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Original Article

Breast cancer outcomes after skin- and nipple-sparing mastectomy in *BRCA* pathogenic mutation carriers versus non-*BRCA* carriers

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ABSTRACT

Our previous study on breast cancer *BRCA* carriers disclosed a high local recurrence (LR) rate in patients who underwent skin sparing (SSM) or nipple sparing mastectomy (NSM) without postoperative radiation therapy (RT), compared to breast conservation surgery or mastectomy with RT. The current study compares the LR rates in *BRCA* versus non *BRCA* carriers after SSM/NSM in relation the receipt of RT.

Methods: The study was approved by the institutional ethics committee. Data collected included patient- (e.g., age), tumour- (e.g., subtype, stage), and treatment-related factors and outcomes. LR was defined as ipsilateral chest wall recurrence. P value ≤ 0.05 was considered statistically significant.

Results: A total of 255 patients (127 *BRCA*, 128 non-*BRCA*) were included. Patients who did not receive RT had an earlier disease stage (most N0). No differences were found for LR rate in non-*BRCA* versus *BRCA* groups per involved breast and per patient. Comparing the subgroup of patients who did not receive RT, there were no statistically significant differences in LR between non-*BRCA* versus *BRCA* (p-value > 0.05). Similarly, there were no significant differences in LR for the subgroup of patients who did receive RT (p-value > 0.05). Regardless of *BRCA* status, patients who received RT had significantly lower LR rates. No differences in overall survival were noted between the groups.

Conclusions: Our results confirm high LR rates after SSM and NSM in patients who are not treated with RT, independent of *BRCA*-status. This mandate further investigation, as previous studies did not show a benefit of postmastectomy RT in the early breast cancer stage of those patients.

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Introduction

More than two decades ago, several randomised controlled trials demonstrated the non-inferior survival after breast conservation surgery (BCS) and radiation therapy (RT), (BCS with RT is regarded as breast conservation therapy, BCT) compared to mastectomy for women with early breast cancer, notwithstanding more local recurrences (LR) in the BCT group [1–3]. Improvements in breast cancer management including screening programs, diagnostic imaging, systemic therapy, and locoregional therapies including surgery and RT, have led to significant reductions in LR (ipsilateral in-breast or chest wall) rates after BCT, with current rates ~ 2.5 % at 10 years [4,5]. Moreover, recent observational studies, as opposed to early trials, reported improved outcomes following BCT compared to mastectomy for early breast cancer stage (stage I-III) [6–12].

In our previous retrospective study [12] we evaluated LR as *first* event in breast cancer *BRCA* pathogenic variant (PV) carriers according to locoregional therapy (BCT, mastectomy, mastectomy with RT). The mastectomy procedures were skin sparing (SSM) or nipple sparing (NSM) with immediate breast reconstruction (either direct to implant or tissue expander to implant). Due to the retrospective nature of the cohort study, the breast cancer stage was not balanced between the groups, and the mastectomy without RT group had an earlier disease stage (i.e., node negative, lower tumour stage, thus no indication for RT). Nevertheless, the cumulative incidence of LR as *first* failure was significantly higher in the SSM/NSM who did not receive postoperative RT compared to BCT (15.3 % versus 5.2 %, $p = 0.049$). In contrast, no LR events occurred in the SSM/NSM group who received RT. The rate of LR reported for the SSM/NSM group without RT was significantly higher than reported in the literature and occurred early after surgery [12].

To evaluate if the high rate of LR in the breast cancer *BRCA* cohort after SSM/NSM without RT is unique to *BRCA* patients, we collected the data of a consecutive cohort of non-*BRCA* patients who underwent SSM/NSM and compared breast cancer outcomes, mainly LR, as *first* event.

Methods

The study was approved by the ethics committee of the Sheba Medical Center. This work was done as part of the requirements for a medical degree (MD) degree for Tel Aviv University (TAU), and the study design was approved a priori by reviewers from TAU. The database created is part of the data collection and curation for the BRILLIANT study [13] and partly used for the SECRET study (NCT06130111) [14].

The updated data of *BRCA* breast cancer patients were retrieved from the oncogenetic unit's database at Sheba Medical Center as previously described [12]. The database includes all *BRCA* patients that were followed-up at the oncogenetic unit (not necessarily operated at Sheba Medical Center)[12]. To identify the non-*BRCA* group we utilized MDClone ©, a programme capable of rapidly accessing real world structured data from different electronic medical records (EMR) (https://www.mdclone.com/) and create a datasheet according to the requested information. The MDClone was queried for "mastectomy," with date of procedure 2009–2022, and including all procedures done at Sheba Medical Center. The EMR prior to 2012 was lacking information, therefore we excluded patients who were diagnosed/operated prior to 2012. We verified that the same patient was not included in both cohorts (i.e., marked as non-*BRCA* via MDClone and listed in the *BRCA* cohort). Data collected for both cohorts included patient characteristics, genetics, breast cancer characteristics, treatments (systemic, surgery, RT), date and site of recurrence, and status at last follow-up. Quality assurance of extraction and collected data was done by the study supervisors (RBM, OKP).

The analysis included patients older than 18 years, diagnosed with breast cancer and who underwent SSM/NSM for treatment of primary breast cancer with at least 6 months of clinical follow-up. *BRCA* breast cancer patients who underwent a mastectomy without RT, and patients who underwent a mastectomy following a lumpectomy without RT due to a positive result of a test for the *BRCA* PV carriers were evaluated in the no postmastectomy RT group. Patients who underwent mastectomy without reconstruction, SSM/NSM after breast cancer recurrence, or clinical T4 regardless of response to primary systemic therapy, were excluded from the study. Fig. 1 summarizes participants' flowchart.

Statistical analysis

Descriptive analyses were performed using descriptive statistics for parametric variables, and median with range for non-parametric

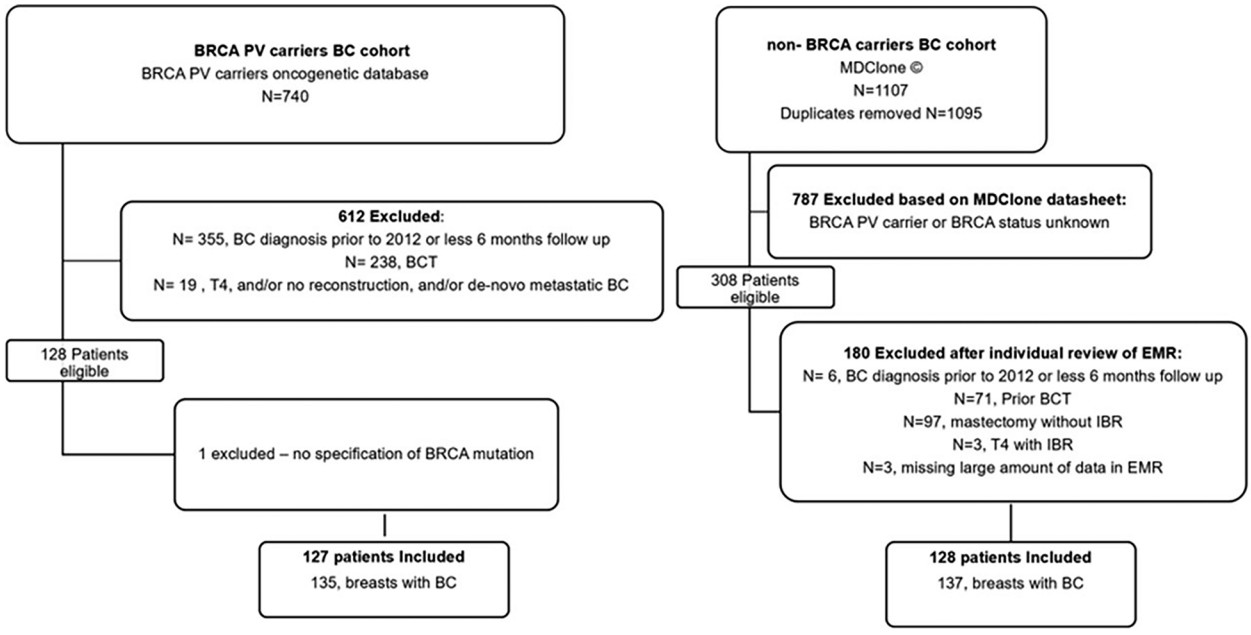

Fig. 1. summarizes participants flowchart. PV- Pathogenic variant; BC – Breast cancer, EMR – Electronic medical records, BCT- Breast conservation surgery with radiation therapy; IBR- Immediate breast reconstruction; T4 – Tumour stage 4, per TNM.

Table 1
The clinicopathologic and treatment characteristics of the non-*BRCA* group versus the *BRCA*-group.

VARIABLE	Non – *BRCA* 137 breasts (in 128 patients)	*BRCA* 135 breasts (in 127 patients)	p-value
Age years, SD (range)	48.3 ± 9.9 9 (26.9–71.4)	42.2 ± 10 (25.3–68.2)	**<0.001**
Subtype			**<0.001**
ER pos, PR pos, HER2 neg	52.6 %	30.9 %	
ER pos, PR neg, HER2 neg	18.2 %	10.9 %	
ER pos, HER2 pos	11.7 %	2.9 %	
ER neg, HER2 pos	9.5 %	0.7 %	
Triple negative	6.6 %	52.2 %	
Breast cancer breast side (left)	53.4 %	46.6 %	0.33
Histology			**<0.001**
IDC	13.9 %	69.6 %	
ILC	10.9 %	0.7 %	
DCIS	11.7 %	16.3 %	
IDC + DCIS	59.9 %	10.8 %	
IDC + ILC	2.2 %	1.5 %	
ILC + DCIS	1.5 %	0	
Tumour Grade			**<0.001**
1	2.2 %	0.7 %	
2	54 %	22.2 %	
3	31.4 %	71.1 %	
T stage			**0.011**
0	10.2 %	17 %	
1	40.1 %	44.4 %	
2	32.8 %	26.7 %	
3	16.8 %	8.9 %	
N stage			0.059
0	53.5 %	65.2 %	
1	36.5 %	22.2 %	
2	5.8 %	3.7 %	
3	4.4 %	6.7 %	
ECE (yes)	8.8 %	4.6 %	0.162
Number of involved LN			**>0.001**
0	60.6 %	81.5 %	
1–3	32.1 %	8.1 %	
>4	7.3 %	9.6 %	
LR	5.8 %	9 %	0.327
Radiation therapy (yes)	51.8 %	36.3 %	**0.011**
Chemotherapy (yes)	54.7 %	63 %	0.169

ER = Estrogen receptor, PR = Progesterone receptor, LR = Local recurrence, Ipsilateral breast cancer recurrence; ECE = Extracapsular nodal extension, IDC = Invasive ductal carcinoma, DCIS = Ductal carcinoma in-situ, ILC = lobular carcinoma. p-value of ≤ 0.05 was considered statistically significant (bold).

variables, including mean, median and range with standard deviation (SD). LR as the *first* failure included all ipsilateral chest wall recurrences, not related to subtype or histology of the breast cancer, without synchronous occurrence of distant failure, while concurrent regional failure was allowed. Regional recurrence without LR was not counted as LR. Disease free survival (DFS) was defined as the time after the end of therapy without any breast cancer event, LR, regional or distant. The X^2 test was applied for testing the statistical significance of the categorical differences between the groups, Kruskal–Wallis test was applied for ordinal variables, T-test for continuous variables with parametric distribution and Mann-Whitney for a-parametric distribution. Hazard ratio (HR) was calculated using COX regression model in both univariable and multivariable approach. Survival analysis using the Kaplan-Meier survival function curve was applied for testing the statistical significance of the difference in DFS between the groups. The HR for survival was calculated and estimated via the Cox regression model. The time-to-event endpoints were censored at the time of competing events. The following events were considered as competing events: distant recurrence, non-breast cancer, contralateral breast cancer treated with systemic therapy, and overall survival. All tests were 2-tailed T-test, and a P value of ≤ 0.05 was considered statistically significant. The statistical analysis was done using SPSS version 29 (IBM SPSS®, SPSS Inc, Chicago, Illinois).

Results

A total of 255 breast cancer patients (127 *BRCA*, 128 non-*BRCA*) were included in our study, with a total of 272 breasts with cancers (i.e., synchronous cancers: 135 breasts in *BRCA group*, 137 breasts non-*BRCA* group). Table 1 summarizes the clinicopathologic and treatment characteristics of the study population. The median age of the non-*BRCA* group was significantly older (48 years) compared to the *BRCA* group (42 years) and the groups varied significantly in tumour histopathology, molecular subtype, and breast cancer stage (Table 1). Chemotherapy (pre or postoperative) was given to 54.7 % of the non-*BRCA* group versus 63 % in the *BRCA* group ($p > 0.05$), and postmastectomy RT in 51.8 % versus 36.3 % ($p < 0.05$), respectively. For both patient groups together, postmastectomy RT was applied in 21.4 % T0-1 and 75 % of T2-3 ($p < 0.001$). Similarly, only 9.3 % of N0 received postmastectomy RT compared to 96.3 % of the patients with N1-3 ($p < 0.001$). Correspondingly, 44.8 % of the patients with T1 or 42.6 % with N0 received chemotherapy versus 76.8 % of the patients with T2-3 and 80.7 % with N1-3 ($p < 0.001$). There was a high correlation between T- and N-stage and receipt of chemotherapy and postmastectomy RT.

At a median follow up of 58.5 month (10.5–125.5) for non-*BRCA* and 62.5 months (7.5–136.5) for *BRCA* patients, there were no significant differences in the cumulative incidence rates of LR: 5.8 % in the non-*BRCA* versus 8.7 % in the *BRCA* group ($p > 0.05$).

Figs. 2A and B shows the Kaplan-Meier curve for LR in the non-*BRCA* versus the *BRCA* groups per breast with cancer (i.e., bilateral breast cancer was counted twice, and the analysis was performed per breast) (2A) and per patient (2B). Table 2 summarizes the clinicopathologic and treatment characteristics of the patients and breasts with/without LR.

As indicated above, the group who did not receive postmastectomy RT had earlier breast cancer stage: most had T0-2 N0 breast cancer, except two patients in the non-*BRCA* group who had a T3N0 breast cancer and two patients who had positive nodes (one patient in each group). Comparing the subgroup of patients who did not receive RT in non-*BRCA* versus *BRCA* groups, there were no statistically significant differences in LR rate ($p = 0.54$). *BRCA* status did not influence LR rates after adjusting for age, grade, subtype, T stage, number of involved lymph nodes, RT and chemotherapy in the multivariable analysis (HR = 1.12, 95 % confidence interval, CI, 0.76–2.8, $p = 0.43$). The group who received postmastectomy RT had T1-3 with nodal involvement except for seven patients in the non-*BRCA* group and five in the *BRCA* group who had N0 disease. There were no significant differences in LR rates for a subgroup of patients who did receive RT in the non-*BRCA* versus *BRCA* groups ($p = 0.25$).

Of the 272 breast cancer breasts of the whole cohort (*BRCA*, non-*BRCA*), 20 (7.35 %) LRs occurred, significantly less in those who received RT ($p = 0.01$) (Fig. 3).

At univariable analysis for factors influencing LR, three variables were found significant: T stage (T0-1 vs. T2-3: HR = 0.149, 95 %CI, 0.034–0.648, p = 0.011), postmastectomy RT (HR = 0.138, 95 %CI, 0.03–0.59, p = 0.008) and chemotherapy (HR = 0.359, 95 %CI, 0.14–0.7, p = 0.029). Those factors remain significant for reducing LR risks, when adjusted to age, grade, subtype and *BRCA* status in a multivariable analysis: T stage (T0-1 vs. T2-3: HR = 0.34, 95 %CI, 0.12–0.88, p = 0.026), postmastectomy RT (HR = 0.67, 95 %CI, 0.31–0.91, p = 0.036), chemotherapy (HR = 0.76, 95 %CI, 0.54–0.93, p = 0.042). No significant overall survival differences were found between non-*BRCA* versus *BRCA* groups (p = 0.81) (Fig. 4).

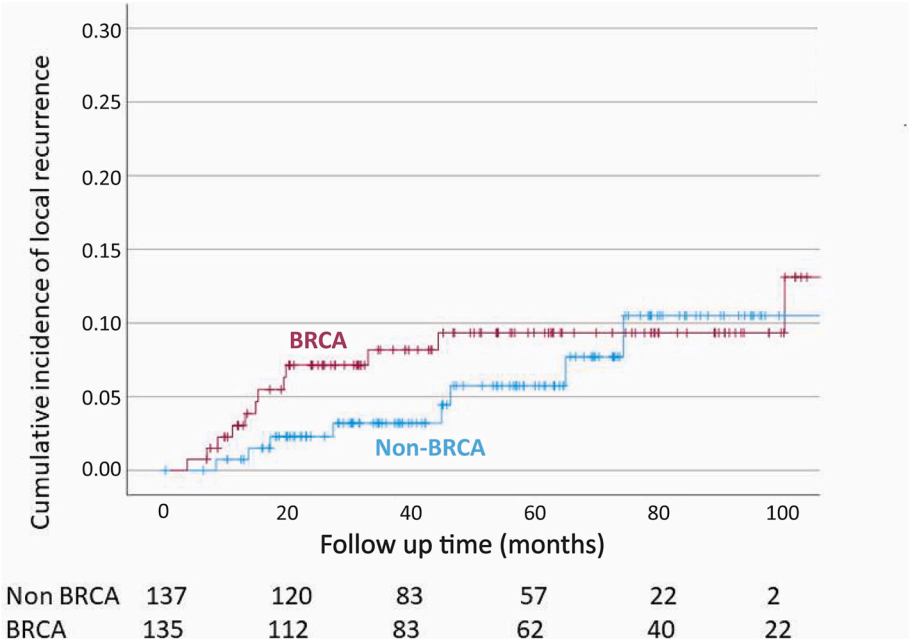

Fig. 2A. Kaplan-Meier curve for cumulative incidence of local recurrence per breast cancer breast (n = 272 breasts) in the *BRCA* vs non BRCA carrier (p-value > 0.05).

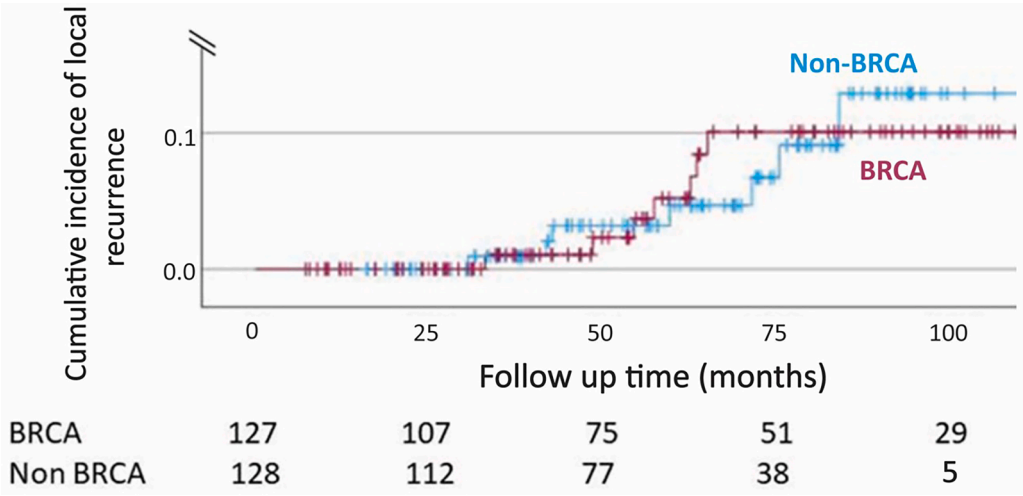

Fig. 2B. Kaplan-Meier curve for cumulative incidence of local recurrence per patient (n = 255) in the *BRCA* vs non *BRCA* carrier (p-value > 0.05).

Discussion

BRCA PV mutation carriers are at risk for developing breast cancer, with a cumulative risk of 72 % for *BRCA1* and 69 % for *BRCA2* by the age of 80 years [15]. SSM/NSM are considered as a safe option, both as a risk reducing procedure or as a therapeutic intervention in both *BRCA* PV carriers and non-*BRCA*-carriers [16–20]. Our previous study including only *BRCA* PV carriers reported that the cumulative incidence of LR as *first* failure was significantly higher in the SSM/NSM without post-mastectomy RT cohort compared to both SSM/NSM with RT and BCT [12]. As most of the LR occurred within two years after surgery we assumed that the main driver of early LR was the presence of residual tumour cells within the skin flap and the residual breast tissue [21]. In addition, we were concerned that, since SSM/NSM tend to have more residual breast tissue [10,13,22], these LR rates might be related to new primaries in a high risk population such as *BRCA* PV carriers [23].

The current study aimed to evaluate the differences in LR rates as *first* event (not regional recurrences) after SSM/NSM in the breast cancer *BRCA* cohort compared to non-*BRCA* carriers [24]. As a consecutive cohort, the study groups were unbalanced: the *BRCA*-patients were younger, had more invasive high grade ductal histology, triple negative subtype, and were less likely to be treated with chemotherapy or RT due to less advanced breast cancer stage compared to the non-*BRCA* group. Chemotherapy and postoperative RT remained significant for reducing the risk of LR, after adjusting to age, grade, subtype, and *BRCA* status. There were no differences in overall survival between groups even though the non-*BRCA* had more advanced breast cancer stage. A recent publication of an unplanned analysis from the EORTC 22922/10925 trial according to different treatment components, showed that more advanced breast cancer stage (T and N stage) was associated with worse overall survival, regardless of treatment [25]. However, intensified locoregional therapy (surgery and RT) was associated with less LR, regardless of breast cancer stage [25].

Locoregional recurrences after SSM/NSM were reported in

Table 2
The clinicopathologic and treatment characteristics of the patients with/without local recurrence.

VARIABLE	LR 20 breasts	No LR 252 breasts	p − value
Age years, (range)	45.5 (25–79)	42.8 (28.3–65)	0.271
BRCA (yes)	60 %	48.6 %	0.327
Subtype			0.129
ER pos, PR pos, HER2 neg	43.5 %	26.3 %	
ER pos, PR neg, HER2 neg	14.9 %	15.8 %	
ER pos, HER2 pos	6.9 %	15.8 %	
ER neg, HER2 pos	4.4 %	10.5 %	
Triple negative	30.2 %	31.6 %	
Breast cancer breast side (left)	15 %	51.8 %	**0.002**
Histology			0.685
IDC	55 %	40.3 %	
ILC	0 %	6.3 %	
DCIS	20 %	13.8 %	
IDC + DCIS	25 %	36.4 %	
IDC + ILC	0 %	2 %	
ILC + DCIS	0 %	0 %	
Tumour Grade			0.455
1	0 %	1.7 %	
2	52.6 %	41 %	
3	47.4 %	57.2 %	
T stage			**0.014**
0	16.7 %	13.9 %	
1	72.2 %	40.6 %	
2	11.1 %	31.5 %	
3	0 %	13.9 %	
N stage			**0.043**
0	84.2 %	57.8 %	
1	5.3 %	31.5 %	
2	10.5 %	4.4 %	
3	0 %	6.4 %	
ECE (yes)	5.3 %	6.8 %	0.793
Number of involved LN			0.086
0	90 %	69.4 %	
1–3	0 %	21.8 %	
>4	10 %	8.7 %	
Radiation therapy (yes)	10 %	47 %	**0.001**
Chemotherapy (yes)	35 %	60 %	**0.029**

ER = Estrogen receptor, PR = Progesterone receptor, LR = Local recurrence, Ipsilateral breast cancer recurrence; ECE = Extracapsular nodal extension, IDC = Invasive ductal carcinoma, DCIS = Ductal carcinoma in-situ, ILC = lobular carcinoma. p-value of ≤ 0.05 was considered statistically significant (bold).

retrospective studies to have an overall rate of 0–4.4 %, depending on the follow up duration [26–28]. A *meta*-analysis did not find significant differences in breast cancer outcomes including LR and locoregional recurrences between immediate breast reconstruction versus delayed, and recommended that patients should be considered for immediate breast reconstruction if they desire and are eligible per disease [28]. SSM/NSM and immediate reconstruction are contraindicated in patients where a radical resection of the tumour is not possible or in patients with inflammatory breast cancer, in whom skin and dermal lymphatics are extensively involved, regardless of response to primary systemic therapy [26–28]. If the preoperative imaging shows that the tumour (invasive or DCIS) is located in proximity to the skin, the surgery should be planned to remove all tumour foci, possibly including the overlying skin, to assure a radical resection of the neoplasia [26,27]. Tramm et al, reported cases of pure DCIS recurrence after SSM/NSM. A histopathological analysis showed that residual pure DCIS can be found in the breast glands within the subcutaneous tissue including the fascia (within the skin flap). An evaluation of the preoperative mammography showed microcalcifications going up to the skin [21]. Therefore, it is essential to planning the surgical procedure to have a radical resection and mark the superficial margins of the mastectomy specimen to allow for histopathology evaluation and reporting [21,29]. Orientation of the high-risk region will also allow that the radiation oncologist can assure sufficient dose coverage of the volumes that might bare residual tumour cells and residual breast tissue in case there is an indication for RT [30,31].

We recognize that our study has limitations, and these outcomes might not necessarily reflect the outcomes in all breast cancer centres. It is a single institution retrospective with unbalanced study groups. We did not evaluate the LR rate after simple or total mastectomy. Due to the retrospective nature of the study, the differences between SSM versus NSM, surgeons' expertise, breast cancer factors such as tumour focality, lymphovascular invasion, and tumour distance from the skin, nor the effect of different systemic therapies on LR can be evaluated. In addition, all margins were reported as negative, however, the superficial margins were not reported/specified in the reports. Radiation therapy was not reported according to the European Society for Radiotherapy and Oncology (ESTRO) essential requirements for reporting radiation therapy [32]. Nevertheless, the number of patients collected is high for this specific population (*BRCA* PV carriers) undergoing a specific surgical procedure. In addition, similar to our previous publication, we report a high LR rate in patients in breast with early breast cancer stage after SSM/NSM in whom postmastectomy RT is not indicated. More important, our results show that the high LR rates are most probably not related to the *BRCA* status. These finding are concerning as the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [33] *meta*-analysis did not report a benefit of applying postmastectomy RT in patients with node- negative breast cancer who underwent total mastectomy or modified radical mastectomy, even though the studies included in the EBCTCG had systemic therapy regimens that were less effective compared to systemic therapies available nowadays [33]. Our main concern is that the discrepancy with our study might be a result of the more extensive surgical resection done in the trials included in the EBCTCG *meta*-analysis which included non-skin sparing procedures (mostly modified radical mastectomy) and included axillary lymph node dissection [33]. We assume that the LRs are a result of residual breast tissue, and possibly tumour cells within the flap and/or dermal lymphatics, after SSM/NSM [13,14,22,34]. Also, the amount of residual breast tissue is related to surgeon's expertise in performing the procedure [35,36]. Therefore, we recommend that all treatment's aspects, including the type of surgery will be planned within the framework of a multidisciplinary meeting while thoroughly reviewing the diagnostic imaging, and discussing the pitfalls of each approach. Tumour location, focality and proximity to the skin/nipple should be considered for planning the surgical details including the optimal site of the surgical incision, and whether or not to resect part of the skin above the reference tumour. As radiation therapy raises the risk of complications and implant loss [29,37], it should be used only when indicated and not to compensate for uncertainty or for anticipated poor outcomes (like positive margins) due to poor planning of surgical techniques. In the meanwhile, we continue our work in collaboration with different groups to improve the outcomes of breast cancer patients who underwent mastectomy and are planned for receiving postmastectomy RT.

CRediT authorship contribution statement

Nir Moshe: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ory Haisraely:** Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Ofer Globus:** Writing – review & editing, Software, Resources. **Renata Faermann:** Writing – review & editing, Visualization, Resources. **Narmeen Abu-Shehada:** Writing – review & editing. **Debbie Anaby:** Writing – review & editing. **Einav Gal Yam:** Writing – review & editing. **Nora Balint Lahat:** Writing – review & editing. **Shira Galper:** Writing – review & editing. **Tehillah Menes:** Writing – review & editing. **Josef Haik:** Writing – review & editing. **Miri Sklair-Levy:** Writing – review & editing. **Cecille Oedegaard:** Writing – review & editing. **Thorsten Kuehn:** Writing – review & editing. **Monica Morrow:** Writing – review & editing, Supervision. **Philip Poortmans:** Writing – review & editing, Supervision. **Rinat Bernstein-Molho:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization.

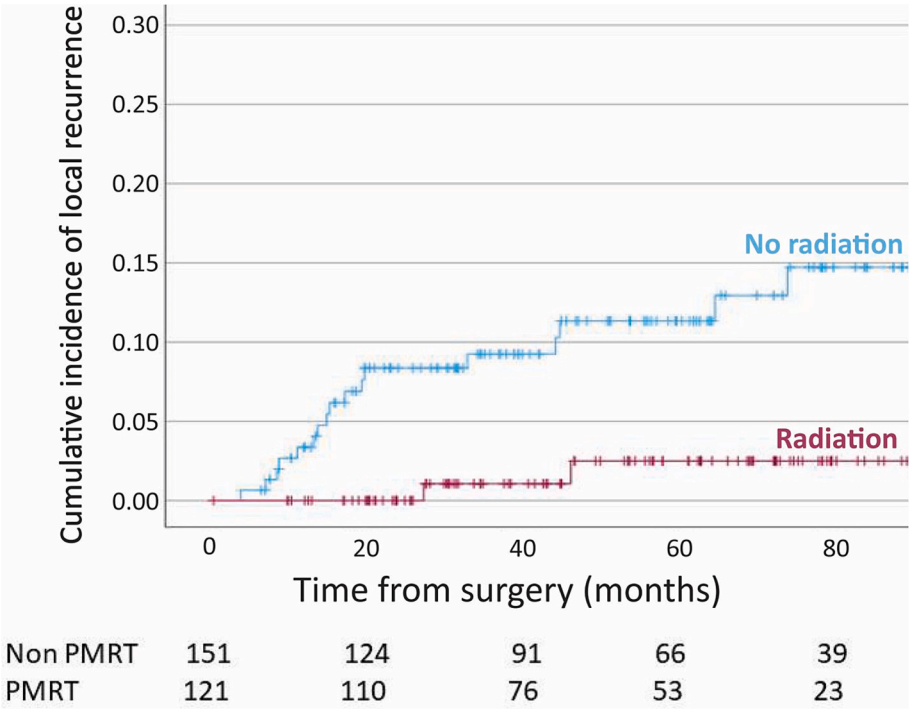

Fig. 3. Kaplan-Meier curve for local recurrences comparing postmastectomy radiation therapy (PMRT) versus not, irrespective of *BRCA* status, per breast (n = 272) (p-value = 0.01).

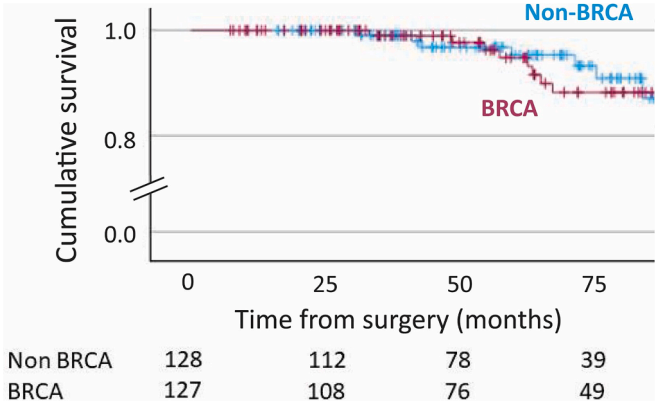

Fig. 4. Kaplan-Meier curve for overall survival in the *BRCA* vs non-*BRCA* carriers, per patient (n = 255) (p-value > 0.05).

Orit Kaidar-Person: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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