Long-term changes in blood counts after intraoperative radiotherapy for breast cancer—single center experience and review of the literature

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Background: Intraoperative radiotherapy (IORT) for breast cancer is used as an upfront boost or as accelerated partial breast irradiation (APBI). To date, no description of blood count changes after IORT are available. Our analysis shows blood count changes in breast cancer patients up to 5 years after IORT ± whole breast radiotherapy (WBRT).

Methods: IORT was given as APBI in 58 patients (IORT/APBI-group) and as a boost in 198 patients (IORT/WBRT-group). A median dose of 20 Gy was given intraoperatively with low energy X-rays [INTRABEAM (TM) System] and additionally 46 Gy/2 Gy per fraction to the whole breast, if WBRT was added. Blood counts were collected preoperatively, after 90 days and through year 1–5 of follow-up. Dunnett's tests were used to calculate changes in blood counts over time. Additionally, platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR) and derived neutrophil-to-lymphocyte ratio (dNLR) were calculated for each time point.

Results: Significantly decreases in the IORT/WBRT-group were seen for erythrocytes, hemoglobin, platelets and leucocytes and an increase for lymphocytes for the total follow-up period. In the IORT/APBI-group significantly decreases were seen for erythrocytes and hemoglobin for the total follow-up period. Regarding changes during follow-up compared to the preoperative value, much more significant changes were seen in the IORT/WBRT-group compared to IORT/APBI-group without any relevant impact of chemotherapy. Regarding PLR-, NLR- and dNLR-values the rate of patients over the range improved over time in both groups.

Conclusions: IORT/APBI seems to have a smaller effect on blood counts compared to IORT/WBRT. Furthermore, PLR-, NLR- and dNLR-values improved over time, suggesting a positive effect on outcome after IORT in general.

Keywords: Intraoperative radiotherapy (IORT); whole breast radiotherapy (WBRT); accelerated partial breast irradiation (APBI); blood counts; breast cancer

Introduction

Breast cancer is not only the most common tumor worldwide, but also the most common malignancy-related cause of death (1). The standard treatment of primary breast cancer consists of breast conserving surgery (BCS) followed by whole breast radiotherapy (WBRT) and, when indicated, an additional boost to the tumor bed. Over the past years, various procedures for accelerated partial breast irradiation (APBI) were developed, which can be used as advanced boost or sole radiotherapy to reduce or even replace postoperative whole breast irradiation (WBI). One of these procedures is intraoperative radiotherapy (IORT), in which the tumor bed only is irradiated directly after tumor resection using, e.g., a miniaturized X-ray source.

Radiotherapy can result in acute and chronic side effects. Changes in blood cell count, usually in the form of decreased cell numbers, can occur (2). The different blood cells (leucocytes, erythrocytes, and platelets) can all interact with carcinomas in one way or another (3,4). Preoperative changes in blood parameters show predictive relevance for survival and absence of recurrence concerning different tumor entities (5-7). Especially, platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR) and derived neutrophil-to-lymphocyte ratio (dNLR) were associated with prognosis (8-11). An additional change of blood counts due to therapeutic irradiation could have further negative effects. The degree of side effects caused by radiotherapy depends on several factors, including the total dose applied and the irradiated volume. In contrast to WBRT, usually given in 1.8–2.0 Gy per fraction over 5–6 weeks during 5 days per week to the whole breast, only a single dose of 20 Gy to a small volume is applied during IORT (12). This means, that after IORT, the fractionation effect is absent so anticancer effects of leucocytes and other immunological effects can take place in the surrounding tissue immediately after irradiation (13,14). Therefore, cumulative irradiated volume hosting blood cells in IORT is smaller, which might result in less changes of blood cell counts (*Figure 1*). To date, there are no longitudinal analyses on changes of blood cell counts following IORT for breast cancer.

The aim of this analysis was to determine the impact of IORT on the different blood parameters over a period of 5 years after irradiation, and to evaluate whether there are differences between IORT as APBI and IORT as an advanced boost with subsequent WBRT.
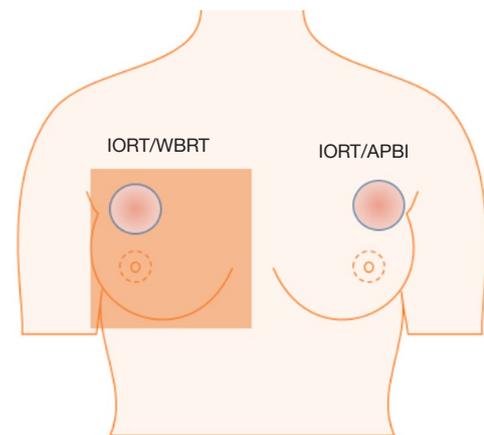

Figure 1 Irradiated volume during WBRT and IORT. WBRT is given in several fractions in a greater volume compared to IORT given as a single shot. In the IORT/WBRT-group both, WBRT and IORT, were applied, whereas in the IORT/APBI-group only the small IORT volume was irradiated. WBRT, whole breast radiotherapy; IORT, intraoperative radiotherapy; APBI, accelerated partial breast irradiation.

Methods

Patients

Between 2008 and 2013, 256 breast cancer patients at the age of 26–90 years were treated with IORT as part of BCS. In 198 cases, IORT was used as an upfront boost with 12–20 Gy in combination with WBRT with 45–56 Gy (IORT/WBRT-group). In 58 cases, IORT was used as sole APBI with 12–20 Gy (IORT/APBI). Some patients were treated within the prospective studies TARGIT A, TARGIT E (lderly), and TARGIT boost quality registry (BQR). Ten patients received neoadjuvant chemotherapy, 85 patients received adjuvant chemotherapy, 194 patients received endocrine therapy, 26 patients received Trastuzumab therapy, and 11 patients received bisphosphonate therapy (*Table 1*). All patients approved the informed consent and the current analysis was also approved by the institutional review board (application number: 2016-866R-MA).

Technique

IORT is given with a miniaturized X-ray source (INTRABEAM®-System, Carl Zeiss Meditec AG, Oberkochen, Germany), which emits low-energy X-rays (maximum energy 50 kV). Spherical applicators with

Table 1 Patient and treatment characteristics

Characteristics	Total patients (n=256)	IORT/WBRT-group (n=198)	IORT/APBI-group (n=58)	P value
General				
Age at IORT, year	63 [26–90]	61 [32–90]	68 [26–86]	0.0005 (*t*-test)
Neoadjuvant chemotherapy, n (%)				0.1228 (Fisher)
No	246 (96.1)	188 (95.0)	58 (100.0)	
Yes	10 (3.9)	10 (5.1)	0	
Study, n (%)				<0.0001 (Chi^2)
TARGIT A	39 (15.2)	25 (12.6)	14 (24.1)	
TARGIT E	25 (9.8)	16 (8.1)	9 (15.5)	
TARGIT BQR	79 (30.9)	76 (38.4)	3 (5.2)	
IORT as boost off-study	81 (31.6)	81 (40.9)	0	
IORT as APBI off-study	32 (12.5)	0	32 (55.2)	
Operation				
Performance status, n (%)				0.2162 (Fisher)
0	247 (96.5)	193 (97.5)	54 (93.1)	
1	4 (1.6)	2 (1.0)	2 (3.4)	
Unknown	5 (2.0)	3 (1.5)	2 (3.4)	
Tumor characteristics				
Localization, n (%)				–
Left side	128 (50.0)	100 (50.5)	28 (48.3)	
Right side	128 (50.0)	98 (49.5)	30 (51.7)	
Tumor size (mm)	Median: 13	Median: 15	Median: 12	0.0074 (*t*-test)
	Mean: 13.98 [0–35]	Mean: 14.52 [0–35]	Mean: 11.98 [4–35]	
Histology, n (%)				0.0813 (Fisher)
Ductal invasive	210 (82.0)	159 (80.3)	51 (87.9)	
Tubulo-lobular/invasive	34 (13.3)	31 (15.7)	3 (5.2)	
Mucinous	6 (2.3)	4 (2.0)	2 (3.5)	
Tubular invasive	3 (1.2)	2 (1.0)	1 (1.7)	
Medullar	2 (0.8)	2 (1.0)	0	
DCIS	1 (0.4)	0	1 (1.7)	
Grading, n (%)				0.1017 (Chi^2)
1	42 (16.4)	38 (19.2)	4 (6.9)	
2	149 (58.2)	112 (56.6)	37 (63.8)	
3	56 (21.9)	43 (21.7)	13 (22.4)	
Unknown	9 (3.5)	5 (2.5)	4 (6.9)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total patients (n=256)	IORT/WBRT-group (n=198)	IORT/APBI-group (n=58)	P value
T stage, n (%)				0.0406 (Fisher)
0	2 (0.8)	2 (1.0)	0	
1	2 (0.8)	2 (1.0)	0	
1a	12 (4.7)	7 (3.5)	5 (8.6)	
1b	59 (23.0)	43 (21.7)	16 (27.6)	
1c	135 (52.7)	103 (52.0)	32 (55.2)	
2	44 (17.2)	40 (20.2)	4 (6.9)	
is	1 (0.4)	0	1 (1.7)	
x	1 (0.4)	1 (0.5)	0	
N stage, n (%)				–
0	197 (77.0)	156 (78.8)	41 (70.7)	
1	2 (0.8)	1 (0.5)	1 (1.7)	
1mi	5 (2.0)	4 (2.0)	1 (1.7)	
1a	30 (11.7)	28 (14.1)	2 (3.4)	
2	1 (0.4)	1 (0.5)	0	
2a	6 (2.3)	5 (2.5)	1 (1.7)	
3	1 (0.4)	1 (0.5)	0	
3a	2 (0.8)	2 (1.0)	0	
x	12 (4.7)	0	12 (20.7)	
M stage, n (%)				0.0075 (Fisher)
0	243 (94.9)	194 (98.0)	49 (84.5)	
1	5 (2.0)	1 (0.5)	4 (6.9)	
x	8 (3.1)	3 (1.5)	5 (8.6)	
L stage, n (%)				0.0733 (Chi^2)
0	184 (71.9)	138 (69.7)	46 (79.3)	
1	59 (23.0)	51 (25.8)	8 (13.8)	
x	13 (5.1)	9 (4.5)	4 (6.9)	
V stage, n (%)				0.6881 (Fisher)
0	233 (91.0)	181 (91.4)	52 (89.7)	
1	9 (3.5)	8 (4.0)	1 (1.7)	
x	14 (5.5)	9 (4.5)	5 (8.6)	

Table 1 (*continued*)

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Table 1 (*continued*)

Characteristics	Total patients (n=256)	IORT/WBRT-group (n=198)	IORT/APBI-group (n=58)	P value
Estrogen receptor, n (%)				0.2502 (Chi^2)
Positive	217 (84.8)	171 (86.4)	46 (79.3)	
Negative	37 (14.5)	26 (13.1)	11 (19.0)	
Unknown	2 (0.8)	1 (0.5)	1 (1.7)	
Progesterone receptor, n (%)				0.3412 (Chi^2)
Positive	198 (77.3)	156 (78.8)	42 (72.4)	
Negative	55 (21.5)	40 (20.2)	15 (25.9)	
Unknown	3 (1.2)	2 (1.0)	1 (1.7)	
IORT-data				
Dose (Gy)	Mean: 19.78	Mean: 19.76	Mean: 19.86	0.5949 (u-test)
	Median: 20 [12–20]	Median: 20 [12–20]	Median: 20 [12–20]	
Applicator size (cm)	Mean: 4.1	Mean: 4.1	Mean: 4.2	0.2461 (u-test)
	Median: 4.0 [2.5–5.0]	Median: 4.0 [2.5–5.0]	Median: 4.0 [3.0–5.0]	
IORT time (min)	Mean: 31.8	Mean: 31.6	Mean: 32.8	0.4793 (*t*-test)
	Median: 28 [12–53]	Median: 28 [12–53]	Median: 28 [18–52]	
WBRT-data				
Days between BCS and WBRT	–	Mean: 97.8	–	–
		Median: 55 [22–307]		
Dose	–	Mean: 47.17	–	–
		Median: 46.0 [45–56]		
Duration (days)	–	Mean: 34.4	–	–
		Median: 34 [16–56]		
Systemic therapy				
Chemotherapy				<0.0001 (Chi^2)
No	169 (66.0)	118 (59.6)	51 (87.9)	
Yes	85 (33.2)	79 (39.9)	6 (10.3)	
Unknown	2 (0.8)	1 (0.5)	1 (1.7)	
Hormone therapy, n (%)				0.0029 (Fisher)
Tamoxifen	100 (39)	86 (43.4)	14 (24.1)	
AI	53 (20.7)	39 (19.7)	14 (24.1)	
Tamoxifen + AI	40 (15.6)	33 (16.7)	7 (12.1)	
Faslodex	1 (0.4)	1 (0.5)	0	
No therapy	55 (21.5)	32 (16.2)	23 (39.7)	
Unknown	7 (2.7)	7 (3.5)	0	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total patients (n=256)	IORT/WBRT-group (n=198)	IORT/APBI-group (n=58)	P value
Trastuzumab, n (%)				0.0013 (Chi^2)
No	156 (60.9)	101 (51.0)	55 (94.8)	
Yes	26 (10.2)	25 (12.6)	1 (1.7)	
Unknown	74 (28.9)	72 (36.4)	2 (3.4)	
Bisphosphonate, n (%)				0.0194 (Fisher)
No	244 (95.3)	192 (97.0)	52 (89.7)	
Yes	11 (4.3)	5 (2.5)	6 (10.3)	
Unknown	1 (0.4)	1 (0.5)	0	

WBRT, whole breast radiotherapy; IORT, intraoperative radiotherapy; APBI, accelerated partial breast irradiation; BQR, boost quality registry; DCIS, ductal carcinoma in situ; BCS, breast conserving surgery; AI, aromatase inhibitor.

different diameters (2.5–5.0 cm) were used for homogenous irradiation of the tumor bed immediately after tumor resection for 12–53 minutes. Details using low energy X-rays for IORT were published elsewhere (15).

WBRT was applied with dedicated linear accelerators using standard single fractions of 1.8–2.0 Gy per week up to 46.0–56.0 Gy treatment dose.

Systemic treatment was given according to current recommendations.

Data collection

Blood counts were measured preoperatively and during a 5-year-follow-up period. Partial blood counts contained the parameters erythrocytes, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets, and leucocytes. These were preoperatively available for all patients, 1–90 days after IORT for 214 patients, during the first year for 139 patients, during the second year for 86 patients, during the third year for 66 patients, during the fourth year for 51 patients, and during the fifth year for 35 patients. Furthermore, complete blood counts with neutrophils, lymphocytes, monocytes, eosinophils, and basophils were acquired. These were preoperatively available for nine patients, 1–90 days after IORT for 66 patients, during the first year for 87 patients, during the second year for 44 patients, during the third year for 36 patients, during the fourth year for 18 patients, and during the fifth year for 19 patients.

Statistics

Primary analysis was the analysis of variance of all measures over time for each radiotherapy type. Additionally, variance analysis in the form of Dunnett's-tests was performed for the IORT/APBI-group and the IORT/WBRT-group separately. Therefore, blood values were compared with their preoperative values and controlled for significant changes. Adjusted P values were calculated and considered significant for P<0.05. Dunnett's-tests have several advantages over *t*-tests. For each parameter, a global P value is calculated, which shows changes over the total follow-up period. By adjusting P values, the 5%-significance level can be ensured, although various single tests are performed. Finally, data analysis using variance analysis is more efficient than several *t*-tests, especially if sparse data is available as it is the case at the end of the follow-up period of this analysis.

The same analysis was performed for all patients without chemotherapy, to face a potential impact of chemotherapy on the results. This analysis was performed only for the partial blood count parameters as number of complete blood counts was very low in this group.

Besides, PLR-, NLR- and dNLR-values were calculated for each period and patients were assigned to the groups "below normal range" and "above normal range" for each period. The percentages of both groups were calculated and shown in a diagram over time. The normal range was determined considering several studies that showed a correlation between the ratios and the prognosis of tumor patients. The normal range for PLR was set to 185 (10,16),

for NLR to 4 (8,11,17-19) and for dNLR to 2 (11).

Results

White blood cells

In the IORT/WBRT-group, significant changes in leucocyte counts could be seen during the total follow-up period. All postoperative values were below the preoperative value, but the value in the first year was the only one that decreased significantly.

In the IORT/APBI-group, no significant changes could be found (*Table 2*).

However, the patients without chemotherapy showed a significant increase of leucocyte values in the first 90 days after BCS/IORT in the IORT/WBRT-group. In the IORT/APBI-group, no significant changes could be found (*Table 3*).

In the Dunnett's-tests, the only significant change in complete white blood counts was a significant increase of lymphocyte counts for the total follow-up period in the IORT/WBRT-group (*Table 2*).

Red blood cells

In the IORT/WBRT-group, significant declines of the erythrocyte counts were shown for the total follow-up period as well as for every single postoperative time point compared to the preoperative values and for the first ninety days as well as for the first, third and fifth year in hematocrit.

In the IORT/APBI-group there was a significant change in the total follow-up period as well as a decrease in the first year after BCS/IORT compared to the preoperative value (*Table 2*). The same changes were found in the analysis of hematocrit (not shown).

The analysis of the patients without adjuvant chemotherapy showed no significant changes in the IORT/APBI-group for erythrocytes and hematocrit (*Table 3*).

Furthermore, there were significant changes of hemoglobin values in the IORT/WBRT-group during the total follow-up period as well as in the first 90 days, first year and fifth year after BCS/IORT.

In the IORT/APBI-group, significant changes of hemoglobin values were observed in the total follow-up period as well as an isolated decrease in the first year after BCS/IORT (*Table 2*).

In the analysis of the patients without chemotherapy, the same changes were found (*Table 3*).

Additionally, in the IORT/WBRT-group, significant changes of MCV, MCH and MCHC could be seen during the total follow-up period. Compared to preoperative values, a significant increase of MCV values in the third year as well as of MCH values in the third and fourth year after BCS/IORT could be seen.

The same changes were found in the analysis of patients without chemotherapy. On the contrary, MCHC values showed a significant decrease instead of increase during the first 90 days and during the first year after BCS/IORT. In the analysis of patients without chemotherapy, only changes in the first 90 days were found.

In the IORT/APBI-group, no significant changes could be found for erythrocyte indices (not shown) in the total group as well as in the patients without chemotherapy.

Platelets

In the IORT/WBRT-group, significant changes of platelet counts were seen during the total follow-up period. Compared to preoperative values, significant decreases were found between the first and the fifth year after BCS/IORT (*Table 2*). In the analysis of the patients without chemotherapy, significant changes could be found for the total follow-up period as well as for the first, second, fourth and fifth year after BCS/IORT (*Table 3*).

However, in the IORT/APBI-group, no significant change could be seen in the total group as well as in the patients without chemotherapy.

Ratios

PLR

Preoperative and until 90 days after IORT, more than half of the patients' PLR-values were below the normal range of 185. During the first year, this percentage decreased and almost 60% of the patients were above the normal range. Afterwards, the percentage of patients below the normal range increased again and it leveled out between 65% and 80% (*Figure 2*).

NLR

More than half of the preoperative NLR-values were below the normal range of 4. This percentage increased almost continuously after BCS/IORT and it leveled out between

Table 2 Changes in blood counts in IORT/WBRT-group and IORT/APBI-group (Dunnett's-tests)

Parameter	Type of radiotherapy	Global P value	Preoperative	1–90 days	1st year	2nd year	3rd year	4th year	5th year
Erythrocytes (mil/µL)	IORT/WBRT	<0.0001	4.5 (SD, 0.36)	4.3 (SD, 0.39)	4.1 (SD, 0.38)	4.3 (SD, 0.39)	4.3 (SD, 0.46)	4.3 (SD, 0.53)	4.3 (SD, 0.41)
	P value		–	<0.0001	<0.0001	0.0015	0.0002	0.0024	0.0068
	Patients at risk		198	181	120	70	52	41	26
	IORT/APBI	0.0357	4.5 (SD, 0.51)	4.3 (SD, 0.48)	4.2 (SD, 0.61)	4.2 (SD, 0.73)	4.5 (SD, 0.64)	4.3 (SD, 0.56)	4.3 (SD, 0.61)
	P value		–	0.4131	0.0064	0.1149	0.9748	0.9691	0.9986
	Patients at risk		58	33	19	16	14	10	8
Hemoglobin (g/dL)	IORT/WBRT	<0.0001	13.4 (SD, 1.14)	12.9 (SD, 1.15)	12.3 (SD, 1.15)	12.9 (SD, 1.11)	13.0 (SD, 1.21)	12.9 (SD, 1.35)	12.7 (SD, 1.20)
	P value		–	<0.0001	<0.0001	0.0584	0.0949	0.0908	0.0259
	Patients at risk		198	181	120	70	52	41	26
	IORT/APBI	0.0055	13.3 (SD, 1.52)	12.6 (SD, 1.32)	12.1 (SD, 1.58)	12.3 (SD, 2.13)	13.1 (SD, 1.53)	12.8 (SD, 1.50)	12.8 (SD, 1.70)
	P value		–	0.1211	0.0008	0.0633	0.9623	0.9006	0.9911
	Patients at risk		58	33	19	16	14	10	8
Platelets (/nL)	IORT/WBRT	<0.0001	262 (SD, 61.63)	263 (SD, 77.90)	248 (SD, 71.43)	239 (SD, 65.54)	237 (SD, 55.34)	229 (SD, 70.06)	236 (SD, 76.62)
	P value		–	0.9988	0.0026	<0.0001	0.0130	0.0018	0.0406
	Patients at risk		198	181	120	70	52	41	26
	IORT/APBI	0.7945	258 (SD, 78.30)	258 (SD, 78.64)	244 (SD, 70.83)	236 (SD, 108.82)	233 (SD, 71.41)	213 (SD, 67.08)	245 (SD, 88.58)
	P value		–	0.9971	1.0000	0.9939	0.8922	0.4786	0.9877
	Patients at risk		58	33	19	16	14	10	8
Leucocytes (/nL)	IORT/WBRT	0.0047	7.1 (SD, 2.19)	6.9 (SD, 2.73)	6.3 (SD, 2.93)	6.7 (SD, 3.04)	6.4 (SD, 1.82)	6.4 (SD, 1.97)	6.2 (SD, 1.89)
	P value		–	0.4750	0.0002	0.4666	0.2624	0.7078	0.6252
	Patients at risk		198	181	120	70	52	40	26
	IORT/APBI	0.2349	7.2 (SD, 1.92)	8.0 (SD, 3.62)	6.5 (SD, 2.65)	6.8 (SD, 2.54)	6.2 (SD, 1.93)	5.6 (SD, 1.04)	6.5 (SD, 1.91)
	P value		–	0.2162	0.9694	0.9989	0.9954	0.9783	0.9964
	Patients at risk		58	33	19	16	14	10	8

Table 2 (*continued*)

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Table 2 (*continued*)

Parameter	Type of radiotherapy	Global P value	Preoperative	1–90 days	1st year	2nd year	3rd year	4th year	5th year
Lymphocytes (%)	IORT/WBRT	0.0037	19.0 (SD, 7.42)	29.8 (SD, 15.08)	22.6 (SD, 11.27)	23.3 (SD, 12.17)	24.8 (SD, 6.65)	26.9 (SD, 10.23)	26.0 (SD, 7.71)
	P value		–	0.0996	0.9811	0.5604	0.6891	0.5034	0.4014
	Patients at risk		7	63	82	37	29	14	12
	IORT/APBI	0.6873	36.5 (SD, 18.17)	15.6 (SD, 11.09)	26.6 (SD, 16.33)	27.9 (SD, 7.02)	23.5 (SD, 8.57)	27.0 (SD, 4.69)	26.7 (SD, 8.66)
	P value		–	0.2627	0.4193	0.5139	0.3371	0.5107	0.5427
	Patients at risk		2	3	5	7	7	4	7

Global P value, change for the total follow-up period; SD, standard deviation; WBRT, whole breast radiotherapy; IORT, intraoperative radiotherapy; APBI, accelerated partial breast irradiation.

Table 3 Changes in blood counts in IORT/WBRT-group and IORT/APBI-group (Dunnett's-tests) in patients without chemotherapy only

Parameter	Type of radiotherapy	Global P value	Preoperative	1–90 days	1st year	2nd year	3rd year	4th year	5th year
Erythrocytes (mil/µL)	IORT/WBRT	<0.0001	4.5	4.4	4.3	4.3	4.2	4.2	4.2
	P value		–	0.0004	0.0010	0.0321	0.0010	0.0194	0.0351
	IORT/APBI	0.2201	4.5	4.3	4.3	4.3	4.6	4.4	4.5
	P value		–	0.4290	0.1395	0.2643	1.0000	0.9282	0.9996
Hemoglobin (g/dL)	IORT/WBRT	0.0003	13.5	13	12.9	13	13	13	12.5
	P value		–	0.0001	0.0051	0.5660	0.1301	0.4166	0.0329
	IORT/APBI	0.1075	13.3	12.5	12.3	12.5	13.3	13.2	13.2
	P value		–	0.1802	0.0465	0.2158	0.9891	0.9543	0.9944
Platelets (/nL)	IORT/WBRT	<0.0001	258	259	234	238	244	224	234
	P value		–	1	<0.0001	<0.0001	0.3271	0.0001	0.0003
	IORT/APBI	0.5980	255	256	241	228	252	213	259
	P value		–	0.9934	0.9998	0.9850	0.5978	0.9474	1.0000
Leucocytes (/nL)	IORT/WBRT	0.1694	7.1	7.1	6.5	6.6	6.4	6.1	6.6
	P value		–	1	0.0788	0.3170	0.9025	0.8934	0.9993
	IORT/APBI	0.1598	7.1	8.3	6.8	7.1	6.5	5.2	6.5
	P value		–	0.0451	1.0000	0.9994	0.9995	0.9965	0.9999

Global P value, change for the total follow-up period; WBRT, whole breast radiotherapy; IORT, intraoperative radiotherapy; APBI, accelerated partial breast irradiation.
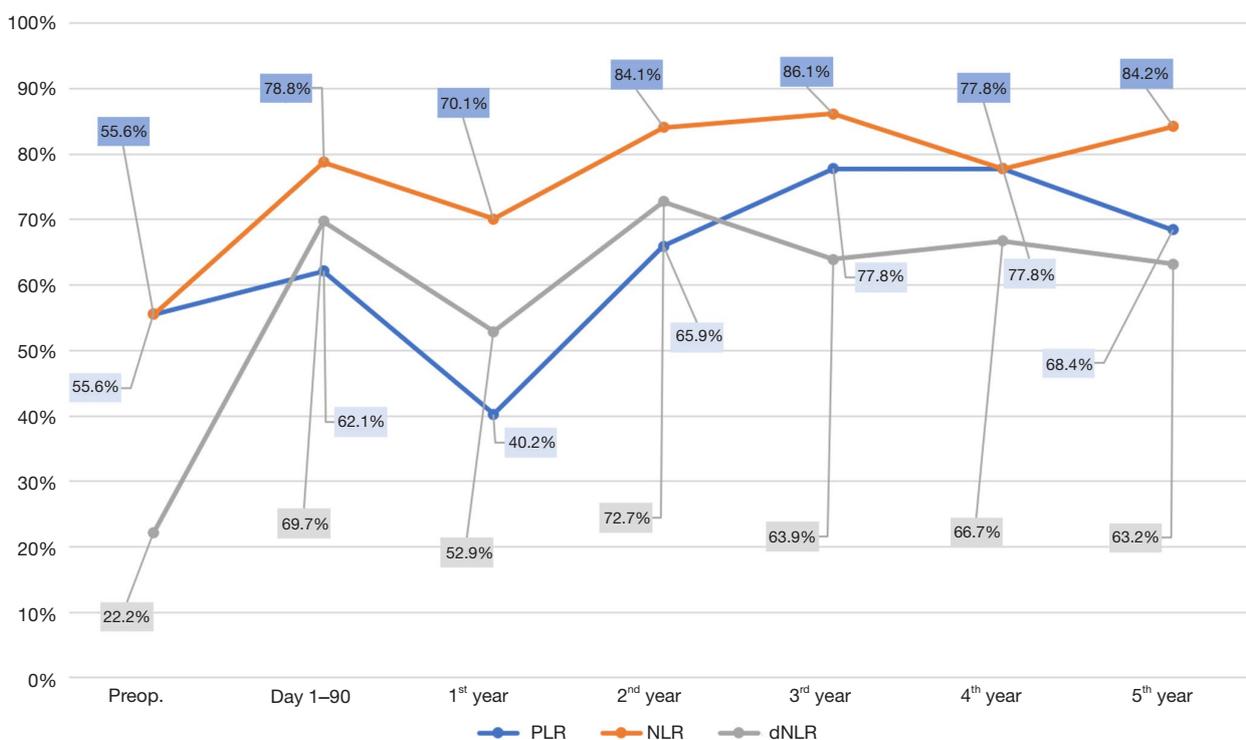
Figure 2 Percentage of patients with a NLR (normal range 4), PLR (normal range 185), dNLR (normal range 2) below normal range over time. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio.

77% and 87% (*Figure 2*).

dNLR

Preoperatively, almost 80% of dNLR-values were above the normal range of 2. During the first 90 days, there was a steep increase of patients below the normal range. After a temporary decrease of this percentage during the first year, it leveled out between 63% and 73% (*Figure 2*).

Discussion

In the IORT/WBRT-group of the current analysis, significant changes of erythrocytes, platelets, and leucocytes could be observed during a follow-up of 5 years. In contrast, significant changes in the IORT/APBI-group could only be observed temporarily for the red blood cells (*Figure 3*). In the analysis of the patients without chemotherapy, significant changes were also more often in the IORT/WBRT-group compared to the IORT/APBI-group. This is the first longitudinal long-term description of blood cell counts after BCS/IORT and the first comparison of IORT/APBI *vs.* IORT/WBRT. The degree of side effects on blood and other organs due

to radiotherapy depends on different biological, physical, physiological and individual factors (20). The effect of external radiotherapy of the breast and other organs on different blood parameters was content of several studies, however, many of those studies had follow-up periods of only a few weeks. A summary of several of these studies is shown in *Table 4*.

Red blood cells

Multiple studies showed changes of red blood cell counts after radiotherapy (2,24,29,30). In the current analysis significant changes could be seen especially in the IORT/WBRT-group. Erythrocytes and hematocrit were decreased significantly in the whole follow-up period, hemoglobin was decreased significantly at the beginning and at the end of the follow-up period. The changes in erythrocyte indices indicate radiotherapy to have an effect on morphology and content of erythrocytes as well. Other studies could not find changes in red blood cells after radiotherapy at all (28,32,34) or changes were normalized after only a few weeks (24,30).
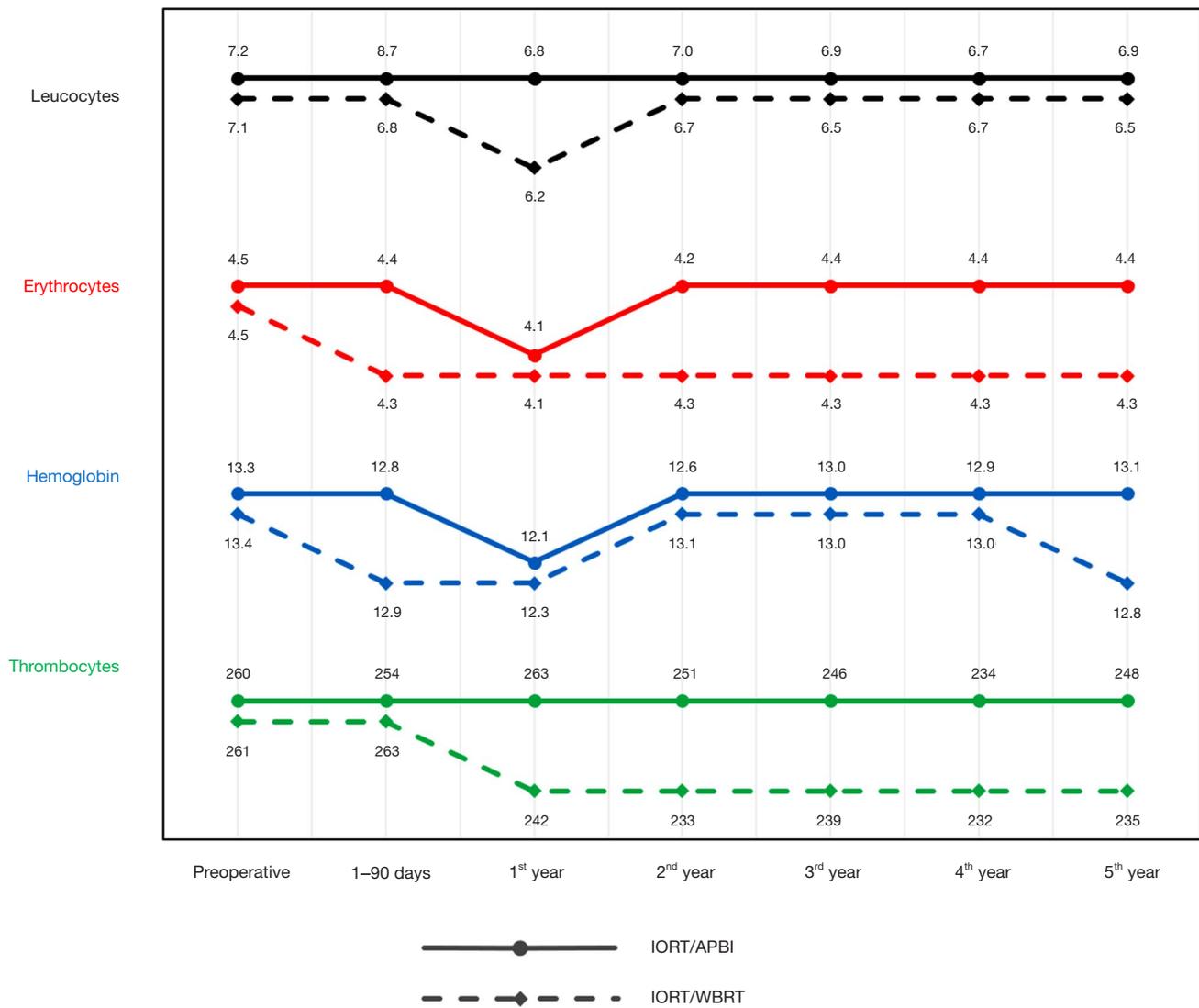
Figure 3 Blood count changes during a follow-up of 5 years after IORT/APBI and IORT/WBRT. WBRT, whole breast radiotherapy; IORT, intraoperative radiotherapy; APBI, accelerated partial breast irradiation.

In contrast to the IORT/WBRT-group, significant changes of red blood cells in the IORT/APBI-group were only temporary within the first year after IORT and showed a better recovery during follow-up compared to the IORT/WBRT-group. This is in line with the results of Shahid *et al.* who showed that the extent of the decrease of erythrocytes depends on the delivered dose (2).

Erythrocytes and hemoglobin are responsible for oxygen transport. Gao *et al.* showed that patients with anemia during or after radiotherapy had a significantly worse prognosis (4). Anemic conditions can cause tumor hypoxia,

which leads to reduced radiosensibility of tumors (35). Furthermore, hypoxic tumors can release various substances like hypoxia-inducible factor 1 (HIF-1), that can enhance malignant behavior of tumor cells (36). In some studies, the treatment of anemia for patients with breast cancer did not influence survival and recurrence (37,38). However, Zhang *et al.* could show that preoperative anemia is an independent prognostic factor for survival and absence of recurrence (39). Therefore, IORT as APBI could have an advantage over WBRT due to its lower influence on red blood cells.

Table 4 Overview of studies concerning changes in blood counts after radiotherapy

Author	Therapy	Points of time	Patients	Entity	Er	Hb	Hct	MCV	MCH	MCHC	Pl	Le	Ne	Ly	Mo	Eo	Ba
Lundell et al. (21)	RT	Directly	48	Breast	✓	✓	✓	✓	✓	✓	✓	→	→	→	–	–	–
Blomgren et al. (22)	RT	Directly	73	Breast	✓	✓	✓	✓	✓	✓	✓	✓	✓	→	✓	✓	✓
Baral et al. (23)	RT	Directly	110	Breast	✓	✓	✓	✓	✓	✓	✓	✓	✓	→ [b]	✓	✓	✓
		2 years															
Plowman et al. (24)	RT	Directly	23	Medulloblastoma	✓	→	✓	✓	✓	✓	→	→	→	→	→	✓	✓
		2 months				[a]					[a]	[a]	[a]	[a]	[a]		
	RT	RT	30	Hodgkin lymphoma	✓	–	✓	✓	✓	✓	→	→	→	→	(↓)	✓	✓
	RT					(↓)					→	→	→	→	→		
		3 months				[b]					(n)	(n)	(n)	[a]	[a]		
Toivanen et al. (25)	RT	Directly	9	Breast	✓	✓	✓	✓	✓	✓	✓	→	✓	→	–	✓	✓
		6 months	10	Breast								[b]		[b]	[b]		
Shukla et al. (26)	RT	Directly	185	Breast	✓	✓	✓	✓	✓	✓	✓	→	✓	→	✓	✓	✓
		1–5 years										[b]		[b]			
Hu et al. (27)	RT	Directly	123	Nasopharyngeal	✓	✓	✓	✓	✓	✓	✓	→	✓	→	✓	✓	✓
		6–8 weeks												[b]			
Kuhnt et al. (28)	RT	Directly	194	Breast	–	✓	✓	✓	✓	✓	✓	→	✓	→	–	✓	✓
Kleinberg et al. (29)	RT + ChT	Directly	101	Astrocytoma	✓	→	✓	✓	✓	✓	→	→	✓	→	✓	✓	✓
Geinitz et al. (30)	RT	Directly	41	Breast	✓	→	✓	✓	✓	✓	→	→	→	→	→	✓	✓
		2 months				[a]					[b]	[b]	[b]	[b]	[b]		
Zachariah et al. (31)	RT	Directly	299	different	✓	✓	✓	✓	✓	✓	→	→	→	→	✓	✓	✓
Standish et al. (32)	RT + ChT	Directly	14	Breast	–	–	(↓)	✓	✓	✓	→	→	→	→	→	–	→
		6 weeks										[b]		[b]			
Mellios et al. (33)	RT + ChT	6–8 weeks	162	Breast	✓	✓	✓	✓	✓	✓	✓	→	→	→	→	✓	✓
	RT	6–8 weeks	52	Breast	✓	✓	✓	✓	✓	✓	✓	→	→	→	→	✓	✓

Table 4 (*continued*)

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Table 4 (*continued*)

Author	Therapy	Points of time	Patients	Entity	Er	Hb	Hct	MCV	MCH	MCHC	Pl	Le	Ne	Ly	Mo	Eo	Ba
Shahid et al. (2)	RT + ChT	Directly	42	Larynx, breast, blood, brain	→	→	→	–	→	→	→	–	–	→	/	/	/
	RT	Directly	18	Larynx, breast, blood, brain	→	→	→	→	→	→	←	←	←	→	/	/	/
Kao et al. (34)	RT + ChT	Directly	21	different	/	–	/	/	/	/	→	→	→	→	/	/	/
Wersal* (current study)	IORT ± WBRT ± ChT	Preoperative, 90 days, 1–5 years	IORT/WBRT: 198	Breast	→	→	→	←	←	←	→	→	–	←	–	–	–
	ChT		IORT/APBI: 58		→	→	–	–	–	–	–	–	–	–	–	–	–

Er, erythrocytes; Hb, hemoglobin; Hct, hematocrit; Pl, platelets; Le, leucocytes; Ne, neutrophils; Ly, lymphocytes; Mo, monocytes; Eo, eosinophils; Ba, basophils; RT, radiotherapy; ChT, chemotherapy; WBRT, whole breast radiotherapy; IORT, intraoperative radiotherapy; APBI, accelerated partial breast irradiation; /, not specified; –, no difference; ↓, decreased; ↑, increased; (↓), slightly decreased; r, remains decreased in follow-up period; n, normalized in follow-up period; h, cell count higher than initial; (n), normalized incompletely; *, results shown for total follow-up period.

Platelets

Radiotherapy of breast cancer and other tumors can also have an effect on the number of circulating platelets. In contrast to the results of Shahid *et al.* showing slightly increased platelet counts, most studies found decreased platelet counts after radiotherapy (2,29-31,34). In the analysis of Plowman *et al.*, platelet counts recovered after 2 months at least partly, whereas Geinitz *et al.* could show decreased platelet counts even 2 months after radiotherapy of breast cancer (24,30). The results of the current analysis showed significant decreases of platelet counts in almost every postoperative period in the IORT/WBRT-group as well. In contrast, no such significant decrease could be seen using IORT as APBI.

The most common causes of thrombocytopenia in tumor patients are chemotherapy and radiotherapy (40). Consequences of thrombocytopenia, other than hemorrhage, are the delay and reduction of chemo- or radiotherapy to avoid a further decrease in platelet counts (41). Ling *et al.* could show that an increase of platelets after the resection of esophagus carcinoma is associated with improved survival (42). In contrast, thrombocytosis in other malignant diseases correlated with poorer prognosis for recurrence-free and overall survival (OS) in several studies (5,43). Many malignant diseases may cause paraneoplastic thrombocytosis. Cancer cells can activate platelets in different ways, which can be seen by increased plasma levels of markers of platelet activation *in vivo*. As activated platelets can stimulate tumor progression especially in terms of metastatic spread, a vicious circle can occur (44). On the other hand, thrombopenia or reduced platelet counts can counteract metastatic spread (45,46).

Generally, platelets seem to have a negative effect on tumor diseases, so reduced platelet counts could be advantageous. However, it is not yet known, which effects a radiation-induced decrease of platelets has on carcinomas and if there is a difference between intraoperative and external beam radiotherapy. This should be content of further investigations.

White blood cells

Changes in leucocyte counts after radiotherapy of different tumor entities were investigated in several studies. While Shahid *et al.* showed a slight increase of leucocyte counts, in most other studies decreased leucocyte counts were found (2,21,28,29,31,33,34). In the current analysis for the

total group, the IORT/WBRT-group showed a significant decrease of leucocyte counts during the first year after BCS/IORT as well. In contrast, no significant change could be seen in the IORT/APBI-group. In the analysis of patients without chemotherapy however, no significant changes could be found in the IORT/WBRT-group and a significant increase of leucocytes was shown in the first 90 days after BCS/IORT. Plowman *et al.* described the recovery of leucocyte counts two months after radiotherapy (24). In other studies, leucocyte counts were still decreased up to 5 years after radiotherapy (25,26,30,32). Additionally, the degree of decrease was shown to be dependent on the delivered dose as well as simultaneous chemotherapy (2,29).

Leucocytes are an important component of the innate and adaptive immune system of the human body. The decrease of leucocyte counts can impair the immune system and increase the risk for infections (47). Several of the above-mentioned studies could not find clinical relevance of leucopenia after radiotherapy (29,31). Mild leucopenia after chemotherapy could even be associated with better survival, whereas severe leucopenia after chemotherapy correlated with poorer prognosis (48,49). The degree of impairment of the immune system due to radio- or chemotherapy therefore seems to be dependent also on other factors than mere leucocyte counts. Hence, a closer look on leucocyte subpopulations and their interaction with tumors is necessary.

Neutrophils and lymphocytes form the largest part of leucocytes. Both of them show pro-tumor as well as anti-tumor functions (50). Irradiation seems to have the strongest effect on lymphocytes, as they responded most sensitive to it in several studies (2,28,31,47). In the current analysis, there also was a significant change in lymphocyte counts in the IORT/WBRT-group over the total follow-up period, which could not be seen in the IORT/APBI-group. In the analysis of normal limits, a decrease of lymphocyte counts could be seen shortly after BCS/IORT, which recovered at the end of the follow-up period. Decreased lymphocyte counts correlated often with poorer prognosis (27,51). Additional to quantitative changes, the functions of lymphocytes can be influenced as well. The regular reaction of lymphocytes to specific antigens can give information on the immune status and can be suppressed by carcinomas (52,53). Fractionated radiotherapy can have similar effects on lymphocyte functions and it can therefore weaken the patient's immune system even more (22,23). Lower radiation exposure due to IORT could be advantageous, by sparing the immune system.

There are various explanatory approaches, why radiotherapy can have effects on peripheral blood cells.

Bone marrow, harboring hematopoietic stem cells and main site for production of blood cells, is vulnerable to radiotherapy, as its tolerance dose is lower than that of other organs (20). Radiotherapy of breast cancer may lead to hypoplasia and aplasia of bone marrow within the sternum, that can still be seen after more than 10 years (54,55). Irradiation of bone marrow with IORT is lower or marginal compared to standard EBRT due to rapid attenuation of dose in the surrounding tissue. On the other hand, the percentage of irradiated bone marrow and lymphatic tissue during radiotherapy of breast cancer is not really large enough to cause such long lasting changes (29,30). In addition to that, studies showed, that blood counts recovered while the bone marrow was still hypoplastic and that there is no correlation between the regeneration of bone marrow and blood counts (56,57).

The direct toxic effect of radiation or the effect of released toxic substances on circulating blood cells while irradiation of the breast as shown by Geinitz *et al.* might also have an impact on blood counts (30). Especially damage of DNA seems to play a major role in this (58). This might be more relevant when IORT is given in addition to WBRT in comparison to IORT as APBI as both irradiation time and volume is much higher when IORT is given as a boost.

Irradiation can lead to apoptosis of natural killer cells as well as T- and B-lymphocytes, especially when given in several fractions (59). Belletti *et al.* showed positive changes in cytokine expression and the whole micromilieu after IORT within the wound fluid (13). Fabris *et al.* also showed that proliferation of breast cancer cells is reduced by changes in expression of miR 223 after IORT by targeting the EGF pathway (14). And this was not only a local but systemic effect of IORT in mice and patients. Veldwijk *et al.* also showed a dose-dependent cohort effect after large single doses supporting the hypothesis that radiotherapy might cause non-targeted effects, especially after IORT (large single dose) (60). All these effects were described after IORT as APBI. One may speculate if these effects might disappear when fractionated EBRT of the whole breast is added. Especially the analysis of the patients without chemotherapy imply this hypothesis, as there was a significant increase in the IORT/APBI-group within day 1–90 (showing a stimulation of the immune system), while in the same period leucocytes were unaltered in the IORT/WBRT-group. The interval between IORT and EBRT was <90 days in 123 (62%) patients. So most patients in

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the IORT/WBRT-group have had started EBRT in this period of decrease of the leucocytes again supporting this hypothesis.

Altogether, low energy X-ray IORT as APBI seems to have less negative effects on blood cells, especially on white blood cell count, than IORT with additional WBRT in our analysis. This might be a possible explanation of positive systemic effects after IORT or APBI in general with a possible stimulation of the immune system and therefore maybe long-lasting effects on the outcome, especially survival, as shown in different randomized trials (*Table 5*) with different techniques for APBI. In the TARGIT A study even a significantly lower non-breast-cancer mortality for IORT compared to WBRT could be found (63). Vaidya *et al.* performed a meta-analysis concerning the outcome of APBI with different techniques with more than 5,000 patients (67).

The current analysis of PLR, NLR and dNLR supports a positive effect of IORT on outcome: At the end of the

follow-up period more patients were below normal ranges than before surgery for all three ratios, which is related to better outcome (*Figure 2*). In several studies concerning different tumor entities, the pre-therapeutic ratios were independent prognostic factors for recurrence and survival (10,11,17). Furthermore, newer studies could show post-therapeutic ratios to be prognostically relevant as well (68-70). Iwase *et al.* could also observe, that NLR is higher at the time of recurrence and that high NLR-values at the time of recurrence are associated with poorer prognosis. In addition, an increase between initial NLR and NLR at the time of recurrence indicates poorer prognosis (71). Similar associations could be seen for different tumor therapies. An increase of NLR or PLR during or after therapy was associated with poorer total and disease-free survival (DFS) in several studies (70,72,73). Simultaneously, patients had a better prognosis if NLR decreased after chemotherapy or targeted therapy (69,73). Therefore, also dynamic changes of PLR and NLR seem to be prognostically relevant.

Table 5 Overview of long-term outcomes after APBI with different techniques

Author, year	Design	Patient number	Median follow-up (min, max)	Local recurrence	Survival	Other results
Veronesi *et al.*, 2013 (61)	Single-center	ITT: 1,305	All patients: 5.8 (4.1–7.7) years	IBR (5 years)	OS (5 years)	No significant difference
	Randomized	PPA: 1,186	WBI: 5.9 (4.2–7.8) years	PBI: 4.4% (95% CI, 2.7–6.1)	PBI: 96.8% (95% CI, 95.3–98.3)	Contralateral BC (P=0.34)
	Prospective		PBI: 5.5 (4.0–7.4) years	WBI: 0.4% (95% CI, 0.0–1.0)	WBI: 96.9% (95% CI, 95.5–98.3)	Distant metastasis (P=0.94)
	Parallel assignment			P=0.0001	P=0.59	Primary cancer other sites (P=0.88)
	Open label			TBR (5 years)		Significant different side effects
				PBI: 2.5% (95% CI, 1.2–3.8)		Skin: in favor of PBI (P=0.0002)
				WBI: 0.4% (95% CI, 0.0–1.0)		Fat necrosis: in favor of WBI (P=0.04)
				P=0.0003		Pulmonary fibrosis: in favor of PBI (P<0.0001)
				Regional recurrence (5 years)		PPA: similar findings for all results
				PBI: 1.0% (95% CI, 0.2–1.9)		
				WBI: 0.3% (95% CI, 0.0–0.8)		
				P=0.03		

Table 5 (*continued*)

Table 5 (*continued*)

Author, year	Design	Patient number	Median follow-up (min, max)	Local recurrence	Survival	Other results
Polgár *et al.*, 2013 (62)	Single-center	ITT: 258	All patients: 10.2 (1.5–13.5) years	IBR (5/10 years)	OS (5/10 years)	Contralateral BC (5/10 years)
	Randomized			PBI: 4.0%/5.9% (95% CI, 1.6–10.2)	PBI: 93.7%/79.7% (95% CI, 72.5–86.9)	PBI: 6.4%/8.3%
	Prospective			WBI: 3.3%/5.1% (95% CI, 1.1–9.1)	WBI: 90.0%/82.1% (95% CI, 75.5–88.7)	WBI: 2.4%/6.4%
	In-block assignment			P=0.77	P=0.73	P=0.56
	Open label			TBR (5/10 years)	CSS (5/10 years)	Distant metastasis (5/10 years)
				PBI: 1.6%/2.4% (95% CI, 0.0–5.1)	PBI: 98.4%/94.4% (95% CI, 89.9–98.9)	PBI: 6.4%/7.3%
				WBI: 1.6%/3.4% (95% CI, 0.1–6.7)	WBI: 95.3%/91.7% (95% CI, 86.8–96.6)	WBI: 6.3%/11.5%
				P=0.72	P=0.34	P=0.61
				Regional recurrence (5/10 years)	DFS (5/10 years)	Cosmetic outcome: in favor of PBI (P<0.01)
				PBI: 1.6%/2.4%	PBI: 88.8%/85.3% (95% CI, 79.0–91.6)	
				WBI: 1.7%/1.7%	WBI: 90.5%/83.6% (95% CI, 77.0–90.2)	
				P=0.65	P=0.97	

Table 5 (*continued*)

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Table 5 (*continued*)

Author, year	Design	Patient number	Median follow-up (min, max)	Local recurrence	Survival	Other results
Vaidya *et al.*, 2014 (63)	Multi-center	ITT: 3,451	All patients: 29 [12–52] months	IBF (5 years)	BC mortality	No significant difference
	Randomized		Early patients: 5 years	PBI: 3.3% (95% CI, 2.1–5.1)	PBI: 2.6% (95% CI, 1.5–4.3)	BC deaths pre-path (P=0.72)
	Prospective			WBI: 1.3% (95% CI, 0.7–2.5)	WBI: 1.9% (95% CI, 1.1–3.2)	BC deaths post-path (P=0.35)
	Open label			P=0.042	P=0.56	Significant difference in favor of PBI
	Stratified			Pre-pathology stratum	Non-BC mortality	Non-BC death pre-path (P=0.016)
	Center			IBF: no significant difference (P=0.31)	PBI: 1.4% (95% CI, 0.8–2.5)	Non-BC death post-path (P=0.32)
	Proposed timing of delivery (pre-/post-pathology)			Post-pathology stratum	WBI: 3.5% (95% CI, 2.3–5.2)	Non-inferiority
				IBF: significantly different in favor of WBI (P=0.069)	P=0.0086	Established for whole cohort and pre-path
					Overall mortality	Not established for post-path
					PBI: 3.9% (95% CI, 2.7–5.8)	
					WBI: 5.3% (95% CI, 3.9–7.3)	
					P=0.042	
Livi *et al.*, 2015 (64)	Single-center	ITT: 520	All patients: 5.0 (3.4–7.0) years	IBR (5 years)	OS (5 years)	No significant difference
	Randomized	PPA: 506	WBI: 5.3 (3.8–7.0) years	PBI: 1.5% (95% CI, 0.1–3.0)	PBI: 99.4%	Axillary nodal recurrence (P=0.86)
	Prospective		PBI: 4.8 (2.7–7.0) years	WBI: 1.4% (95% CI, 0.0–2.8)	WBI: 96.6%	Contralateral BC occurrence (P=0.31)
	In-block assignment			P=0.86	P=0.057 (causes of death not significantly different)	Distant metastasis (P=0.87)
	Open label					Significant difference in favor of PBI
						Skin toxicity (P=0.0001)
						Cosmetic results (P=0.045)
						PPA: similar findings for all results

Table 5 (*continued*)

Table 5 (*continued*)

Author, year	Design	Patient number	Median follow-up (min, max)	Local recurrence	Survival	Other results
Strnad *et al.*, 2016 (65)	Multi-center	ITT: 1,328	All patients: 6.6 (5.8–7.6) years	IBR (5 years)	DFS (5 years)	Distant metastasis (5 years)
	Randomized	ATA: 1,184		PBI: 1.44% (95% CI, 0.51–2.38)	PBI: 95.03% (95% CI, 93.34–96.75)	PBI: 0.80% (95% CI, 0.10–1.50)
	Prospective			WBI: 0.92% (95% CI, 0.12–1.73)	WBI: 94.45% (95% CI, 92.54–96.40)	WBI: 0.93% (95% CI, 0.12–1.74)
	In-block assignment			P=0.42	P=0.79	P=0.81
	Open label			PPA: similar findings	OS (5 years)	No significant difference
	Stratified			Regional recurrence (5 years)	PBI: 97.27 (95% CI, 96.00–98.56)	BC deaths (P=0.84)
	Center			PBI: 0.48% (95% CI, 0.00–1.02)	WBI: 95.55% (95% CI, 93.82–97.31)	Second primary in ipsilateral breast, contralateral breast and sites other than breast
	Menopausal status			WBI: 0.18% (95% CI, 0.00–0.54)	P=0.11	Grade 2–3 late skin side-effects, subcutaneous tissue effects and grade 3 fibrosis
	Tumor type			P=0.39		Significant difference
						Grade 2–3 breast pain (P=0.0389 in favor of PBI)
Coles *et al.*, 2017 (66)	Multi-center	ITT: 2,018	All patients: 72.2 (61.7–83.2) months	IBR (5 years)	Any BC related event (5 years)	Distant recurrence (5 years)
	Randomized			WBI: 1.1% (95% CI, 0.5–2.3)	WBI: 3.7% (95% CI, 2.5–5.4)	WBI: 1.4% (95% CI, 0.7–2.6)
	Prospective			PBI: 0.5% (95% CI, 0.2–1.4)	PBI: 4.0% (95% CI, 2.8–5.9)	PBI: 1.6% (95% CI, 0.8–2.9)
	In-block assignment			P=0.420	P=0.982	P=0.838
	Open-label			Loco-regional recurrence (5 years)	All-cause mortality (5 years)	Significant difference in favor of PBI
				WBI: 1.1% (95% CI, 0.5–2.3)	WBI: 5.0% (95% CI, 3.6–7.0)	Breast harder or firmer (P=0.024)
				PBI: 0.8% (95% CI, 0.3–1.8)	PBI: 3.7% (95% CI, 2.5–5.4)	Breast appearance change (P<0.0001)
				P=0.761	P=0.693	

APBI, accelerated partial breast irradiation; ITT, intention-to-treat; PPA, per-protocol analysis; CI, confidence interval; ATA, as-treated analysis; WBI, whole breast irradiation; PBI, partial breast irradiation; BC, breast cancer; OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; IBR, ipsilateral breast recurrence; TBR, tumor bed recurrence; IBF, in-breast failure.

Limitations

Sample size, especially in the IORT/APBI-group, and decreasing number of available blood counts over time are a limiting factor of this analysis. Moreover, blood parameters are influenced by a wide range of diseases and the special role of IORT or irradiation in general is not clear. Due to the retrospective character of the current analysis, there is a high probability, that patients with available blood counts had other diseases or on the other hand presented cumulatively with an inconspicuous follow-up.

Conclusions

In the IORT/WBRT-group significant changes of blood counts were more frequent than in the IORT/APBI-group regardless of applied chemotherapy. IORT/APBI seems to have a smaller effect on blood counts compared to IORT/WBRT. Furthermore, PLR-, NLR- and dNLR-values improved over time, suggesting a positive effect of IORT in general regarding outcome parameters.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients approved the informed consent and the current analysis was also approved by the institutional review board (application number: 2016-866R-MA).

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