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Teaching Case

Skin recurrence in the radiation treatment of breast cancer

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Clinical presentation

A 34 year old premenopausal, nulliparous, BRCA-negative woman was referred to our department after surgical excision and a pathological diagnosis of a breast cancer recurrence at the previous lymph node biopsy and lumpectomy scar. At age 30 years, the patient detected a small palpable mass in the left upper outer quadrant and was subsequently diagnosed with pT1bN0, Stage IA breast cancer. An ultrasound detected a hypoechoic nodule that measured $0.5 \times 0.6 \times 0.5$ cm^3 at the 2 o'clock axis, which was approximately 3 cm from the nipple. The initial ultrasound recorded the mass as BIRADS-4, for which a biopsy is recommended. Due to the density of both breasts, the mass appeared occult on the mammography. An ultrasound-guided core biopsy was performed and the test results revealed mixed, moderately differentiated, invasive, ductal and lobular carcinoma.

The patient underwent a left breast lumpectomy and sentinel lymph node biopsy in early 2013. The surgical pathology demonstrated a 1 cm, well differentiated, invasive, ductal carcinoma with negative margins (>0.5 cm) and no evidence of lymphovascular invasion. Intermediate-grade ductal carcinoma in situ of the solid type was present in 1 of 9 blocks. An immunohistochemistry showed estrogen-receptor positivity at 99%, progesterone receptor positivity at 99%, a Ki-67 of 10%, and HER2/Neu negativity at 1+.

The patient had a dense and relatively small breast. She was treated with hypofractionated radiation,[1] 4256 cGy in 16 fractions using 6 MV photon beam.[2-4] She was treated in the prone position. No boost was delivered because the 5-year outcomes of the institutional prone technique was comparable with that of standard treatment.[5] No bolus or other skin dose augmentation was used. Figure 1a shows the dose distribution with isodose lines. Figure 1b shows dose color wash, which appears to bring a bit more clarity for evaluation with a clearer skin dose representation and indicates that the skin dose was only 60% of the prescribed dose (Fig 1c). Figure 1d shows that the 90% prescription coverage begins at 0.5 cm from the skin surface. The patient received adjuvant tamoxifen as of March 2013 but did not receive chemotherapy.

Investigations/imaging findings

The patient was closely followed. Magnetic resonance imaging (MRI) was performed in 2014 and demonstrated a 0.6 cm area of subcutaneous enhancement that was contiguous with the postsurgical scar in the left breast and believed to represent postsurgical changes (Fig 2a). An ultrasound was performed in 2015 and showed a $1.0 \times 0.3 \times 0.8$ cm^3 oval mass with a circumscribed margin in the left-breast peri-areolar region at the site of the

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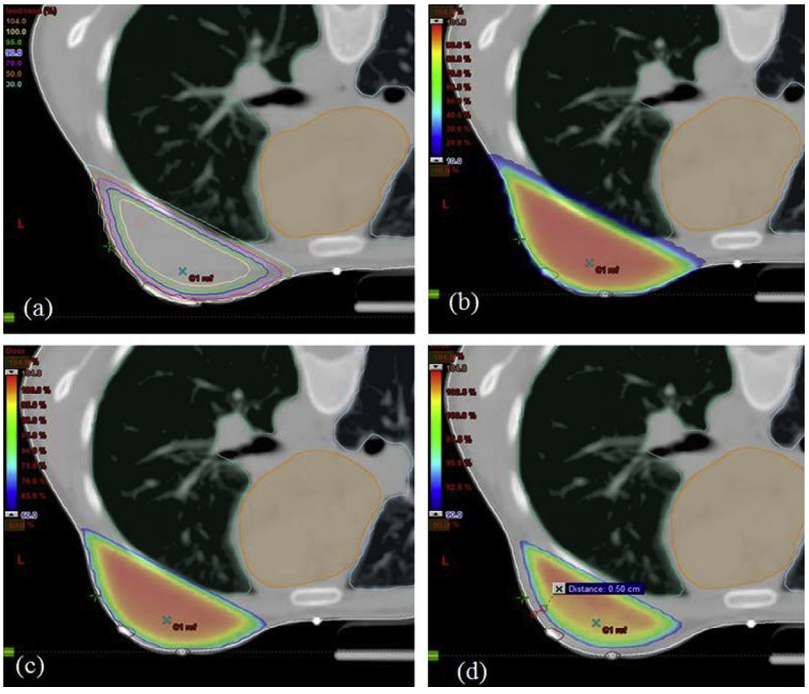

Figure 1 Original treatment plan of patient treated in 2013 for left breast in prone position. (A) Isodose distributions. (B) Color wash that indicates default setting. (C) Color wash that shows 60% coverage. (D) Color wash that shows 90% coverage 0.5 cm from the surface.

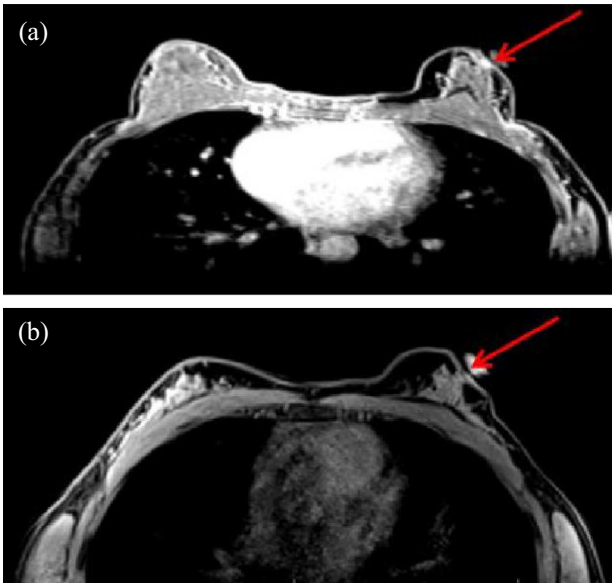

Figure 2 Magnetic resonance image of patient in 2014. Vitamin marker E overlies the left upper breast and shows the site of the prior lumpectomy. The red arrow (superimposed on vitamin E marker) indicates the area of subtle architectural distortion without abnormal enhancement. (B) Magnetic resonance image from 2016 with a 0.6 cm area of subcutaneous enhancement that is contiguous with the postsurgical scar.

patient's scar, which corresponds to the enhancement on prior MRI scans. These changes were thought to be most likely benign in nature; however, an MRI scan in 2016 confirmed the previous findings of the 0.6 cm area of subcutaneous enhancement contiguous with the postlumpectomy scar and again noted that it likely represents evolving postsurgical changes as shown in Figure 2b.

In September 2016, two superficial masses were palpated on the lateral aspect of the sentinel, lymph-node, biopsy incision as well as the lateral aspect of the prior breast surgery incision, which corresponds to the imaging abnormalities that were described on the prior ultrasound and MRI scan. A fine-needle aspiration at the sentinel, lymph-node biopsy incision showed metastatic adenocarcinoma that was morphologically consistent with the known breast primary.

Treatment

The patient subsequently underwent left breast lumpectomy, resection of the left axillary mass, and a sentinel lymph-node biopsy. The pathology of the left lumpectomy specimen demonstrated recurrent invasive ductal carcinoma that involved the dermis and superficial mammary parenchyma with invasive carcinoma that extended to the lateral margin and 0.1 cm from the superior margin. The left axillary incision revealed a 0.5 cm recurrent, invasive, ductal carcinoma that involved the dermis and subcutis. Two lymph nodes were removed and tested

negative for carcinoma. The tumors were described as morphologically similar to the prior left breast carcinoma and both foci were associated with scar tissue. The immunohistochemistry showed estrogen receptor positivity at 99%, progesterone receptor positivity at 99%, a Ki-67 of 10%, and HER2/Neu negativity at 1 + . The fluorescent in situ hybridization was additionally requested for the HER2/Neu status and tested negative with a final ratio of 1.63.

On the basis of clinical and pathological information and in particular the positive lateral margin in the setting of recurrent disease, the patient and her treatment team decided that she would undergo a left skin-sparing mastectomy, right prophylactic skin-sparing mastectomy, bilateral subpectoral tissue expander placement, and excision of the left axillary incision. The surgical pathology revealed no abnormalities in the right breast and the left breast had no residual carcinoma with changes that were consistent with prior radiation. Lastly, the left axillary scar excision showed no residual carcinoma.

After the mastectomy, the patient underwent postmastectomy radiation therapy. The patient was treated in the supine position, to the left chest wall, left axilla (nodal levels II and III), and left supraclavicular fossa (both to a dose of 5000 cGy in 25 fractions using a 3-dimensional conformal technique). The postmastectomy radiation was the patient's second course of radiation with the intent of targeting the tissue expander-reconstructed left chest wall and regional nodes. The potential toxicities that are associated with the treatment and particularly in the setting of reirradiation were discussed with the patient and consisted of high-grade dermatitis, infection, necrosis, loss of chest wall reconstruction, high-grade fibrosis, and lymphedema.

Outcome, follow-up, and discussion

Skin recurrence in breast cancer is very rare and usually attributed to specific clinical and pathological factors.[6,7] In the case of this patient, the low superficial dosing of the initial prone breast irradiation, coupled with the lack of a boost in this young patient, may have contributed to her recurrence. Although a boost is considered standard of care in a young patient with invasive breast cancer,[8] the treating physician at the time did not include a boost as part of this patient's initial treatment plan.

With regard to prone positioning, our institution has a long history of treating patients in the prone position on the basis of prospective research that compares prone and supine positioning.[3,5] In megavoltage beam treatment, the finite buildup at the skin dose is relatively lower and can potentially underdose the skin, fail to eradicate micrometastatic disease, and allow for recurrence to clinically manifest. Skin dose in any radiation treatment plan is a complex function of physical parameters that include source-to-skin distance, field size, beam-modifying devices (eg, tray and wedge), beam angles, and unique clinical parameters that can mandate a standard dose to be increased or decreased.[9-11] An optimum surface dose achieves the primary treatment goal while minimizing the incidence of skin toxicities such as erythema, desquamation, edema, fibrosis, and telangiectasias, which is an imperative issue in breast radiation given the potential for unfavorable cosmetic outcomes. However, too low a dose can result in cancer recurrence at the skin as in the case of this patient.

The use of hypofractionation in a woman who is 31 years old at the time of her initial treatment is usually not provided on the basis of the 2011 American Society for Radiation Oncology guidelines[12] that recommended hypofractionation in women age >50 years. Our institution has conducted many protocols that investigated hypofractionation (with a concomitant boost) in patients with early stage breast cancer of all ages and thus has a long history of utilizing hypofractionation in younger women. Recent research that has been presented in abstract form shows acceptable outcomes and cosmesis in this subset of women age <50 years who are treated on these protocols with hypofractionation.[13]

For breast cancer treatment especially, which utilizes 2 opposing tangential beams, measuring the actual skin dose can be elusive.[14] Surface dose in breast radiation has been extensively studied[14-22]; however, suboptimal skin dosing is a planning subtlety that can be easily overlooked. Additionally, most treatment planning systems are well known to provide inaccurate skin dose estimates and are thus routinely disregarded. Akino et al[18] emphasize the importance of calculation grid size due to volume averaging and steep buildup dose to correctly assess skin dose. Several other studies using phantoms and various types of detectors have provided an evaluation of treatment planning systems for surface/skin dose.[19,23]

A reanalysis of the treatment planning with analytical anisotropic algorithm (Eclipse version 11.6) was performed with a variable grid size and showed that a 90% coverage with 1×1 mm^2 was achieved within 4 mm compared with 5 mm for 2.5×2.5 mm^2. Additionally, changes up to 3% were observed in the maximum and mean doses in breasts with a calculation grid size. These differences are due to volume averaging, which is more pronounced in build regions such as those within skin surfaces at the breast.

Another important aspect of this case is the fact that the patient received reirradiation to the chest wall after breast irradiation 3 years prior. After reviewing her prior fields, her heart and lung doses were determined to be relatively low and the ribs were only partially covered by the full dose region. The brachial plexus was not included in the prior field. As such, we treated the patient with conventional fractionation even though we discussed alternative fractionation with a twice daily dosing to 45 Gy as per the Radiation Therapy Oncology Group study 1014, which investigated partial breast reirradiation in patients who had previously

received whole breast irradiation.[24] This clinical scenario was different because our patient did not have a second breast conserving surgery but had a mastectomy at recurrence.

An alternative would have been to utilize hyperthermia, although this is not a practice routinely used at most institutions including our own.[25] The brachial plexus was contoured and a plan sum was created including both the current and prior fields and the cumulative dose to organs at risk was examined by the treating physician and physicist and were deemed within acceptable constraints. The cumulative doses were as follows 5515 cGy for brachial plexus (maximum dose), 176 cGy for heart dose (mean), 498 cGy for spinal cord (maximum dose), and 16% for ipsilateral lung V20.

Prone treatment is a good choice for left breast treatment to reduce the heart and lung dose but cone down in prone set up is not performed. To provide an adequate surface, the bolus can be placed easily in the supine position. To reduce the heart and lung dose, deep-inspiration breath hold in the supine position is a growing trend[26-28] that has now been adapted at our institution on a clinical trial.

Teaching points

This teaching case provides a number of teaching points for future reference. First, skin dose in supine breast treatment is inherently higher than prone due to tangential beam angle that increases obliquity and the skin dose[11] while reducing buildup depth. Second, proper dose visualization using color wash is imperative in plan evaluation and especially in prone positioning where skin dose is naturally lower than with supine set up. Third, dose calculation should always be performed with the smallest calculation grid size, especially for small structures and dose gradient areas.[18]

Fourth, in patients with a very superficial tumor bed, prone positioning may not be appropriate given the frequent difficulty in achieving optimal surface dosing. Alternatively, boosting these patients in the supine position with a bolus or personal bra[29] may be desirable to increase the dose to the tumor bed and overlying tissue. Finally, the use of a boost in younger patients lowers the risk of local recurrence and should not be omitted.[8]

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