Review Article

Radiation therapy in breast cancer: a narrative review on current standards and future perspectives

Orit Kaidar-Person[1,2,3], Birgitte V. Offersen[4,5]

[1]Breast Cancer Radiation Therapy Unit, Sheba Medical Center, Ramat Gan, Israel; [2]Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel; [3]GROW-School for Oncology and Developmental Biology (Maastro), Maastricht University, Maastricht, The Netherlands; [4]Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark; [5]Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark

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Correspondence to: Orit Kaidar-Person, MD. Radiation Oncology, Sheba Medical Center, Ramat Gan, Israel. Email: orit.kaidarperson@sheba.health.gov.il.

Abstract: Mastectomy and reconstructive procedures have been refined over the decades, allowing for aesthetic outcomes close to the native breast shape and in symmetry with the contralateral intact breast or even to improve breasts appearance and symmetry. Similarly, improvements in radiation oncology can help reduce treatment related toxicity and improve outcomes. However, postmastectomy radiation therapy (PMRT) is associated with poor cosmetic outcomes and increased rate complications in patients who undergo breast reconstruction. Radiation therapy planning should be guided by disease stage, risk of recurrence, correct definition of the target volumes and treatment objectives. Currently, there are guidelines endorsed by European Society for Radiotherapy and Oncology (ESTRO) for target volume delineation for breast cancer and elective nodal volumes, including after immediate reconstruction. Correct target volume delineation, along with meticulous radiation planning, total dose and fractionation, dose homogeneity, and organs at risk (OAR) doses are significant for reducing radiation-induced toxicity. Currently, tremendous efforts are done by different groups to improve aesthetic outcomes without compromising disease outcomes in breast cancer patients who are candidates for mastectomy and radiation therapy. The current paper summarizes key principles in PMRT, considering new surgical techniques for immediate breast reconstruction and new, partly experimental radiation techniques including future trials and proton beam irradiation.

Keywords: Breast cancer; mastectomy; reconstruction; radiation; radiotherapy; postmastectomy

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Introduction

Breast cancer treatment should be supported by a multidisciplinary team from time of breast cancer diagnosis until end of follow up (1,2), and the team should recommend therapy based on evidence-based guidelines. This approach may not-only increase patient's satisfaction from treatment but also facilitate treatment decision and management and possibly lead to a better outcome (2). Careful evaluation by the multidisciplinary team including breast radiologists, plastic and breast surgeons, pathologists, radiation, and medical oncologists should guide the treatment approach to improve outcomes (3). Factors such as tumour related findings (e.g., tumour size, molecular subtype), distance of the tumour foci from skin/subcutaneous and/or nipple areola complex, benefit from systemic therapy (pre *vs.* postoperative), breast size and shape, tumour-size/breast-size ratio and location of the tumour lesion within the breast,

patient's comorbidities, body habitus and contralateral breast shape, patient's wishes and expectations, and surgeon's expertise, have significant implications on the treatment approach (3).

Surgical techniques change constantly to improve aesthetic results (4-6). Mastectomy and reconstructive procedures have been refined over the decades, allowing for aesthetic outcomes close to the native breast shape and in symmetry with the contralateral intact breast or even to improve breasts appearance and symmetry (4). Furthermore, in many cases this can be achieved at the time of the mastectomy [i.e., immediate breast reconstruction (IBR)] (7). Nevertheless, the most important notion guiding the team is to maintain oncological safety as a priority and clearly communicate it to the patient. Thus, the treatment approach should not lead to a delay or compromise on oncological treatment (8).

For years, IBR was considered a contraindication if postmastectomy radiation therapy (PMRT) was planned, mainly due to a concern of reconstruction failure and major complications (9,10). Lately, the number of patients receiving PMRT in the setting of IBR increases (11-13). In this changing reality, along with advances in radiation therapy techniques, we should work together to improve PMRT outcomes in the setting of mastectomy and IBR (14,15). The current paper summarizes key principles in radiation therapy and PMRT, considering new surgical techniques for IBR and new, partly experimental PMRT techniques. We present the following article in accordance with the Narrative Review reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-16/rc).

Key principles of current radiation techniques

The key principles for any radiation therapy planning is to clearly define radiation "target volumes" (i.e., areas at risk of subclinical tumour spread), organs at risk (OAR) (i.e., healthy tissues placed in proximity to the target volume whose irradiation could cause damage), dose and fractionation. These should be also applied in the setting of PMRT (16-18).

The radiation oncologist should clearly define the radiation planning objectives, considering patient, disease, and treatment related factors. Patient related factors such as age and comorbidities can dictate the dose constraints to various OARs and/or planning objectives for the target volume coverage (e.g., compromising medial coverage if the tumour bed is lateral, to reduce the cardiac dose) (16,17,19). By performing a mindful physical examination at initial patient visit prior to radiation planning and considering the physical properties of the radiation beam (photons *vs.* electrons *vs.* protons), the radiation oncologist can to some extent predict potential side-effects and difficulties in covering target volumes/avoiding OARs (e.g., the area of infra-mammary fold, medial contralateral breast, heart, lung) and which radiation technique should provide a potential advantage in treatment (fewer side effects with adequate target coverage).

Correct delineation of the target volumes in some cases can reduce the OARs doses (20).

When deciding on radiation technique, the radiation oncologist should keep in mind the different dose distribution, low *vs.* high dose regions and exposure of OARs, and uncertainties in treatment planning, as these may differ significantly by different techniques such as tangential alignment versus volumetric intensity modulated radiation therapy (IMRT) with potential low dose bath. The radiation technique should be decided after considering pro and cons of each approach. A recent publication led by physicists and clinical oncologists from the Danish Breast Cancer Group (DBCG) in collaboration with a multidisciplinary group of international experts nicely shows how different radiation techniques used for planning PMRT cases with implant-based IBR can significantly differ in dose distribution, mainly exposure of OARs, even when planning the same patient case and the same target volumes (16). Therefore, radiation planning should be done meticulously, and decisions should be taken with consideration of disease control and reducing potential toxicity.

PMRT indications and therapeutic value

In the setting of mastectomy, nodal disease is the main indication for PMRT (21). The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis is a landmark publication to establish the role of PMRT in reducing the rate of locoregional recurrences (LRR) as first event after 10-year. The impact of PMRT in reducing the 10-year rate of LRR was correlated with nodal disease stage. For nodal disease stage pN0, the LRR rate was 1.6% for the no-PMRT group versus 3% in the PMRT-group; for the pN1-3 group the LRR rate was 20.3% for the no-PMRT group versus 3.8% for the PMRT group; and for the pN4+ group the LRR rate was 32.1% for the no-PMRT group versus 13% for the PMRT group (21,22). Therefore, for many years, advanced nodal involvement remained the

key indication for PMRT (22,23). However, current trials support de-escalation of surgical intervention in patients with low nodal tumour load, and there is an increased application of PMRT to eradicate potential subclinical disease within the regional lymphatics in patients treated with less radical axillary lymph node dissection (24,25). Additionally, there is an increase in the rate of patients who are eligible for breast conserving therapy, but opt for mastectomy and IBR, leading to increased number of PMRT in the setting of IBR. Even though there is no robust data from randomised controlled trials for the use of sentinel node biopsy instead of axillary dissection in mastectomy patients, nor that regional nodal irradiation is sufficient in mastectomy patients with low nodal tumour burden, some of the data guiding this approach is extrapolated from enrolling patients after breast conserving therapy. The landmark EBCTCG PMRT publication (21) also showed the impact of PMRT to the chest wall and regional lymph nodes in 870 patients, with T3 (>5 cm) pN0 who underwent axillary sampling. PMRT to chest wall and regional lymphatics showed statistically significant advantage for reducing the 10-year risk of LRR or any recurrence and a trend towards reducing the breast cancer mortality or any mortality at 20-years. Therefore, along with trials that established the role of regional irradiation instead of axillary dissection in patients with low-nodal disease burden, the EBCTCG subgroup analysis provides additional support for this approach (21).

Furthermore, other clinical and histological factors were suggested to be associated with a high risk for LRR after mastectomy. These include young age at diagnosis (26-29), T3 tumour (30-35), tumour muscle invasion (35,36), high tumour grade (29,35,37), lymphovascular invasion (28,35,37), negative hormone receptor (29-31,38,39), extracapsular nodal tumour extension (32), and a high 21-gene-recurrence score (40,41). Therefore, these factors should be taken into account when considering postoperative radiation but their significance as a sole indicator to support PMRT is not reported in the literature, and therefore unknown.

A thought provoking issue is that in the trials establishing the role of PMRT, the surgical approach included more radical types of mastectomies (i.e., without skin preservation) and axillary clearance (21) thus, less probability for residual breast tissue and less dermal lymphatics (42). Current mastectomy techniques aim to facilitate breast reconstruction by skin sparing (with/without nipple sparing), there is tendency to leave various amounts of residual glandular tissue to facilitate breast reconstruction and allow for better aesthetic outcome of the neo-breast (42). However, as the native skin and subcutaneous tissue are preserved in these surgeries, the dermal plexus, an important lymphatic route for draining the mammary region and may harbour tumour cells, is left intact (43). Thus, the local recurrence risk might be increased in high-risk node-negative patients in which PMRT is not performed (44). Many of the guidelines for breast reconstruction do not provide information in-which cases these procedures should be avoided or in-which PMRT is indicated in patients who are without nodal involvement (45). Using new RT techniques (e.g., imaging-based, deep-inspiration breath hold) and defining the volumes according to ESTRO delineation guidelines (16-18) can contribute reducing the dose to OARs without compromising the target coverage (20). Therefore, the potential therapeutic benefit of PMRT in this setting might be greater comparted to RT based on bony landmarks (46-48). However, PMRT techniques may vary significantly in OAR exposure and target coverage (47,49), and more sophisticated advanced techniques might not necessarily provide an advantage, so careful evaluation of RT plans is recommended. Therefore, it is encouraged to use techniques to reduce the OARs dose such as deep inspiration breath-hold or continuous air way pressure mask (CPAP) and mindfully consider the pros and cons of each RT technique used (47,48). Especially as most of these patients will have a long-term survival which puts them at risk for recurrences or/and RT-related complications.

The target volumes

The target volumes are areas that potentially harbour subclinical disease. Contouring target volumes for chest wall and elective nodal irradiation according to guidelines will help avoiding excessive radiation to adjacent tissues (17,18). In case of IBR, the implant (tissue expander or permanent implant) may be positioned *ventral* or *dorsal* to the major pectoral muscle. The ESTRO-ACROP guidelines for PMRT in early breast cancer indicate that the target volume includes the residual subcutaneous glandular tissue and the subcutaneous lymphatics and that the major pectoral muscle serves as the anatomical *dorsal* border for mastectomy. Therefore, the breast glandular tissue position is dependent of the implant location. In case of muscle invasion, local inclusion of that part of the pectoral muscle is advised, and in case of rib cage invasion the ribs/intercostal muscles should also be focally included in the target volume, although these patients are usually not candidates for

IBR (17). We recommend using these guidelines when planning early breast cancer radiation therapy, but the delineation should be adopted per case accordingly, using available preoperative/pre-systemic therapy imaging for planning and identifying the risk areas for recurrence.

The timing of PMRT in the setting of reconstruction

Reconstructions can be immediate, delayed, or delayed–immediate. Immediate reconstructions are performed at mastectomy, whereas delayed reconstructions are usually performed 6–12 months (or years) after the completion of mastectomy and adjuvant therapy, when the patient is recovered from treatment related toxicity (50). Different factors dictate the timing of reconstruction (50). Immediate reconstruction is facilitated by skin sparing (SSM) or nipple sparing mastectomy (NSM, i.e., sparing of the skin and nipple and areola complex). By contrast, delayed-breast reconstruction was the common approach after non-skin sparing procedure, especially if patients were planned for PMRT prior to surgery. This approach allowed for the irradiated skin to be replaced with healthy skin from a donor site.

Delayed-immediate reconstruction involves placing tissue expanders at the time of mastectomy (50). This may allow to maintain or expand the skin and pectoralis muscle to create a pocket for the implant. Additionally, the decision on PMRT can be based on the final pathology report. Usually, patients not planned for PMRT complete reconstruction with an implant or flap, whereas patients planned for PMRT undergo PMRT with a tissue expander followed by later definitive reconstruction. The immediate-delayed approach permits the opportunity to avoid irradiating an autologous flap (if planned), gradually expand the pectoralis muscle to serve as a pocket for a permanent implant, and the benefits of providing an immediate breast mound for the patient after mastectomy.

In the past, immediate reconstruction was considered contraindicated if PMRT was planned, however, recently more studies are reporting its use (11,12,50).

Unfortunately, there is no consensus regarding the timing of the reconstruction (immediate, delayed, or delayed-immediate) in the setting of PMRT and the treatment approach varies significantly among centres and countries. The rate of reconstruction failure varies substantially from 0% to 40%, depending on whether PMRT was delivered to the tissue expander or to the permanent implant. Recent publications suggest that PMRT to tissue expander is associated with a higher rate of complications while others did not find significant differences (51-53).

Therefore, further trials are needed to determine the optimal approach for reconstruction in the setting of PMRT with regards to timing if a two-stage expander/implant reconstruction is planned.

Bolus

Bolus was commonly used for PMRT chest wall irradiation (without reconstruction) to serve as a tissue equivalent material placed on the skin to shift the 95–100% isodose line to the skin and subcutis to reduce the local recurrences in these volumes (54). However, bolus was the most important independent risk factor for severe skin toxicity in case of PMRT without strong evidence for lower rates of local recurrence (55,56). Importantly, its use in the setting of SSM/NSM, varies between institutions, and little data is available with regards to complications/failure of the reconstruction (55,56). Therefore, until further data become available, the routinely use of a bolus in these cases is not recommended and should be considered on an individual basis if there is a concern for a high-risk area that is not getting full coverage (55,56).

Radiation boost

Historically, radiation boost in the setting of PMRT was aimed to provide an additional radiation dose to the mastectomy scar to reduce local recurrences in this area (57). A study by Massachusetts General Hospital (57), evaluated whether a chest wall boost was independently associated with reconstruction complications in the setting of breast reconstruction. The study cohort included patients who had delayed reconstruction procedures. Radiation boost was significantly associated with infection, skin necrosis, and implant exposure. For implant-based reconstruction, the addition of the boost was independently associated with higher risks of implant failure. Most importantly, the addition of the boost was not associated with improving local tumour control, even in high-risk subgroups (57). Therefore, we do not recommend routine use of boost in case of IBR.

Dose and fractionation

Practice patterns vary widely among centres and countries

with regards to total dose and fractionation schedule for breast cancer patients who underwent mastectomy with/without IBR. The most common used fraction sizes in case of IBR is 1.8–2 Gy to a total dose of 50–50.4 Gy (58). However, some countries adopted the moderate hypofractionation regimens (e.g., 40 Gy delivered in 15 fractions over 3 weeks) to the chest wall and regional nodes, even in the setting of IBR, based on long-term data from the START A/B trials, showing reduced toxicity of hypofractionation scheme compared to normo-fractionation (1.8–2 Gy per fraction to 50–50.4 Gy) (59). Even though there is little data from clinical trials specifically evaluating hypofractionation in the setting of IBR to support its use, and there are several ongoing clinical trials, based on the long-term data of hypofractionation in breast conserving therapy, there is no reason to believe that its outcome will be inferior to conventional fractionation (58-61).

Proton-based RT

Proton therapy has not been widely used nor investigated for adjuvant breast cancer RT, because there are only few proton centers across the world. However, due to the properties of proton therapy it is possible to achieve optimal dose coverage of relevant targets and at the same time ensure low dose to OAR compared with photon RT. The use of volumetric based-photon planning (i.e., arc-based intensity modulated radiation therapy, vIMRT) for breast cancer might not achieve dosimetric advantage over tangential field-based planning (49). The use of vIMRT often results in large volumes receiving a low dose "bath", which may result in unexpected toxicity (if these organs were not contoured and taken into consideration while planning) (62), and possibility for secondary cancer as many of these patients are long-term survivors (63).

In an energy-dependent manner, proton therapy will deposit the majority of its dose in tissue depths defined by the Bragg peak (64). In practice, this translates into (I) the ability to deliver the peak energy to target volumes of irregular 3-dimensional shape using pencil-beam scanning technology, (II) a sharp dose fall-off following deposition of energy in the target and (III) reduction of the integral dose to the patient. Within millimeters, the exit dose drops off from 90% to 10%, resulting in the virtual absence of an exit dose. The effectiveness, safety and feasibility of proton therapy has been reported in few small cohort studies with limited follow up, and there is a lack of clinically controlled randomised trials documenting benefit from proton therapy, evaluated either as higher tumour control and/or as fewer morbidities.

The potential of proton therapy for PMRT is to lower the dose to heart and lung without a compromise on dose to chest wall target on regional nodes. However, proton therapy has an estimated 10% higher radiobiologic effective dose (RBE), and studies imply that the relative effect may be even higher, leading to a higher risk of morbidities from OAR than anticipated (65). Most studies on proton therapy in early breast cancer have been single-institution and retrospective with no formal research plan (66,67), but fortunately, well-designed trials are also made. Seventy patients requiring loco-regional RT including internal mammary node irradiation were treated with proton therapy in a phase II trial from Boston 2011–2016 (68). Inclusion criteria were >20 Gy was received by >5% of the heart or >20 Gy to the left anterior descending artery with conventional photon RT. The doses were 1.8–2.0 Gy (RBE), 25–28 fractions. The primary endpoint was grade 3 or worse radiation pneumonitis or any grade 4 toxicity within 3 months from proton therapy. Mastectomy was done in 93%, and 83% of these pursued reconstructions. At median 55 months follow-up, and the 5-yr LRR and OS were 1.5% and 91%, respectively, and only one patient developed grade 2 pneumonitis as the highest morbidity score. As of 2021, there are 2 phase III randomised controlled clinical trials investigating gain and risk from proton therapy in breast cancer patients. The RadComp trial (NCT 02603341) is a pragmatic randomised trial testing proton *vs.* photon RT for patients with stage II-III breast cancer with an indication for loco-regional RT including internal mammary node irradiation (69). The primary endpoint is major coronary event reduction by proton therapy, hypothesizing a reduction in the 10-year major coronary events rate from 6.3% to 3.8% compared to photons. The trial aims for 1,278 patients accrued during 2016–2022. The other trial open for inclusion since 2020 is the DBCG Proton trial (NCT04291378), where patients operated for breast cancer or DCIS can be included if photon treatment planning with strict criteria for dose coverage of breast, chest wall and nodal volumes reveals a mean heart dose ≥4 Gy and/or V20lung ≥37% (trial protocol is available on Google). The primary endpoint is 10-year risk of heart disease, hypothesizing a 10-year reduction from 10.2% (photon) to 6.3% (proton). The baseline 10-year risk of heart disease in Danish women 60 years old is 5.8%. The trial aims for 1,502 patients. Both the RadComp and the

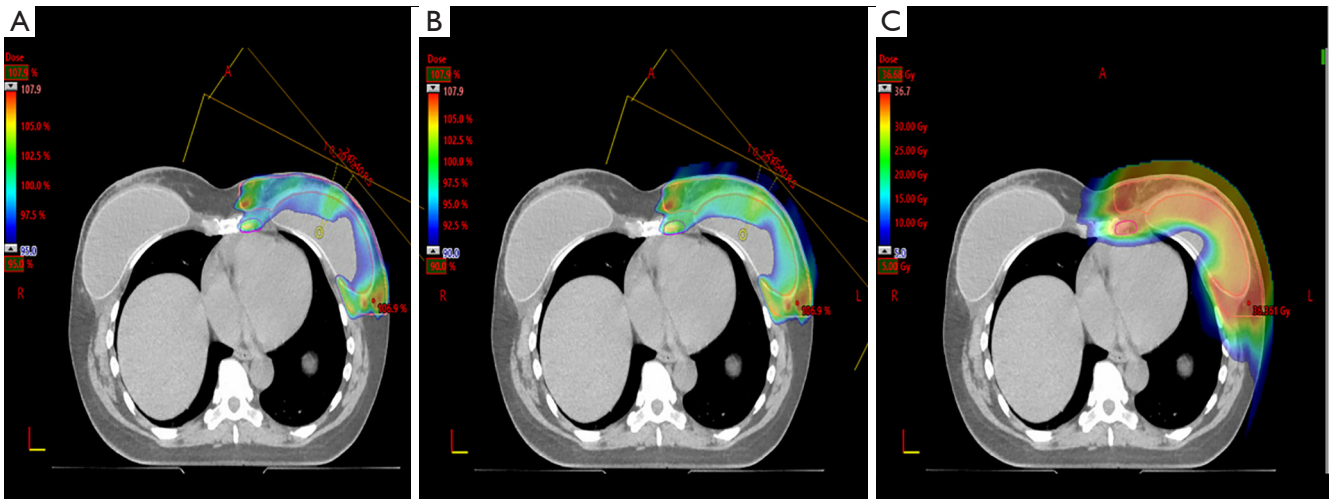

Figure 1 Patient operated with bilateral mastectomy, and with an indication for postmastectomy radiation therapy on the left side. The treatment planning is based on proton therapy 50 Gy/25 fractions. The target (pink line) is the tissue ventral to the implant and the internal mammary nodes. The implant is highlighted with a yellow line. The dose distributions indicate 95% (A), 90% (B), and 5 Gy doses (C). The two en face beam angles are indicated in (A,B). The plan emphasizes the dosimetric properties of proton plan, that the peak dose is deposit at a certain depth at the location of brag-peak without an exit dose as opposed to photon-based planning.

DBCG trials have several secondary endpoints including extensive reporting of loco-regional radiation associated morbidities and documenting the pattern of recurrence.

Since proton therapy requires a higher precision in daily therapy due to the properties of the beam (*Figure 1* to show en face beam arrangement and dose very close to heart), and one of the main reasons for using proton therapy in breast cancer is concern of heart disease, it is likely that future reporting of results from proton trials will include reporting of doses to substructures of the heart. An automated atlas for delineating 25 substructures of the heart has been reported from Denmark, but other countries are likely to develop similar atlases (70). However, providing RT on a single planning-CT-scan according to strict institutional guidelines does not guarantee that the treatment is reproducible. For example, by using cine images recorded during each radiation fraction, it is possible to detect a quite substantial variation in the heart position in some patients, whilst for other patients the position of the heart is robust during the whole treatment period (71).

Future trials

Currently there are several trials aiming to improve the outcomes of patients who are planned for mastectomy, reconstruction and are candidates for PMRT (*Table 1*). Some are aimed to evaluate the fractionation protocols as FABREC (NCT03422003) and RTCharm (NCT03414970) that are planned to compare conventional *vs.* hypofractionated regimens in breast cancer patients with IBR. The DBCG RT Recon trial is aimed to evaluate the timing of reconstruction (immediate *vs.* immediate-delayed) and fractionation (allows for conventional and moderate-hypofractionation). While trials such as Primary Radiotherapy And DIEP flAp Reconstruction Trial (PRADA) (NCT02771938), aim to evaluate preoperative radiation in patients who are planned for mastectomy and autologous-based reconstruction.

Conclusions

Breast cancer treatment evolved significantly with improvement in surgical and RT techniques. Radiation planning should be guided by disease stage, risk of recurrence, correct definition of the target volumes and treatment objectives. Meticulous RT planning, total dose and fractionation, dose homogeneity, and OAR doses are significant for reducing RT toxicity. The multidisciplinary team should work together in aim to improve the outcomes of mastectomy patients in both in clinic and in planning future trials.

Table 1 Ongoing trials of postmastectomy radiation therapy for patients who are planned for reconstruction

Trial name (NCT)	Accrual targets (number of patients)	Accrual study start year	Design	Primary end point
DBCG RT Recon trial NCT03730922	590	2020	Prospective randomized	Surgical complications of immediate-delayed versus delayed reconstruction in patients who are planned for PMRT
FABREC (NCT03422003)	400	2018	Prospective randomized	Patient reported outcomes (note: reconstruction complications and oncological outcome are secondary endpoints)
RTCharm (NCT03414970)	880	2018	Prospective randomized	To evaluate whether the reconstruction complication rate at 24 months post radiation is non-inferior with hypofractionation
Primary Radiotherapy And DIEP flAp Reconstruction Trial (PRADA) (NCT02771938)	60	2016	Interventional non-randomized	Number of participants with presence of open breast wound at 4 weeks after DIEP surgery

NCT, ClinicalTrials.gov Identifier; PMRT, postmastectomy radiation therapy; DIEP, deep inferior epigastric perforator.

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