3	112	58.9	0.368
T2	60	31.9	60	31.6	0.944
Histological type					
Invasive ductal carcinoma	163	86.7	167	87.9	0.726
Invasive lobular carcinoma	25	13.3	23	12.1	0.769
Intraductal component	41/188	21.8	61/190	32.1	0.025*
Grading					
G1	29	15.4	26	13.7	0.63
G2	111	59.0	110	57.9	0.83
G3	48	25.6	54	28.4	0.54
Nodal status					
N negative	126	67.0	117	61.6	0.270
N1mic	8	4.3	14	7.4	0.197
N positive	54	28.7	59	31.0	0.463
Hormone receptor status					
ER neg/PR neg	38	20.2	27	14.2	0.123
ER neg/PR pos	2	1.1	2	1.1	0.992
ER pos/PR neg	23	12.2	16	8.4	0.224
ER pos/PR pos	125	66.5	145	76.3	0.035*
Adjuvant therapy					
Chemotherapy	50	26.6	36	18.9	0.077
Hormonal therapy	104	55.3	139	73.2	0.0003*
Combined chemotherapy and hormonal therapy	12	6.4	9	4.7	0.485
No adjuvant therapy	22	11.7	6	3.2	0.002*

sive lobular breast cancer and subsequent external beam electron boost irradiation to the tumor bed with 12 Gy in 2 Gy fractionation. Adjuvant therapy in group 1 consisted of chemotherapy in 26.6% of patients and of hormonal therapy in 55.3% of patients. 6.4% of patients received combined chemotherapy and hormonal therapy. 11.7% of patients received no adjuvant medical therapy.

In group 2, 190 patients were treated with the same surgical technique of breast conserving surgery in a dedicated IORT unit. One hundred and thirty patients patients had T1 tumors (68.4%) and 60 patients T2 tumors (31.6%). If margins were not clear with a minimum of 3–5 mm in the intraoperative pathologic assessment, reexcison was performed in the same surgical procedure prior to IORT. If margins were not clear in the final pathological report (minimum 3 mm), a secondary reexcison had to be performed. Margins were negative in all patients included in this study. Axillary surgery in group 2 was confined to sentinel lymph node biopsy only, if sentinel lymph nodes were negative. Complete axillary clearance of levels I and II was performed, if sentinel lymph nodes were positive. After complete tumor resection and axillary surgery, the tumor bed surrounding tissue was mobilized and temporarily approximated by sutures, to get the tumor surrounding tissue into the target volume. For depth dose prescription, ultrasound of the approximated tissue was performed and documented. Mean depth dose was 19 mm (6–39 mm). Applicator tubes with diameters of 50–60 mm were inserted with complete skin sparing and fixed by an external fixation frame. Then, patients were ''air-docked'' to the linear accelerator in the operating room. IORT was performed with a linear accelerator (Philips Elektra SL 18). A single fractional dose of 9 Gy was applied to the 90% reference isodose with energies ranging from 4 to 18 MeV. The exact technique of IORT was described previously.[7,8] After wound healing, EBRT to the whole breast with opposed tangential fields was performed with single fractional doses of 1.7 Gy (minimum target dose) per day for 30 days, totaling 51 Gy for patients with invasive ductal breast cancer, and with fractional doses of 1.7 Gy per day for 33 days, totaling 56.1 Gy for patients with invasive lobular breast cancers. Postoperative EBRT was equal in both groups. Adjuvant therapy in group 2 consisted of chemotherapy in 18.9% of patients and of hormonal therapy in 73.2% of patients. 4.7% of patients received combined chemotherapy and hormonal therapy and 3.2% of patients received no adjuvant medical treatment. For patients, who received adjuvant chemotherapy, EBRT was sequenced after completion of chemotherapy. The time delay between IORT and EBRT for those patients was up to 20 weeks.

Statistical methods

The endpoints for treatment comparisons were IBTR and distant recurrence. IBTR was defined as any recurrence within the ipsilateral breast as first event with or without simultaneous distant recurrence. IBTR-free survival was calculated as the time from the date of surgery to the date of the first documented evidence of IBTR confirmed by biopsy. Distant-recurrence-free survival was calculated as the time from the date of surgery to the date of the first documented evidence of distant recurrence. The events included for analysis of disease-free survival were the first recurrence of disease at local, regional or distant site. The Kaplan–Meier plots were generated to estimate IBTR-free survival, distant-recurrence-free survival and disease-free survival and the corresponding survival functions were compared with the Gehan's Wilcoxon test, Cox-F test, the Cox-Mantel test, the log-rank test

and the Breslow's test. All reported *p*-values are based on 2-sided tests. *p*-values less than or equal to 0.05 were considered to be statistically significant. All data analyses were performed using STATISTICA 5.5 (StatSoft, Inc.2000, Tulsa, OK, USA) and SPSS 10.0 (SPSS, Inc.1999, Chicago, IL, USA).

Results

Ipsilateral breast tumor recurrence (Fig. 1)

After a median follow up period of 81.0 months in group 1 and a median follow up period of 51.1 months in group 2, 12 IBTRs (6.4%) could be observed in group 1 and no IBTR could be observed in group 2 (0.0%). The 5 year actuarial rates of IBTR were 4.3% (95% CI, 1.9–8.3%) and 0.0% (95% CI, 0.0–1.9%), respectively ($p = 0.0018$). Mean and median time to IBTR were 45.9 months and 42.5 months, respectively. Seven of 12 patients with IBTR developed distant metastases simultaneously or within 52 months. Five of 12 patients with IBTR are alive without evidence of disease, 2 of 12 patients with IBTR died of disease. The characteristics of patients with local recurrences are shown in Table II.

Distant recurrence (Fig. 2)

Distant recurrences occurred in 24 patients (12.8%) in group 1 and in 8 patients (4.2%) in group 2. The 5-year actuarial rates of distant recurrence were 8.6% (95% CI, 4.9–13.5%) and 4.2% (95% CI, 1.8–8.2%), respectively ($p = 0.08$). Mean and median time to distant recurrence were 41.3 months and 33.5 months, respectively, in group 1, and 36,1 months and 41.5 months, respectively, in group 2. In group 1, 11/24 patients with metastases died of disease and 13/24 patients are alive with disease. In group 2, 4/8 patients with metastases died of disease and 4/8 patients are alive with disease (Table III).

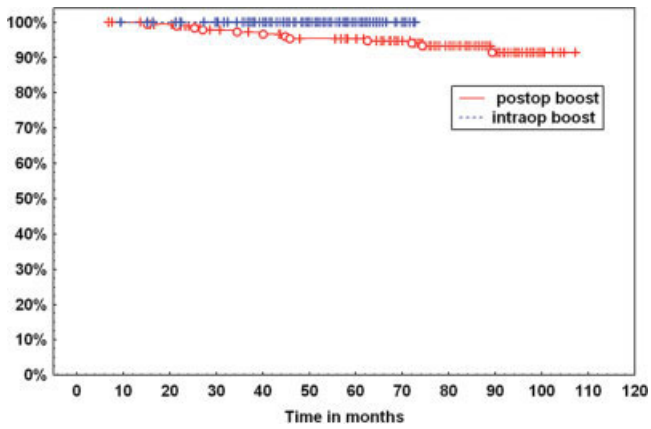

FIGURE 1 – Ipsilateral breast tumor recurrence.

Disease-free survival (Fig. 3)

The crude disease-free survival was 84.6 % in group 1 (29/188 first events, 15.4%) and 95.8% in group 2 (8/190 first events, 4.2%), respectively. The 5 year disease-free survival rates were 90.9% (95% CI, 85.8–94.7%) in group 1 and 95.8% (95% CI, 91.8–98.2%) in group 2 ($p = 0.064$).

Discussion

Five-year ipsilateral breast tumor recurrence rates after breast conserving surgery and radiotherapy vary between 4% and 7%, and correspond to a local failure rate of 1–2% per year. Data from the recent literature show that IBTR after breast conserving surgery can still be decreased. In our series from the Salzburg concept of IORT, we observed no IBTR after a median follow-up of 51 months. These figures support that IBTR rates can be further decreased with modern and highly sophisticated methods of radiotherapy. One weakness of our study is the fact, that this is not a randomized study. Nevertheless, both groups are comparable according to age, menopausal status, tumor size, lymph node size and grading. There was no difference in patients who received adjuvant chemotherapy, but there was a slight but significant difference in patients who received adjuvant hormone therapy in favour of group 2. How far this difference contributes to the fact that no IBTR developed in group 2 cannot be answered, though there is evidence that hormone treatment can reduce local failure rates. Otherwise, all the patients except 1 patient, who developed IBTR in group 1, received adjuvant chemotherapy and adjuvant hormone therapy. Only 3 out of 24 patients, who developed distant metastases had no further adjuvant treatment in group 1.

Extensive intraductal component is a risk factor for local recurrence. In our series, there were more patients with intraductal component in group 2 (IORT group), what perhaps might indicate a worse IBTR rate, but we observed no IBTR in this group.

The development of breast conserving surgery was accompanied by whole breast irradiation. Exclusively whole breast irradiation allowed for breast conserving surgery with equal results as mastectomy concerning local failure rates.[9–15] The additional application of a boost radiation to the tumor bed further reduced local recurrence rates. In the EORTC boost *versus* non boost trial, a 5-year IBTR rate of 4.3% was achieved by an additional 16-Gy boost compared to a 5-year IBTR rate of 7.3% in patients without boost irradiation.[2,3] At present, no group of patients can be identified, which does not benefit from postoperative radiation therapy after breast conserving surgery.[16] Breast irradiation was shown to reduce recurrence rates, but there was no statistically significant reduction in mortality.[17]

TABLE II – CHARACTERISTICS OF PATIENTS WITH IPSILATERAL BREAST TUMOUR RECURRENCE (IBTR), GROUP 1

Patient number	Age (y)	Menopausal status	Histological type	Grading	Tumour size (pT-stage)	Tumour size (mm)	Number of positive nodes/total nodes	Estrogen receptor	Progesterone receptor	Adjuvant therapy	Time to IBTR (months)	Time to distant recurrence (months)	Status
1	32	pre	idc	2	pT2	24	3/12	pos	Pos	cmf	25	42	dod
2	34	pre	ilc	2	pT1b	7	0/16	pos	Pos	cmf	61	–	ned
3	35	pre	idc	1	pT1c	19	3/15	pos	Neg	cmf	27	79	awd
4	36	pre	idc + ilc	2	pT1c	18	17/19	pos	Pos	ec	46	47	awd
5	39	pre	idc	3	pT2	23	0/20	neg	Neg	cmf	72	–	ned
6	47	pre	idc	1	pT1c	18	3/17	pos	Pos	cmf + tam	45	71	awd
7	48	pre	idc	2	pT1c	15	0/23	pos	Pos	cmf	35	–	ned
8	49	pre	idc	3	pT2	45	17/21	pos	Pos	cmf + tam	40	52	awd
9	60	post	idc	3	pT1c	18	0/17	neg	Neg	–	15	27	awd
10	60	post	ilc	2	pT2	25	4/22	pos	Pos	tam	22	22	dod
11	60	post	ilc	2	pT1c	11	0/20	pos	Pos	tam	74	–	ned
12	64	post	idc	2	pT1b	9	0/22	pos	Pos	tam	89	–	ned

Idc, invasive ductal carcinoma; ilc, invasive lobular carcinoma; dod, died of disease; ned, no evidence of disease; awd, alive with disease.

The risk of recurrence in early breast cancer is highest during the first 5 years following diagnosis, irrespective of baseline prognostic factors, and there is still an ongoing discussion if IBTR has an impact on long term survival. Several large series have reported that patients who develop local recurrences within 2 years have a significantly worse outcome than patients who develop local recurrence after more than 5 years, that means the longer the interval between initial treatment and IBTR, the better the outcome.[18,19] The reason for this is not yet quite clear, but may be the biologic aggressiveness of the tumor or the factor that some IBTRs, especially late IBTRs, are not true recurrences but actually new primaries. The 5-year distant recurrence rates after IBTR range between 25 and 40%.[20–22] The question of adjuvant medical treatment on IBTR is still controversial. In patients after neoadjuvant chemotherapy, the occurrence of IBTR is a significant predictive factor of distant metastases.[20–25] Furthermore, there are a number of reports in the literature proposing the development of distant metastases to be increased after formation of IBTR.[26,27] These studies support the hypothesis, that IBTR is a prognostic and predictive factor for distant metastases or even overall survival. For this reason as well as for psychological reasons and health economy reasons, the reduction of local failure rates should be our ambition.

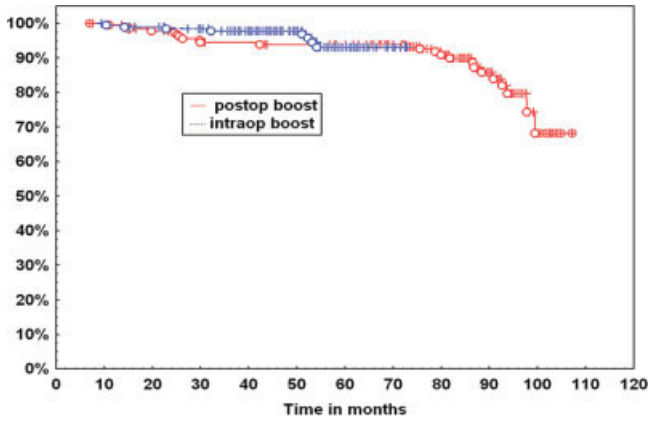

FIGURE 2 – Distant recurrence.

Local failure rates have to be discussed in the primary treatment of breast cancer. Several authors propose partial breast irradiation with different systems[28–34] with regard to the reduction of radiation time and costs. The promising short term results of those studies must not fail to mention that the risk of local or regional recurrence could be increased with those techniques. Furthermore, IBTR could be jointly responsible for potential distant metastases and a potential reduction in overall survival.

All these unanswered questions have to be considered in the propagation of accelerated partial breast irradiation.

With our study, we could demonstrate that immediate IORT boost yields excellent local control and a further reduction of local failure rates is possible compared to standard radiation schemes. Assuming that local failure is responsible for the decrease in survival for patients with breast cancer treated with conservative surgery and postoperative radiotherapy as proposed by some authors,[35–39] our intent should be to further reduce local recurrence rates whenever possible. At this moment exclusively the Salzburg model of IORT considers this fact, all the other models

TABLE III – CHARACTERISTICS OF PATIENTS WITH DISTANT RECURRENCES

Patient number	Age (y)	Meno pausal status	Histological type	Grading	Tumor size (pT-stage)	Tumor size (mm)	Number of positive nodes/total nodes	Estrogen receptor	Progesterone receptor	Adjuvant therapy	Time to distant recurrence (months)	Status
Group 1 (postop boost)												
1	32	pre	idc	2	pT2	24	3/12	pos	pos	cmf	42	dod
2	34	pre	idc	2	pT1c	13	4/20	pos	pos	cmf	30	dod
3	35	pre	idc	1	pT1c	19	3/15	pos	neg	cmf	79	awd
4	36	pre	idc + ilc	2	pT1c	18	17/19	pos	pos	ec	47	awd
5	41	pre	idc	3	pT1a	4	2/17	neg	neg	cmf	30	dod
6	42	pre	idc	3	pT2	28	21/30	pos	pos	ec + tam	44	awd
7	44	pre	idc	1	pT1c	17	0/14	neg	neg	cmf	15	dod
8	47	pre	idc	1	pT1c	18	3/17	pos	pos	cmf + tam	71	awd
9	47	pre	idc	2	pT2	28	15/31	pos	pos	cmf	75	awd
10	47	pre	ilc	2	pT1c	18	1/18	pos	pos	cmf + tam	46	awd
11	49	pre	idc	3	pT2	45	17/21	pos	pos	cmf + tam	52	awd
12	50	post	idc	3	pT2	40	13/21	pos	neg	ec + tam	26	dod
13	53	post	idc	3	pT2	23	0/18	pos	neg	ec	11	dod
14	55	post	idc	2	pT1c	16	3/16	pos	pos	tam	37	awd
15	55	post	idc	3	pT2	21	0/26	neg	neg	cmf	16	dod
16	56	post	idc	3	pT2	31	21/29	pos	pos	ec	26	dod
17	57	post	ilc	2	pT2	25	1/18	pos	pos	tam	78	awd
18	58	post	idc	2	pT2	50	30/30	pos	pos	ec/cmf + tam	79	awd
19	59	post	idc	2	pT1c	14	3/16	pos	neg	tam	25	dod
20	60	post	ilc	2	pT2	25	4/22	pos	pos	tam	22	dod
21	60	post	idc	3	pT1c	18	0/17	neg	neg	–	27	awd
22	66	post	ilc	2	pT1b	9	0/13	neg	neg	–	73	awd
23	71	post	idc	2	pT2	23	0/15	neg	pos	tam	26	dod
24	76	post	idc	3	pT1c	15	0/17	neg	neg	–	14	awd
Group 2 (intraop boost)												
1	46	pre	idc	2	pT2	30	4/21	pos	pos	ec + tam	53	awd
2	53	post	idc	3	pT2	21	1/15	pos	neg	tam	52	awd
3	54	post	idc	3	pT1c	18	1/24	neg	neg	cmf	23	dod
4	55	post	idc	3	pT1c	11	1/19	neg	neg	cmf	51	awd
5	56	post	idc	2	pT1c	18	1/10	pos	pos	tam	14	dod
6	57	post	idc	2	pT2	28	4/26	pos	pos	tam	10	dod
7	62	post	idc	3	pT1c	12	26/26	pos	pos	ec	32	awd
8	76	post	idc	1	pT1c	20	0/10	pos	pos	tam	54	dod

Idc, invasive ductal carcinoma; ilc, invasive lobular carcinoma; dod died of disease; awd, alive with disease.

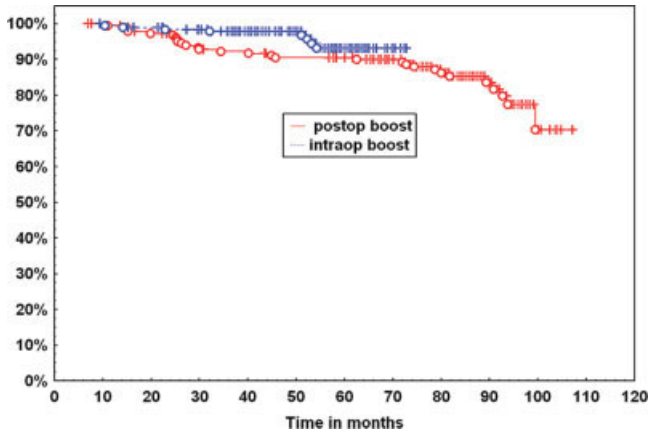

FIGURE 3 – Disease-free survival.

of (accelerated) partial breast irradiation run the risk of an increase in local failure rates associated with the risk of the decrease in overall survival. In this context, one should consider the data provided by Perera *et al*.[40] In this article, the 5-year actuarial rates of ipsilateral breast recurrence was 16.2% in patients who received HDR brachytherapy to the lumpectomy site as the sole radiation. If one discusses the reasons for this high local failure rate, one should bear in mind the risks of partial breast irradiation if not appropriately performed. The reduction of radiation time is extremely attractive from the patient's point of view and the fact not to be irradiated for a time of approximately 6 weeks looks alluring at the first sight, but is not meaningful, as the above mentioned methods (MammoSite, conventional brachytherapy or IMRT) take at least 1 week of therapy. Solely the IORT technique (Milan Model) and the Intrabeam system are the 2 systems that apply the radiation dose intraoperatively as a single dose and do not perform postoperative radiation. As mentioned in an arcticle of Kuerer *et al*.,[41] 3.3% of patients would develop local failure after partial breast irradiation in the non-irradiated breast tissue. With the estimated 216,000 new cases of invasive breast cancer in 2005 in the United States and an estimated breast conserving surgery rate of 70%, approximately 5,000 cases of unnecessary local failures per year could be expected in the United States. The Austrian Health System covers irradiation for all patients with breast cancer, and distances to radiation facilities within Austria are below 2 hr of travel time for nearly all patients. Therefore, the main goal of the Salzburg concept is not to reduce radiation time (which is reduced by 7–10 days), but the main goal is to reduce local failure rates. The non-availability of radiation facilities in the near distance to the patients residence may play a crucial role in other health care systems and, therefore, may play a role in the approach to the problem if a patient decides for mastectomy instead of breast conserving surgery for this reason.[42,43] The longest experience with partial breast irradiation is documented with brachytherapy. Nevertheless, this method is somehow medieval to interlard the breast with multiple catheters, and there is no evidence that the proposed MammoSite system, although FDA approved, can produce the same results. Another problem is that only 20–25% of patients with breast conserving surgery are eligible for the MammoSite procedure.[41,44] The NSABP B-39/RTOG 0413 trial comparing whole breast irradiation followed by optional boost with partial breast irradiation with 3 different techniques (multi-catheter brachytherapy, MammoSite balloon catheter, 3D conformal external beam radiation) started recently to recruit patients. This trial will accrue 3,000 patients over a period of 2 years and 5 months, and it will need years until results will be available. This applies analogously to the Milan model and the Intrabeam system. Until these data are available, it is not yet the time to abandon whole breast irradiation after breast conserving surgery.

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