

## Breast Calcification Relative to Radiation Dose Distribution 21 years after Radiation Therapy: A Case Report and an Argument Against Hypofractionation of Breast Patients

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Received: 12 May 2020; Accepted: 01 June 2020

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### ABSTRACT

Dystrophic calcification in breast tissue and the chest wall is a common finding in patients undergoing definitive therapy including radiation treatment for breast cancer. In this report, we correlate significant and symptomatic dystrophic dense calcification as a late treatment effect associated with radiation therapy and correlate dosimetry and radiation dose and daily dose fractionation asymmetry to the development of calcifications.

**Keywords:** Breast Calcification, Radiation Therapy, Hypofractionation, Dystrophic Calcification, Breast Cancer

### Introduction

The patient was born in 1942. The patient has no family history of malignancy and her personal history was remarkable for degenerative arthritis and a remote history for poorly described colitis, both treated with conservative measures. She had pre-existing allergies to penicillin and sulfa medication. At the age of 52 the patient developed Stage 3C adenocarcinoma of the ovary. The right ovary demonstrated well differentiated cystadenocarcinoma with papillary serous features. Surgery demonstrated no residual disease after TAH-BSO however peritoneal washings were positive for malignancy. She received adjuvant carboplatin and Taxol for 6 cycles and completed her care in March

1995. She was placed on hormone replacement therapy (4 years). She remained well until May of 1998 when imaging of the left breast demonstrated a possible mass that could not be confirmed on compression views. Hormone therapy was discontinued. By September of 1998, the patient felt a palpable asymmetry in the lateral left breast and imaging was again equivocal. Her clinical examination demonstrated a 2.5 cm left breast mass and the patient underwent fine needle aspirate which demonstrated a breast malignancy. Excisional biopsy and axillary lymph node dissection was performed in October 1998 which revealed infiltrating ductal carcinoma measuring 3.5 cm in diameter with ductal carcinoma in situ occupying 25% of the tumor volume with cancerization of the lobules. There was vascular infiltration without perineural invasion. The tumor was ER positive/PR negative and pre-dated Her 2 Neu testing. Two of sixteen lymph nodes were positive for metastatic disease with one lymph node measuring 2.5 cm. After recovery from surgery complicated by cellulitis, the patient received 4 cycles of Adriamycin/Cytoxan and was referred for adjuvant radiation therapy. Radiation was delivered to the breast and regional lymph node areas with 4600 cGy to the breast and supraclavicular region in 200 cGy daily fractions and a boost to the surgical bed of 1400 cGy in 200 cGy fractions using 15 MeV electrons was directed to the surgical cavity. The breast was planned in two dimensions with isodose contour available for review at the isocenter (Fig. 1). A 30-degree wedge was used on both the medial and lateral tangent fields resulting in daily “hot spots” of 220 cGy/day to the medial and lateral breast and a daily “hot spot” of 210-215 cGy at the level of the chest wall. She received 5 years of Tamoxifen therapy. A follow up from her primary surgeon (RQ) in 2000 revealed no palpable abnormalities, however mammography over subsequent years demonstrated calcifications which were progressive in nature (Fig. 2/image from 2019).

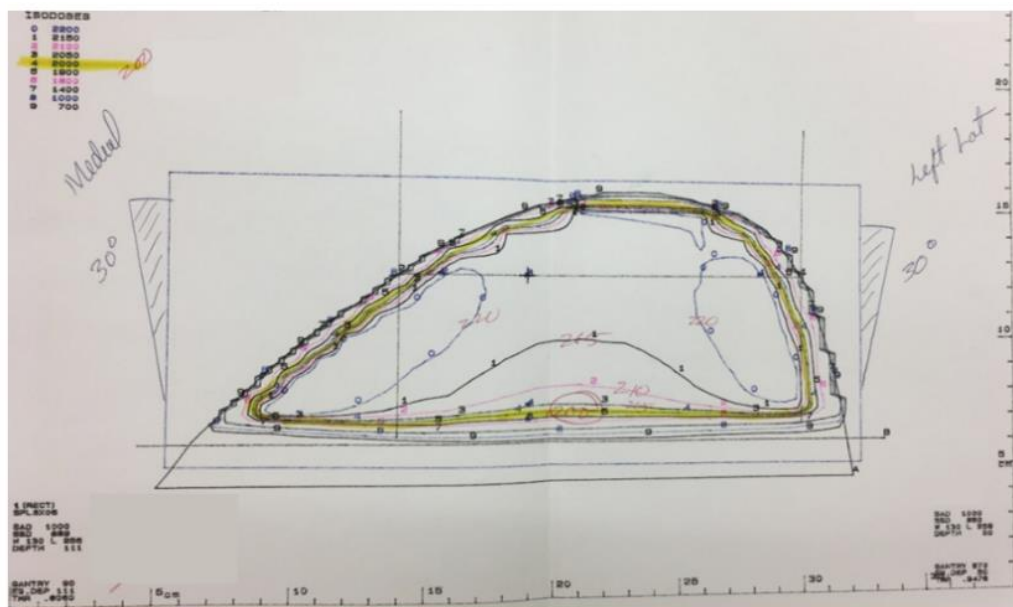
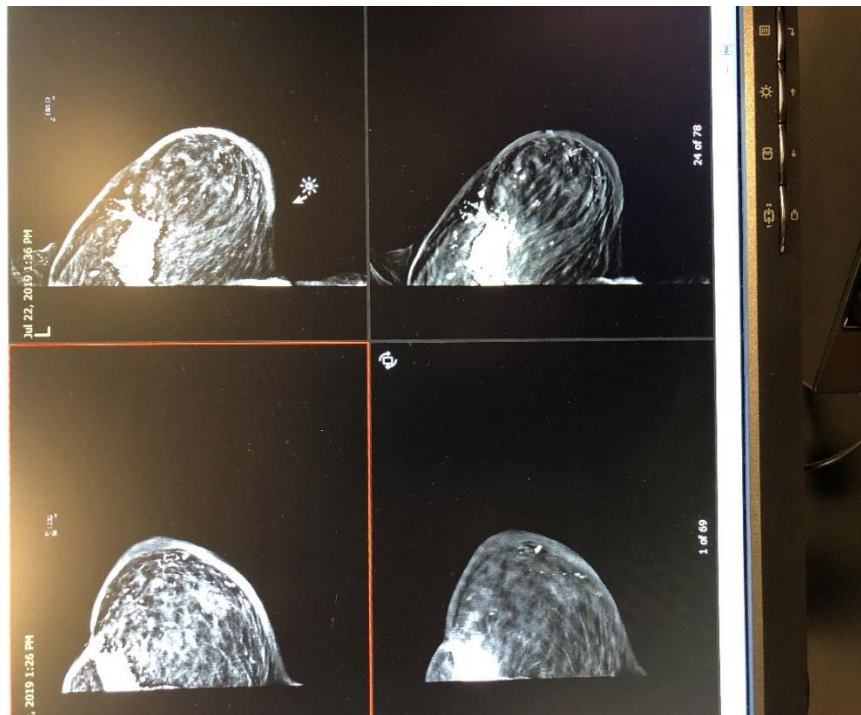
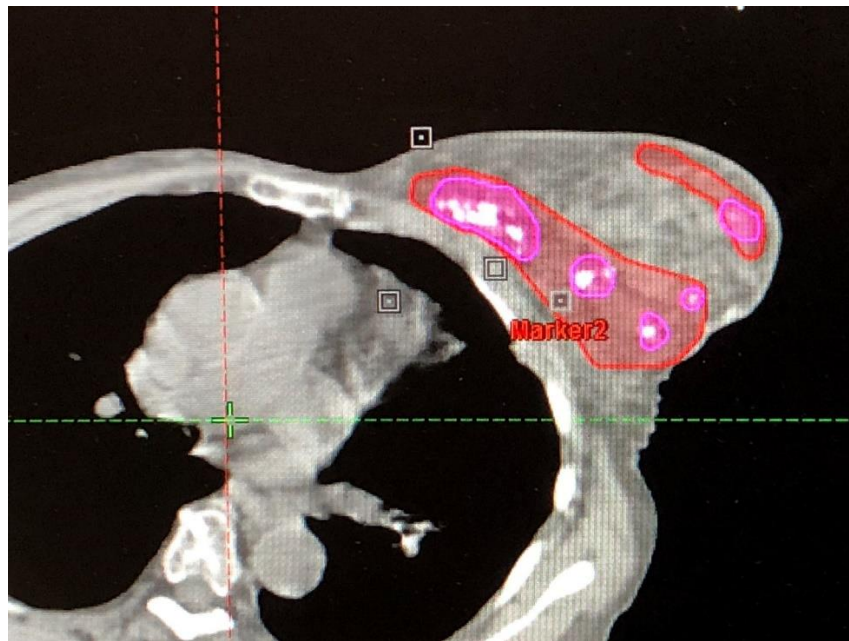


Figure 1: Dosimetry from 1998

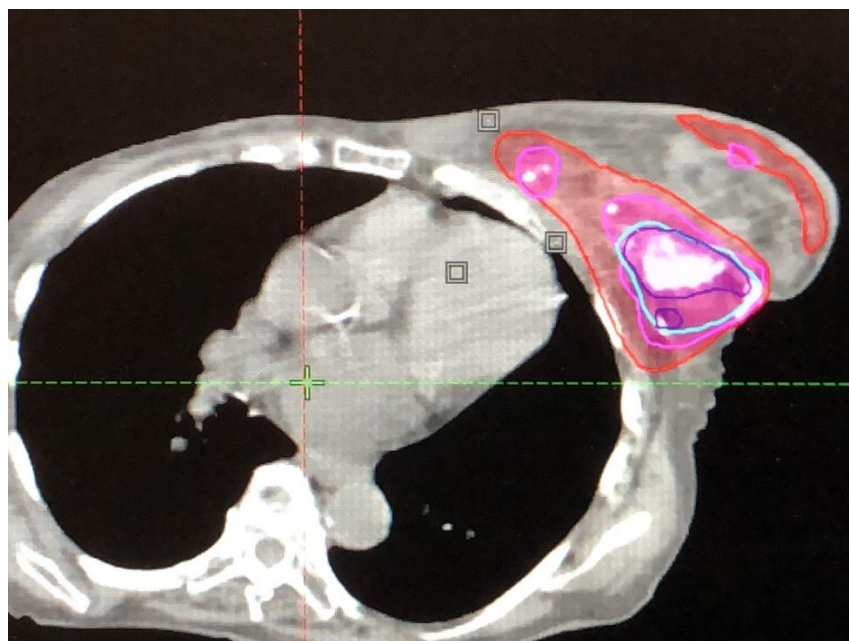


**Figure 2:** Mammography 2019

Over the following two decades the patient developed steatosis which progressed into hepatic cirrhosis and portal varices influencing medical management including extended hospital admissions including intensive care for hepatic encephalopathy. In 2018, abnormalities were identified on breast imaging on the right side and subsequently abnormalities were seen in at least 2 locations of the right breast (upper inner and lower outer) and biopsy of one lesion revealed poorly differentiated adenocarcinoma in 4 cores. The tumor was ER/PR positive and Her 2 Neu negative. Because of medical co-morbidities and multifocal disease, the patient was placed on neoadjuvant hormone aromatase inhibitor and surgical options were re-visited several months later. Attempts were made to remove both lesions with conservative measures, however, lateral margins could not be established with lumpectomy and tumor burden measured at least 4.5 cm with 1 of 2 lymph nodes positive for tumor, therefore despite multiple attempts at conservative therapy, the patient underwent completion mastectomy in May 2019 which revealed no residual carcinoma. The decision was made in team management to offer post-operative radiation therapy to the right chest wall and regional lymph nodes. The patient was brought for right chest wall simulation and with both arms raised for the therapy position, the calcifications of the left breast were easily identified in a pattern reflecting radiation dose asymmetry from her previous therapy (Fig. 3 and Fig. 4). The purpose of this report is to review planning objectives from the left breast treated in 1998 with volumetric reconstruction and correlate geometry and radiation dose distribution with calcification. On physical examination, the calcifications are easily palpated, and interestingly skin integrity is intact without telangiectasia.



**Figure 3:** Dosimetry from 1998 superimposed on a current planning study. Calcifications are seen in area receiving greater than 200 cGy/day (red areas)



**Figure 4:** Dosimetry, including the boost volume, superimposed on a current planning study. Calcifications are seen in area receiving greater than 200 cGy/day (red areas)

## Methods and Materials

For this case report, consent was obtained from the patient for using de-identified objects for research, education, and publication. After double identification, the patient was brought to the four-dimensional planning center for 1) planning to the right chest wall and regional lymph nodes and 2)



reproduction of the fields and dose volume distribution used for radiation therapy in 1998 accepting changes in contour adjusted to pulmonary volume. Treatment in 1998 was delivered to the left breast and regional lymph nodes with a Varian 6 MeV linear accelerator. The patient was planned with 2-dimensional planning geometry with a hot match line between the tangential breast fields and superior regional lymph nodes. Dosimetry through the isocenter is seen in Fig. 1 with daily dose calculated at 200 cGy per day to the entire volume seen at isocenter leaving “hot spots” at 10% and higher in multiple locations. Effort was made to reproduce the therapy position and immobilization device as best as possible to reflect the isodose geometry from that era recognizing contour asymmetry and alteration in the size of the target could not be superimposed with certainty to treatment delivery from 1998. Accordingly, the isodose areas receiving greater than 200 cGy/day were identified and contoured based on planning geometries estimated from the two-dimensional treatment plan and photographs, including estimates of the boost volume as this was accomplished in a different treatment position. The breast volume was contoured as well as all areas of calcification. The boost volume was estimated and contoured and the calcifications within the boost volume were identified and contoured. Statistics were performed with Student T test.

## Results

### Radiation treatment dosimetry and presence of calcification

The breast volume measured 898 cc and within the breast volume the areas receiving greater than 200 cGy/day was 340 cc. Therefore, the estimated breast volume receiving 200 cGy/day or less was 558 cc. The calcifications measured 95 cc and were all located in regions that received greater than 200 cGy/day. Therefore, 28% of the volume receiving greater than 200 cGy/day fractionation was calcified versus 0% of the tissue receiving 200 cGy/day or less ( $p < 0.05$ ). The estimated boost volume treated with 15 MeV electrons was 53 cc and the volume of calcifications within the estimated the boost volume was 32 cc, therefore 60% of the boost volume was calcified (Fig. 3 and Fig. 4).

## Discussion

Calcifications are seen in varying frequency in tissue post radiation therapy, both in patients with intact breast and post mastectomy adjuvant chest wall therapy. These are generally considered clinically insignificant (Cowie and Jones, 1999; Amin *et al.*, 2002; Plazk *et al.*, 2011; Arevalo *et al.*, 2009; Zaka *et al.*, 2008; Lewis and Holt, 2004; Carl and Hartmann, 2002). This patient was treated during the era that volumetric planning was nascent and two-dimensional planning with dose calculated through the isocenter with wedges used to accommodate the slope of the breast in one plane was the standard of care. There are lessons to be learned from this patient which apply to modern management. This patient

has no known risk to serve as an indicator for significant calcification of the breast more than 2 decades post treatment. She has no dystrophic calcifications in other operative sites, therefore the likely most influential component of her care generating calcification is radiation therapy. She did not have exaggerated dermal or subcutaneous acute effects during radiation management. She was treated for cellulitis and did receive chemotherapy which is associated with skin toxicity however her skin showed no pronounced reaction during treatment and today her dermal examination is unremarkable without telangiectasia. One can argue her previous chemotherapy including therapy for ovarian cancer and breast cancer may have influenced outcome, however her skin is intact without dermal or interstitial edema in regions that were not calcified. Reconstructed planning imaging confirms the skin was not an area of exaggerated daily fractionation due in part to build up with the areas of dose asymmetry generated in anticipated medial and lateral soft tissue. The calcifications are exclusively in regions that received more than 200 cGy/day and are most exaggerated in the boost volume where significant aspects of the volume received more than 200 cGy/day to doses more than 6000 cGy due to dose asymmetry generated by 15 MeV electron management in which dose can be as high as 20% higher in the more superficial regions of particle entry. The density and ratio of calcified tissue in the boost volume suggests a dose volume effect as well as an effect from fractionation. In the boost area 60% the entire volume is calcified and on clinical evaluation feels and appears nearly ossified. The great majority boost volume received more than 200 cGy/day with dose calculated to the 100% line at 3.3 cm. Although total dose is a consideration for outcome especially for the density of calcifications in the boost, calcification is far more prevalent in regions receiving more than 200 cGy/day including areas not in the boost volume noted in the medial breast region.

It is well known that acute effects of radiation therapy are not necessarily a predictive indicator for late effects. In this patient who was treated at a prescribed dose of 200 cGy/day, anticipated image outcome on planning computer tomography is seen in volumes receiving 200 cGy/day or less, interestingly best noted in the central left breast region. The mammograms obtained in follow up are deceiving as the relationship to dosimetry is not obvious (Fig. 2). This became more obvious at the time of designing therapy for her right chest wall 21 years after therapy to the left breast. The patient has multiple current medical comorbidities, nevertheless is symptomatic from the calcifications with pain and discomfort, particularly in the boost volume.

Compressed fractionation strategies for breast cancer have become popular worldwide since the publication the first series of reports supporting favorable outcomes with hypofractionation (Whelan *et al.*, 2010). Historically, fractionation plans of greater than 200 cGy/day to targets were commonly used for chest wall radiation therapy when our field was initially used in the care of breast patients 40-50

years ago, however when radiation therapy was applied to intact breast patients, daily fractions of 180-200 cGy/day to target were applied due to concern of both acute and late effects of therapy that were seen with more aggressive daily fractionation schedules. The adjustment to more traditional fractionation schedules was thought to be appropriate as dermal erythema and injury to tissue of limited self-renewal potential including rib, chest wall, lung, and heart were of concern to the application of radiotherapy for these patients and fractionation was thought to be the primary mitigator against both acute and late effects. Our technology of today has shifted this paradigm. These patients were treated with two-dimensional planning with limited ability to modulate areas of radiation dose asymmetry. Accordingly, areas of dose asymmetry could not be adjusted for patient specific planning nor could they be defined or titrated from a volumetric perspective. Modern technology permits modulation of multiple sloped surfaces of the breast and can optimize dose asymmetry with multiple applied strategies including energy and intensity modulation. Publications demonstrating favorable outcome have encouraged modern technology for treatment execution and it is assumed, quite fairly with short term data, that favorable outcome is driven in part by advanced technology (Whelan *et al.*, 2010; Kim *et al.*, 2016; Bekelman *et al.*, 2014; Butler-Xu *et al.*, 2018). These investigators point to cost as a motivation to compress treatments (Bekelman *et al.*, 2014) and indicate that acute effects associated from therapy are ameliorated during hypofractionation due in part to the application of modern technology (Butler-Xu *et al.*, 2018).

The outcome in this patient is sobering and needs to be viewed through the prism of late effects and our unintentional impact on normal tissue. These patients survive their malignancy and we are responsible for late effects and outcome. The regions of dose asymmetry were relatively nominal by both historical and modern standards, yet the outcome in tissue receiving more than 200 cGy/day is extraordinary without a known biomarker predictive for calcification. Importantly, there is little to no calcification in tissues receiving 200 cGy/day or less. In the more recent treatment of the right chest wall in this patient, there is not area receiving more than 200 cGy as modern technology is applied at 180 cGy/day fractionation. To date there are no calcifications recognizing we are only a year away from her right sided chest wall RT.

While we continue to refine our craft and publish favorable outcomes with compressed therapy for breast cancer patients, the clinical euphoria promoted by this approach may be short lived (Bekelman *et al.*, 2014; Butler-Xu *et al.*, 2018; Hemingway, 1995). This patient serves as an unambiguous reminder that our technology may not erase our mistakes of the past. Our first and primary objective is to do no harm. Once applied, therapy can not be withdrawn, and many trained in the era before volumetric planning remember injuries less commonly identified today. Nevertheless,

outcomes such as this need to be avoided and further work needs to be done to optimize how to apply compressed treatment plans including which patients are sub-optimal candidates for this approach. A complete understanding of both breast geometry and predictive biomarkers may help us optimize care. In the care of patients affected by malignancy, the good news always comes first.

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