

Article information: <http://dx.doi.org/10.21037/gs-20-249>.

Major remarks

Comment 1: Local recurrence as specified by the authors only includes recurrence in the original quadrant. This underestimates the true risk of in-breast recurrence. Recurrence rates in the complete ipsilateral breast should be stated in the manuscript.

Reply: At first, we would like to specify the effect from IORT to the tumor bed so we use the original quadrant local recurrence. But for local recurrence in our study, there was only one patient that occurred in ipsilateral breast which was also the same quadrant as the initial one.

Changes in the text:

Assessment (page 7, line 1): local recurrence rate was defined as recurrence in ipsilateral breast and proved by surgical pathology.

Results (page 7, line 22): One of the 81 patients had ipsilateral breast tumor recurrence in the tumor bed which was occurred as the same quadrant as the primary tumor.

Comment 2: Why were patients with re-excision excluded from the analysis? This might underestimate the incidence of local recurrence and adverse events, since patients with re-excision might be at a higher risk of developing both.

Reply: For the timeline of the treatment in this group starts with IORT then we found out that there was a positive margin/gross disease left when the pathology came out. So the patients were undergone re-excision. We decided to exclude these patients because we thought that all area that was treated by IORT had taken out at the second time of surgery and we might not be able to see the effect from IORT.

Changes in the text: (page5, line 22)

Study design: patients who underwent re-excision or mastectomy after IORT from positive margin or with residual gross disease were excluded

Comment 3: It is mentioned that three radiation oncologists and two surgeons evaluated the cosmetic outcome. Were all patients evaluated by the panel or each patient by a single physician? Was the assessment conducted in person or based on photographs? Please specify in the methods-section.

Reply: Three of radiation oncologists and two surgeons evaluated the patients' photographs in the conference (panel).

Changes in the text: (Page 6, line 20)

Assessment of endpoint: Cosmetic outcome was evaluated at at least 12 months after radiation using the Harvard/NSABP/RTOG Breast Cosmesis Grading Scale. Photographs of patients were taken in two positions, two arms up above head and arms at the waist. All photographs were assessed by the panel of three radiation oncologists and two surgeons.

Comment 4: Why was toxicity only assessed after 3 and 6 months? Assessing acute toxicity after 3 months is not representative of the course of radiation dermatitis for example, which reaches its peak close to the end of treatment. Late toxicity such as fibrosis typically occurs after a longer period of follow up. Please comment.

Reply: We have looked back to our data and would like to show the data of toxicity (acute and late) after whole breast irradiation. The data we attached in the prior paper was the toxicity

after IORT , where some of patients had not had whole breast irradiation yet. We defined acute toxicity as a toxicity that occur within 3 months after whole breast radiation. Seventy-four percent of the patients was evaluated acute toxicity at the end of the radiation course, 18.5% was evaluated at 1 month after radiation and 7.4% had the data at 2-3 month after radiation complete. For late toxicity, we had the data of evaluating patients at one year and three years after whole breast radiation and presented in Table2. For cosmetic outcome, median time of cosmetic evaluation is 41 months and 74.1% of the patients was evaluated at more than 2 years after radiation.

Changes in the text:

Assessment of endpoint: Acute toxicity was evaluated at the end of whole breast irradiation and late toxicity was evaluated at one and three years after whole breast irradiation. (Page 6, line 19)

Results: (Page 8, line 5)

Table 2 Acute and late skin toxicities of the patients in the study

Group of patients	Acute toxicity (N, (%))			Late toxicity at 1 year (N, (%))			Late toxicity at 3 year (N, (%))		
	Grade 0	Grade 1	Grade 2	Grade 0	Grade 1	Grade 2	Grade 0	Grade 1	Grade 2
Received chemotherapy for 3–6 months	N = 57			N = 57			N = 52		
	19 (33.3)	32 (56.2)	6 (10.5)	24 (42.1)	33 (57.9)	0	8 (15.4)	37 (71.1)	7 (13.5)
No adjuvant chemotherapy	N = 24			N = 24			N = 23		
	4 (16.7)	17 (70.8)	3 (12.5)	8 (33.3)	16 (66.7)	0	2 (8.7)	18 (78.3)	3 (13.0)

Comment 5: In the table2, the authors separately report the toxicity rates depending on the duration of adjuvant chemotherapy. From my point of view, there is no rationale. I would suggest to combine the two groups. Percentages should be reported in relation to the size of the subgroup (for example: line 1 grade 0 acute toxicity 8 out of 42 patients = 19%, not 9.2%)

Reply: We totally agree with you

Changes in the text: We combined two groups of patients who had received adjuvant chemotherapy.

Minor remarks:

1. The authors state that mastectomy and breast-conserving surgery yield identical outcomes in terms of local recurrence. This is not entirely true, as shown for example by the Milan I - trial, which is also cited by the authors (ref 7). Please rephrase.

Changes in the text: (page5, line2)

Radiotherapy after breast conserving-surgery (BCS) has shown to be equivalent, in terms of the survival outcomes.

2. Since the accelerated partial breast irradiation usually refers to the exclusive treatment of the tumor bed, I would not refer to APBI in this setting.

Changes in the text:

Abstract (page3, line7)

Background: I would remove the sentence " Intraoperative radiation therapy (IORT) is one of the accelerated partial breast irradiation techniques" and add this sentence " Various modalities have been used for tumor bed boost irradiation.

Full paper (page5, line6)

Introduction: I would remove the sentence "

Accelerated partial breast irradiation (APBI) delivers a highly effective dose of radiation while greatly reducing the treatment time. Various APBI techniques have been developed under phase I–III clinical studies, including multicatheter interstitial brachytherapy, balloon catheter brachytherapy, conformal external beam radiation therapy and intra-operative radiation therapy (IORT). APBI has been proposed as a radiation treatment option for selected early stage of breast cancer patients. "

to this sentence

"Tumor bed boost irradiation can be achieved by various techniques such as interstitial brachytherapy, external beam radiotherapy and intraoperative radiotherapy. IORT could be performed with either electron beams or photon beams and delivers a single dose radiation therapy to the tumor bed during surgery."

3. The literature regarding intraoperative boost radiotherapy should be discussed in greater detail. Several reports with long term follow up for 50 kv and electrons have been published and should be mentioned Kaiser et al IJROBP 2018. Pez et al. Strahlenther Onkel 2020.

Reply: I have added more data of those related and updated studies in the discussion part.
change in the text : (page 20 table 3) , (page9 line 11)

4. Page 4, line 18: I would suggest to replace "INTRABEAM SYSTEM" with "low energy photon intraoperative boost irradiation". In the methods section, complete name and manufacturer of the device should be listed.

Changes in the text: (page5 line 14, page6 line6)

Introduction: We assessed the local recurrence, OSR, complication and cosmetic outcome in early breast cancer patients who received the low energy photon intraoperative boost irradiation after BCS in our institution.

Methods

Radiation treatment planning and technique

The low energy photon (INTRABEAM 600, Carl Zeiss Meditec AG, Oberkochen, Germany) was used in the surgical cavity immediately following tumor removal.

5. Page 10, line 13-17: From my point of view, it does not make sense to compare the 3 year OS-rate of this study to the 20 year OS data from the EORTC trial. Please rephrase or remove.

Reply: I would like to change the data of EORTC trial at 20-year OSR to 5-yr OSR which will be cited as the reference number 23.

Changes in the text: (Page9 line 13)

Discussion: The 3-year OSR in this study was 89.8%, which was not markedly different to in those in the Lyon (5-year OSR was 92.9%) and EORTC 22881-10882 (5-year OSR of 91%) trials.