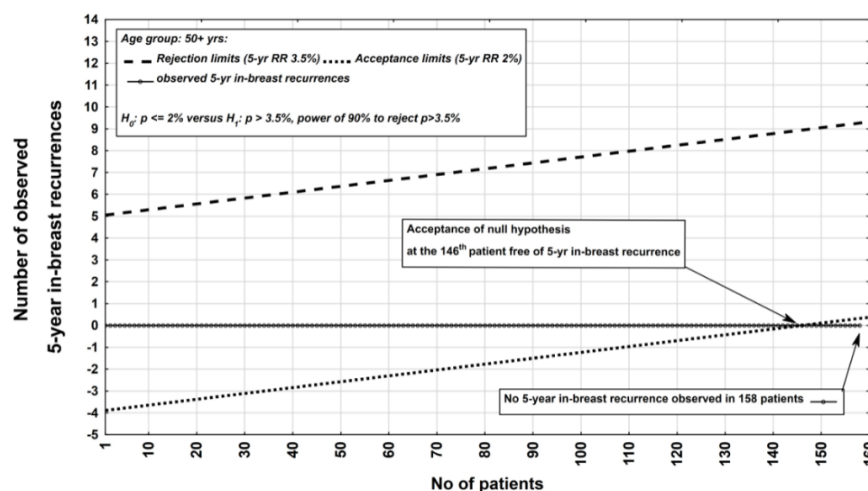


Supplementary Materials: Hypofractionated Whole Breast Irradiation and Boost-IOERT in Early Stage Breast Cancer (HIOB): First Clinical Results of a Prospective Multicenter Trial (NCT01343459)

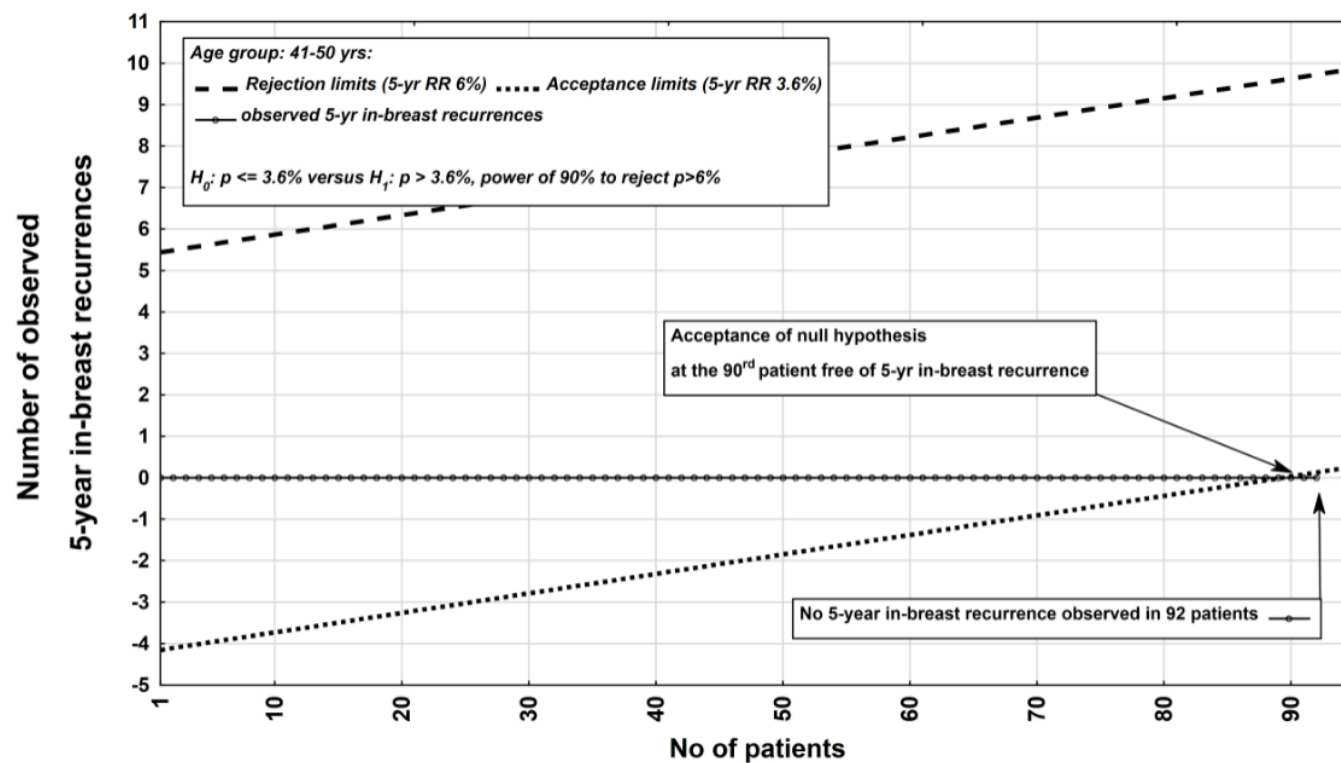
Gerd Fastner, Roland Reitsamer, Christoph Gaisberger, Wolfgang Hitzl, Bartosz Urbański Dawid Murawa, Christiane Matuschek, Wilfried Budach, Antonella Ciabattoni, Juliann Reiland, Marie Molnar, Cristiana Vidali, Claudia Schumacher, Felix Sedlmayer and on behalf of the HIOB Trialist Group



Numbers at risk

FUP, months	I, 1		II, 4-5		III, 13		IV, 24		V, 36		VI, 48		VII, 60		VIII, 72		IX, 79		X, 92		XI, 108	
Median, range	1 (0.2-2.8)		4.6 (2.8-8.7)		12.9(7.9-20.9)		24.5 (18.8-32.8)		36.5 (27.5-44.4)		48.4 (37.5-58.3)		60.3(50.4-69.4)		72.3(63.8-82.7)		84.3(79.4-92.2)		95.8(90-101.5)		102.8 (102-103.6)	
analysis patients	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt
sum patients	657	123	650	122	636	120	597	108	559	100	462	75	339	53	225	34	59	16	16	9	0	1
	780		772		756		705		659		537		392		259		75		25		1	

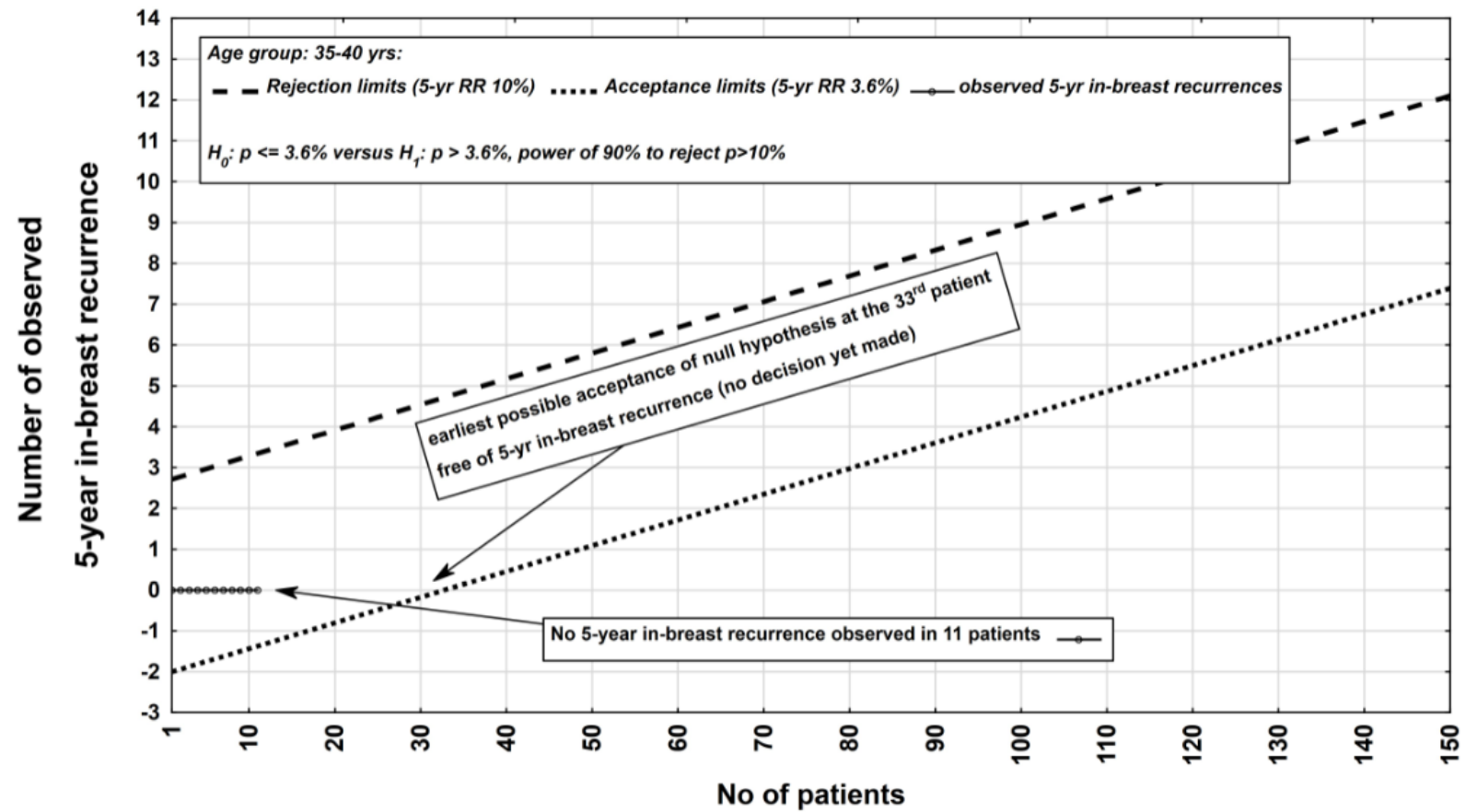
Figure S1. 5-year local recurrence rate: SPRT for age group > 50 years. pp: per protocol, itt: intention to treat, FUP: follow-up.



Numbers at risk

FUP, months	I, 1		II, 4-5		III, 13		IV, 24		V, 36		VI, 48		VII, 60		VIII, 72		IX, 84		X, 96		XI, 108	
Median, range	0.9 (0.3-2.7)		4.6 (2.9-8.6)		12.9(8.8-20.6)		24.4(18.3-32.2)		36.6 (29.3-45.6)		48.7 (41.1-57.6)		60.5 (50.9-68.8)		72.4 (68.7-80.2)		84 (80.8-87.5)		96.2 (93-96.8)		0	
analysis patients	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt
	246	37	245	34	233	27	204	21	166	15	128	12	104	9	72	7	18	4	6	1	0	0
sum patients	283		279		260		225		181		140		113		79		22		7		0	

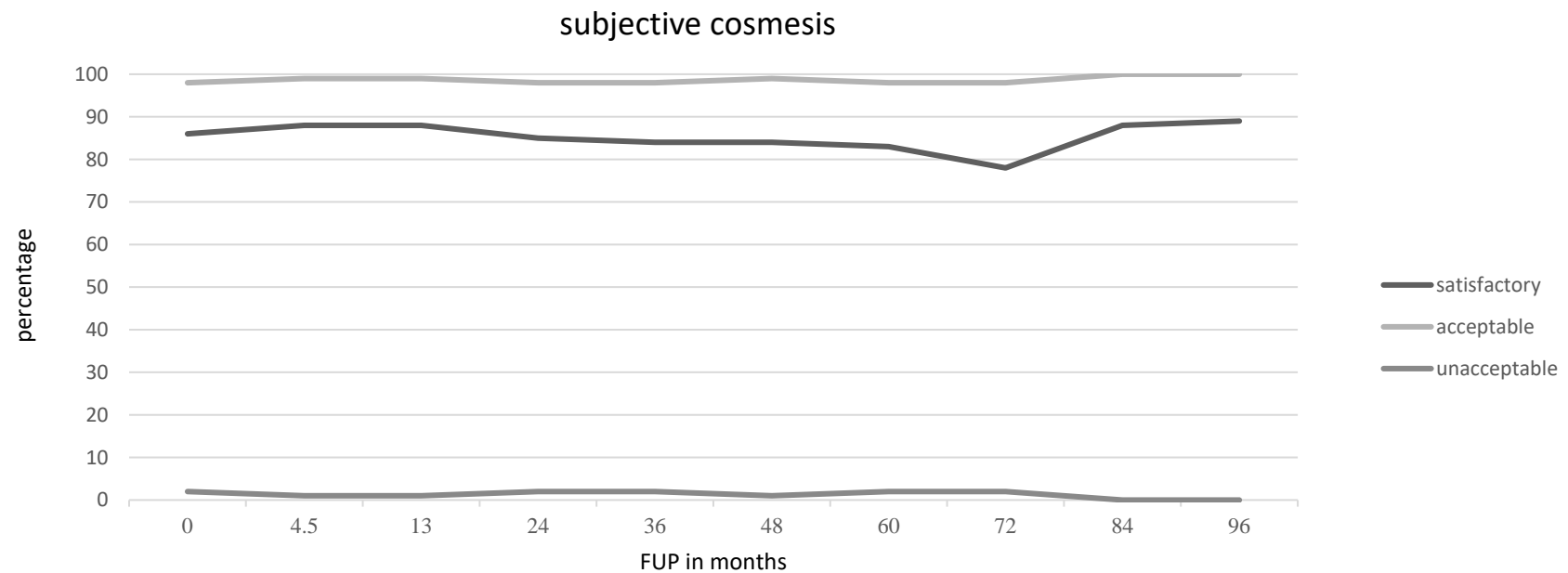
Figure S2. 5-year local recurrence rate: SPRT for age group 41-50 years. pp: per protocol, itt: intention to treat, FUP: follow-up.



Numbers at risk

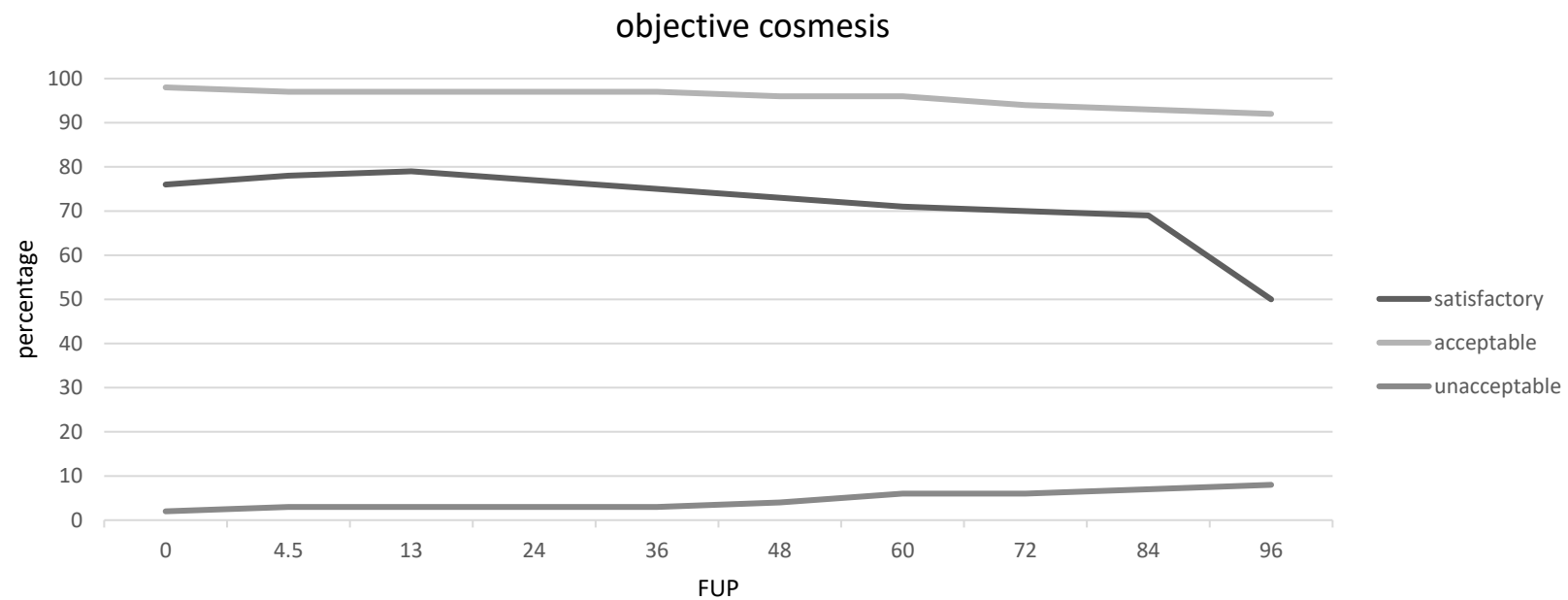
FUP, months	I, 1		II, 4-5		III, 13		IV, 24		V, 36		VI, 48		VII, 60		VIII, 72		IX, 84		X, 96		XI, 108	
Median, range	1(0.5-2.1)		4.7 (3.2-8)		13 (9.4-19.3)		25 (19.6-31.8)		36.9 (30.9-41)		48.9 (42.9-50.8)		60.7 (55-63.3)		72.9 (67-75.6)		79.5 (79.5-79.5)		92.3 (92.3-92.3)		0	
analysis patients	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt	pp	itt
sum patients	36		36		29		24		20		13		11		9		1		1		0	
	40		40		33		28		23		15		13		10		1		1		0	

Figure S3. 5-year local recurrence rate: SPRT for age group 35-40 years.



Number at risk											
Median FUP months	1118	1091	1049	958	863	692	518	348	98	33	1
Range FUP		4.6	12.9	24.5	36.5	48.5	60.4	72.3	84.2	95.9	103.6
		2.8-8.7	7.9-20.9	18.3-32.8	27.5-45.6	37.5-58.3	50.4-69.4	63.8-82.7	79.4-92.2	90-101.5	

Figure S4. Subjective cosmesis over time (ratings patient-reported).



Number at risk											
Median FUP months	1118	1091	1049	958	863	692	518	348	98	33	1
Range FUP		2.8-4.6	7.9-12.9	18.3-24.5	27.5-36.5	37.5-48.5	50.4-60.4	63.8-72.3	79.4-92.2	90-101.5	

Figure S5. Objective cosmesis over time (ratings physician-reported).

Table S1. Exclusion criteria.

Exclusion criteria
negation of inclusion criteria
in-situ carcinoma only
secondary mastectomy
previous RT to the affected breast
mixed connective tissue diseases
chronic pre-existent lung disease
cardiac co-morbidity
distant metastases
observed pregnancy
bilateral breast cancer
multicentricity
Karnofsky Index < 70%
RNI: regional node irradiation;.

Table S2. RTOG CTC-Score version 2 and LENT SOMA scale.

Acute toxicity grade: RTOG-CTCAE Vers. 2 ^Ω		<i>Clinical appearance</i>
	0	None
	1	Faint erythema, dry desquamation
	2	Moderate to brisk erythema, moderate edema, moist desquamation (mostly confined to skin folds and creases)
	3	Confluent moist desquamation > 1,5 cm and not confined to skin folds, pitting edema
	4	Skin necrosis or ulceration of full thickness dermis; may include bleeding no induced by minor trauma or abrasion.
Late toxicity grade: LENT SOMA scale ^Ψ		
	<i>Pain</i>	<i>Clinical appearance</i>
	0	No
	1	Occasional - minimal Hypersensation, Pruritus
	2	Intermittend & tolerable
	3	Persistent & intense
	4	Refractory & excruciating
	<i>Breast edema</i>	<i>Clinical appearance</i>
	0	No
	1	Asymptomatic
	2	Symptomatic
	3	Secondary dysfunction
	<i>Fibrosis</i>	<i>Clinical appearance</i>
	0	No
	1	Barely palpable increased Density
	2	Definite increased density and firmness
	3	Very marked density, retraction and fixation
	<i>Teleangiectasia</i>	<i>Clinical appearance</i>
	0	No
	1	<1/cm2
	2	1/cm2 - 4/cm2
	3	>4/cm2
	<i>Arm lymphedema</i>	<i>Clinical appearance</i>
	0	No

1	2 cm - 4 cm increase
2	>4 cm - 6 cm increase
3	>6 cm increase
4	2 cm - 4 cm increase
<i>Retraction/atrophy</i>	<i>Clinical appearance</i>
0	No
1	10%-25%
2	25% - 40%
3	40% - 75%
4	Whole breast
Ulcers	<i>Clinical appearance</i>
0	No
1	epidermal only,< 1 cm
2	Demal,> 1 cm ²
3	Subcutaneous
4	Bone exposed,necrosis

Ω : reference [29] Ψ : reference [30,31].

Table S3. Cosmesis Score ^Φ.

<i>Single classification</i>	<i>Cosmetic result</i>	<i>Clinical appearance</i>
E0	excellent	no visible therapy related sequelae
E1	good	minimal changes in pigmentation, visible scars, localized teleangiectasia
E2	moderate	clear deformation breast contour, nipple displacement, marked skin changes
E3	bad	Severe retraction or fibrosis, severe teleangiectasia
E4	complication	Skin necrosis
<i>Summary classification</i>	<i>Cosmetic result</i>	
E0, E1	satisfactory	
E2	moderate	
E0,E1,E2	acceptable	
E3,E4	unacceptable	

Φ: reference [32].

Table S4. Technical parameters.

Technical parameters	
<i>IOERT</i> median (range)	
Tubediameter (cm)	6 (4-8)
Electron energy (MeV)	9 (4-15)
Mixed electron energy n (%)	128 (11)
Bevel angle (degree)	22 (0-45)
V90 (ml)	44 (4-104)
<i>Depth calculation: n (%)</i>	
CT	2 (0.2)
Probe/needle	331 (30)
ultrasound	774 (68.8)
ns	12 (1)
<i>Lead-shielding: n (%)</i>	
no	268 (24)
yes	851 (76)
HWBI	
Breast volume (PTV: ml)	1350 (233-2457)
ns (n)	4

MeV: Mega electron Voltage, V90: tissue volume encompassed by the IOERT 90% Isodose (10Gy), ns: not stated, PTV: Planning target volume, ns: not stated.

Table S5. Overview of the clinical status.

Status	n (%)
<i>DM</i>	23 (2)
breast cancer	17 (1.5)
secondary cancers	6 (0.5)
<i>Deaths</i>	25 (2)
breast cancer	6 (0.5)
secondary cancers	8 (0.5)
other reasons	11 (1)
<i>IBR</i>	2 (0.2)
<i>RR</i>	1 (0.1)
<i>Secondary cancer</i>	49 (4)
Contralateral breast cancer	17 (1.5)
Others	32 (3)

DM: distant metastases, IBR: in-breast recurrences, RR: regional recurrence

Table S6. Perioperative major complications (PMJ), LENTSOMA G4 pain, second surgery for cosmetic reasons.

PMJ	patients (n)
hemorrhage	15
prolonged wound healing/disorders	18
seroma	10
wound infection/inflammation	7
no comments	15
patient LENTSOMA G4 pain / point of FUP	comments
patient 1 / months 4/5	accompanied with G3 fibrosis/shrinkage / declined any further FUP
patient 2 / year 3	developed metastases in year 2 / died in year 3 due to disease
patient 3 / months 4/5, year 1	G4 rating resolved in year 2 / lost to FUP thereafter
second surgery for cosmetic reasons	patients (n)
lipofilling	6
excision of liponecrosis	1
breast augmentation	1
breast reconstruction	2
reduction mastopexy	1

FUP: follow up.

Table S7. Cosmesis evaluation

Score	pre-WBI		FUP 4-5 months		FUP 12 months		FUP 24 months		FUP 36 months		FUP 48 months		FUP 60 months		FUP 72 months	
	subj n (%)	obj n (%)	subj n (%)	obj n (%)	subj n (%)	obj n (%)	subj n (%)	obj n (%)	subj n (%)	obj n (%)	subj n (%)	obj n (%)	subj n (%)	obj n (%)	subj n (%)	obj n (%)
E0	278(26)	160(17)	383(38)	240(26)	391(40)	264(29)	347(39)	240(29)	303(37)	220(29)	211(32)	178(30)	138(28)	125(28)	88(27)	81(26)
E1	631(60)	548(59)	513(50)	484(52)	469(48)	447(50)	412(46)	389(48)	378(47)	343(46)	333(52)	257(43)	269(55)	192(43)	171(51)	135(44)
E2	125(12)	207(22)	111(11)	174(19)	107(11)	163(18)	116(13)	162(20)	115(14)	160(22)	100(15)	137(23)	75(15)	101(23)	67(20)	72(24)
E3	14(2)	22(2)	12(1)	23(3)	12(0.9)	24(3)	10(2)	21(3)	10(2)	21(3)	6(1)	20(4)	8(2)	24(6)	6(2)	18(6)
E4					1(0.1)											
eP	1048	937	1019	921	980	898	885	812	806	744	650	592	490	442	332	306
ns	70 (6)	181 (16)	72 (6)	170 (15)	69 (6)	151 (14)	73 (7)	146 (15)	57 (7)	119 (14)	42 (6)	100 (14)	28 (5)	76 (15)	16 (4)	42 (12)

Number at risk	1118	1091	1049	958	863	692	518	348
Median FUP (range)		4.6 (2.8-8.7)	12.9 (7.9-20.9)	24.5 (18.3-32.8)	36.5 (27.5-45.6)	48.5 (37.5-58.3)	60.4 (50.4-69.4)	72.3 (63.8-82.7)

Score	FUP 84 months		FUP 96 months		FUP 108 months	
	subj n (%)	obj n (%)	subj n (%)	obj n (%)	subj n (%)	obj n (%)
E0	27(29)	18(20)	8(28)	5(21)		
E1	55(59)	44(49)	17(61)	7(29)		
E2	11(12)	21(24)	3(11)	10(42)	1(100)	1(100)
E3		6(7)		2(8)		
E4						
eP	93	89	28	24	1	1
ns	5 (2)	9 (9)	5 (15)	9 (27)	0	0

Number at risk	98	33	1
Median FUP (range)	84.2 (79.4-92.2)	95.9 (90-101.5)	103.6

eP: evaluated patients; ns: not stated; subj: subjective (i.e patient-reported); obj: objective (i.e physician-reported)