EVOLUTION OF BREAST CONSERVATION RADIATION TREATMENT TECHNIQUES IN BREAST CANCER : FROM 6 WEEKS TO 3 WEEKS TO 1 WEEK TO 1 DAY AND FROM WHOLE BREAST TO PARTIAL BREAST

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Breast cancer is the most common malignant tumor in women. About 1 in 8 women in the United States will develop invasive breast cancer in their lifetime. It has been estimated that in 2017, over 300,000 women were diagnosed with breast cancer in the United States. Of these cases, 252,710 would be invasive cancer and 63,410 pre-invasive ductal carcinoma in situ. About 40,610 women were expected to die from breast cancer [1]. Over the past 50 years the primary treatment of breast cancer has expanded from Mastectomy (M) to breast preservation options including breast conserving surgery + Radiation Therapy (RT). RT options have evolved from External Radiation Therapy (XRT) to the whole breast given daily for 6 weeks, to XRT to the whole breast given daily for 3 weeks, to Accelerated Partial Breast Irradiation (APBI) given over 5 days, and now Intraoperative Radiation Therapy (IORT) given in 1 day.

Historically, the most common treatment for breast cancer was M. In the 1970s investigators combined breast conserving surgery or Lumpectomy (L) with XRT to the whole breast with results which appeared comparable to M. XRT radiation dosimetry coverage of the breast is illustrated in Figure 1. Multiple randomized trials demonstrated that Modified Radical Mastectomy (MRM) offered no statistically significant difference (NSD) over L + XRT in regard to overall survival (OS), disease free survival (DFS), and local-regional recurrence (LRR) [2-7]. Follow-Up (F/U) ranged from 6-13 years. These trials are summarized in Table 1.

TABLE 1
EARLY STAGE BREAST CANCER RANDOMIZED TRIALS
M vs. L + XRT

				LRR (Chest Wall, Nodes, Breast)		
STUDY	#PTS	T-SIZE	OS DFS	MRM	L + XRT	F/U
NSABP [2]	1219	≤ 4 cm	NSD	8%	8%	8 yrs
WHO [3]	179	≤ 2 cm	NSD	10%	5%	10 yrs
Milan [4]	701	≤ 2 cm	NSD	2%	3%	13 yrs
EORTC [5]	882	≤ 5 cm	NSD	9%	13%	8 yrs
DBCG [6]	859	≤ 5 cm	NSD	6%	5%	6 yrs
NCI [7]	237	≤ 5 cm	NSD	10%	5%	10 yrs

The NSABP reported the same conclusions with 20 year follow-up [8].

Based on all of the preceding data, the National Institutes of Health convened an expert panel which discussed breast cancer in 1990 [9]. They issued a consensus statement, which read "Breast Conservation Treatment is an appropriate method of primary therapy for the majority of women with Stage I/II breast cancer, and is preferable because it provides survival equivalent to total mastectomy and axillary node dissection, while preserving the breast."

More recent years witnessed the shortening (hypofractionation) of XRT courses from 6 weeks to 3 weeks. Three notable randomized trials showed no significant difference (NSD) in local tumor recurrence (LR) or cosmetic results [10-12]. The data are shown below in Table 2 :

TABLE 2
BREAST CONSERVATION RANDOMIZED TRIALS

HYPOFRACTIONATED XRT

STUDY	AUTHOR	#PTS	T-Stage	XRT	FX	LR	F/U
START-A [10]	Bentzen	2236	T1-3	5000	25	3.6%	5-YRS
				4160	13	3.5%	
				3900	13	5.2%	
p-value					NSD		
START-B [11]	Bentzen	2215	T1-3	5000	25	3.3%	5-YRS
				4000	15	2.2%	
p-value					NSD		
Gloucestershire [12]	Owen	1410	T1-3	5000	25	12.1%	10-YRS
				3900	13	14.8%	
				4290	13	9.6%	
p-value					NSD		

Notably, none of these trials employed a 1 week XRT boost to the tumor bed, which has been proven to decrease local tumor recurrence in a randomized trial enrolling 5,318 patients conducted by the European Organization for the Research and Treatment of Cancer [13].

Further reduction in radiation treatment time was achieved with the use APBI to the partial breast using High Dose Rate (HDR) radiation implant or brachytherapy techniques in which RT was completed in 5 days. Forming the logic for APBI, investigators found that for the vast majority of breast cancer patients, RT to the whole breast was unnecessary. The major risk for local recurrence after breast conservation surgery is within 1-2 cm of the tumor bed. The risk of recurrence outside of this region was termed "elsewhere recurrence." As noted above, XRT had been proven to reduce recurrence risk to rates comparable to M. However, XRT did not seem to significantly reduce the risk of elsewhere recurrence. This formed the logic of partial breast irradiation [14]. The data which led to this conclusion are summarized below in Table 3.

TABLE 3
INCIDENCE OF LOCAL RECURRENCE OUTSIDE THE TUMOR BED
RANDOMIZED TRIALS L vs. L + XRT

		ELSEWHERE BREAST RECURRENCE		
STUDY	#PTS	L	L + XRT	F/U
NSABP-B6 [15]	1,265	2.7%	3.8%	125 months
Milan [16]	567	1.5%	0%	39 months
Uppsala-Orebro [17]	197	3.5%	-	64 months
Ontario [18]	837	3.5%	1.0%	43 months

At least two randomized trials published to date have confirmed the results with APBI HDR in 5 days are comparable to daily XRT for 6 weeks with respect to LR and cosmesis [19-20]. These results are summarized below in Table 4.

TABLE 4
BREAST CONSERVATION
RANDOMIZED TRIALS RESULTS OF APBI HDR vs. XRT

AUTHOR	#PTS	BREAST RECURRENCE	F/U
Polgar [19]	128 (HDR)	5.9%	120 months
	130 (XRT)	5.1%	120 months
Strnad [20]	633 (HDR)	1.4%	60 months
(GEC-ESTRO)	551 (XRT)	0.9%	60 months

Regarding HDR Implant, four techniques with significant clinical experience have been established : Mammosite Balloon, Contura Balloon, SAVI Strut, and Multi-plane interstitial catheter. The Mammosite Balloon method is the simplest, but not always successful. Three technical problems were recognized. Firstly, the Balloon can rupture. Secondly, the Balloon may not conform to the surgical cavity resulting in radiation dose inhomogeneity and under treatment of areas at risk for tumor recurrence. Thirdly, the catheter may not remain centered in the Balloon, again resulting in radiation dose inhomogeneity and under treatment of areas at risk for tumor recurrence. Contura Balloon method minimized these problems. The SAVI technique achieved further improvement by utilizing a flexible strut apparatus which can be adjusted to fit the surgical cavity and treat larger lesions. With the Balloon and SAVI options, the devices can be placed at the time of surgery, thereby sparing the patient an added implant procedure. The Multi-Plane interstitial catheter technique offers the most flexibility of all the HDR options, but requires another invasive procedure, and is the most labor intensive method. Radiation dosimetry flexibility is progressively improved with the number of catheters and dwell positions. Therefore, dosimetry improves progressively from Mammosite (1 Catheter in Figure 2), to Mammosite (Multiple Dwell positions in Figure 3), to Contura (5 Catheters in Figure 4 and 5), SAVI (up to 11 Catheters in Figure 6), to Multi-Catheter (no set limit on Catheters in Figure 7).

With respect to APBI HDR brachytherapy complications, Smith et al, reviewed 6,952 APBI HDR implant cases between 2003 and 2007 registered in the Medicare Database [21]. The authors reported 3.95% patients required mastectomy, 16.2% developed infections, and 16.3% experienced non-infection complications which included rib fractures, fat necrosis, and breast pain. All of these complications were significantly higher than in patients who underwent XRT to the whole breast ($p<0.001$). Most of these complications occurred with Mammosite and Contura implant devices. There was no difference in survival.

APBI has been performed using non-invasive techniques like Intensity Modulated Radiation Therapy (IMRT) or Stereotactic Body Radiation Therapy (SBRT). Livi et al, randomized 520 patients with Stage I/II breast cancer to receive APBI IMRT/SBRT vs. XRT [22]. Eligible patients included women older than 40 years of age and tumors ≤ 2.5 cm. Notably, DCIS, angiovascular invasion, and involved axillary nodes were not exclusion criteria. The IMRT/SBRT dose regimen was 3000 cGy in 5 daily fractions vs. 6000 cGy in 30 daily fractions with XRT. With a median follow-up of 5 years, LR was 1.5% in both groups ($p=0.86$). There also was no significant difference in 5 year overall survival, 96.6% with XRT vs. 99.4% with APBI IMRT/SBRT ($p=0.06$). APBI IMRT/SBRT was superior to XRT with respect to acute radiation side effects ($p=0.0001$), late effects ($p=0.004$), and cosmetic outcome ($p=0.045$).

Finally, APBI has been performed using Intra-Operative Radiation Therapy (IORT) in 1 fraction. Two randomized trials have reported favorable LR results, though inferior to daily XRT x 6 weeks [23-24]. The results are summarized below in Table 5.

TABLE 5
BREAST CONSERVATION

RANDOMIZED TRIAL RESULTS OF IORT x 1 day vs. XRT x 6 weeks

STUDY	#PTS	TREATMENT	LR	F/U	P-VALUE
TARGIT [23]	1,730	XRT	1.3%	5-yrs	-
	1,721	IORT	3.3%	5-yrs	0.042
ELIOT [24]	654	XRT	0.7%	5-yrs	-
	651	IORT	5.3%	5-yrs	0.0002

IORT has a number of disadvantages. Firstly, LR has been slightly higher than with whole breast XRT. This could be due to the limited technology of the IORT radiation delivery systems. IMRT/SBRT gives much more flexibility in radiation delivery whereby larger tumors and irregular cavities can be safely covered. Secondly, IORT is delivered before final surgical pathology results are available. In the TARGIT Trial, 21.6% of patients in the IORT arm received whole breast XRT because of adverse pathology findings including positive surgical margins and positive lymph nodes. Thirdly, seroma and fat necrosis are not unusual with IORT. In the ELIOT Trial, 16% of IORT patients developed fat necrosis.

As noted above, APBI IMRT/SBRT has been done in 5 days with results comparing favorably to whole breast XRT x 6 weeks. The targeting and subsequent treatment technique calls for insertion of fiducial markers to outline the surgical cavity. This can be done with individual fiducial insertion which can be time consuming and challenging technically. Another method involves placement of a series of fiducials inside of a prepared device called Biozorb. The Biozorb device is then placed inside the surgical cavity. Investigators have published favorable results with the use of Biozorb [25]. Cross et al, reported excellent targeting results in 108 patients who underwent Biozorb fiducial placement for radiation treatment targeting. Seven of these patients underwent APBI SBRT. Biozorb fiducial devices are shown in Figure 8. Biozorb placement for a patient is shown in Figure 9. Radiation treatment planning targeted to Biozorb is shown in Figure 10.

Cosmetic results after breast conservation XRT given daily x 6 weeks have been reported as good to excellent in 80-90% of cases as reported by both patients and physicians [26-29]. Examples are shown in Figures 11 and 12. However, at least 90% of patients experience Grade 2 or higher XRT skin reactions manifested by erythema, dry or moist desquamation [30]. An example is given in Figure 13. While these reactions typically heal like a routine sunburn within a few weeks after completing XRT (See Figure 14), long-term cosmetic results can be poor as shown in Figure 15. Significant decreased radiation exposure to the skin and whole breast thru the use of APBI/SBRT has been shown in a randomized trial summarized above. The result of this improved dosimetry with APBI/SBRT has been shown in turn, to reduce radiation acute effects including skin reactions, radiation late effects, and achieve better long-term cosmesis. In the APBI/SBRT group only 2.0% patients had Grade 2 or higher skin reactions [22]. Maximum radiation doses are considerably reduced with APBI/SBRT (D_m < 105%) compared to APBI/HDR (V 200 < 10%). APBI/SBRT case examples are shown Figure 16 and 17.

The National Comprehensive Cancer Network Guidelines for breast conservation RT currently include XRT x 6 weeks, XRT x 3 weeks, APBI HDR x 5 days, and APBI XRT x 5 days, in the pathways for breast conservation RT. Based on the most recent data, APBI IMRT/SBRT should be incorporated soon. Current data in a randomized trial have shown that with APBI IMRT/SBRT, patients can undergo non-invasive breast conservation RT in 5 days with excellent cosmetic results superior to XRT x 6 weeks. We believe APBI IMRT/SBRT targeted to Biozorb can be done in 1 day.

Figure 1

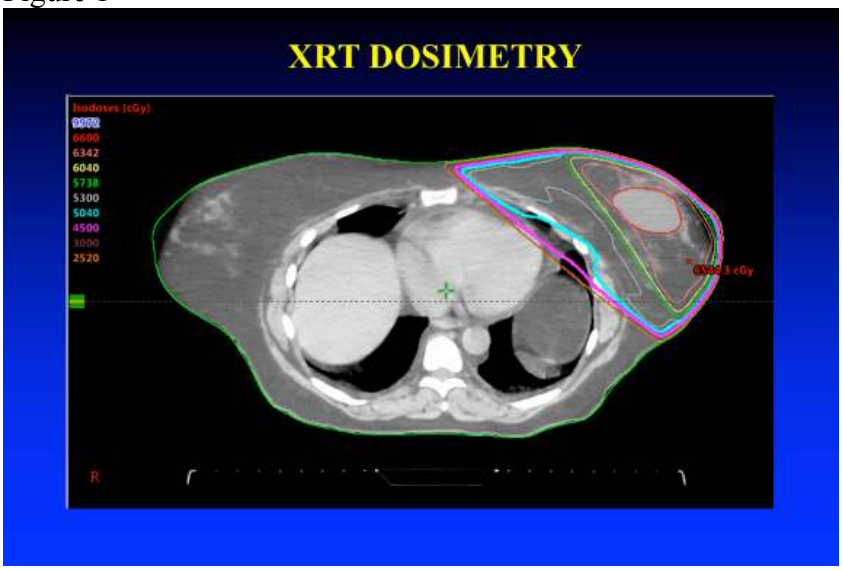

Figure 2

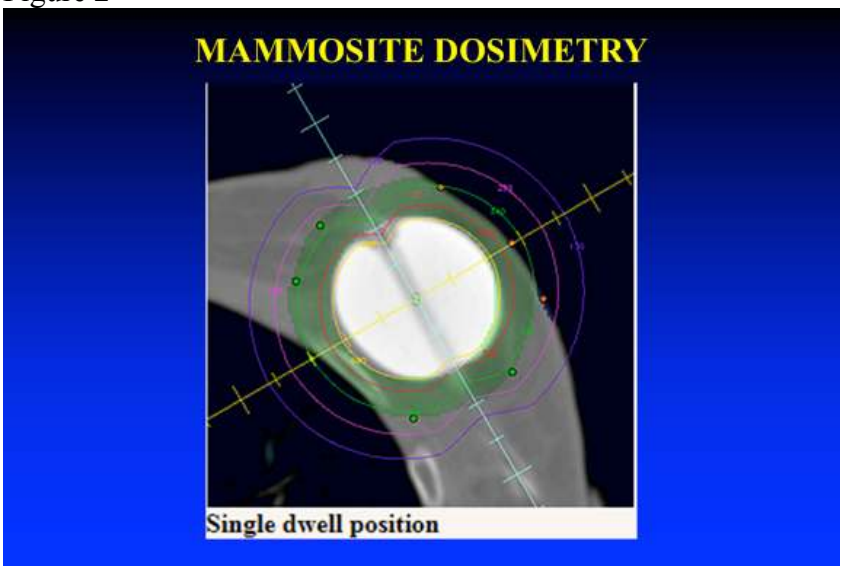

Figure 3

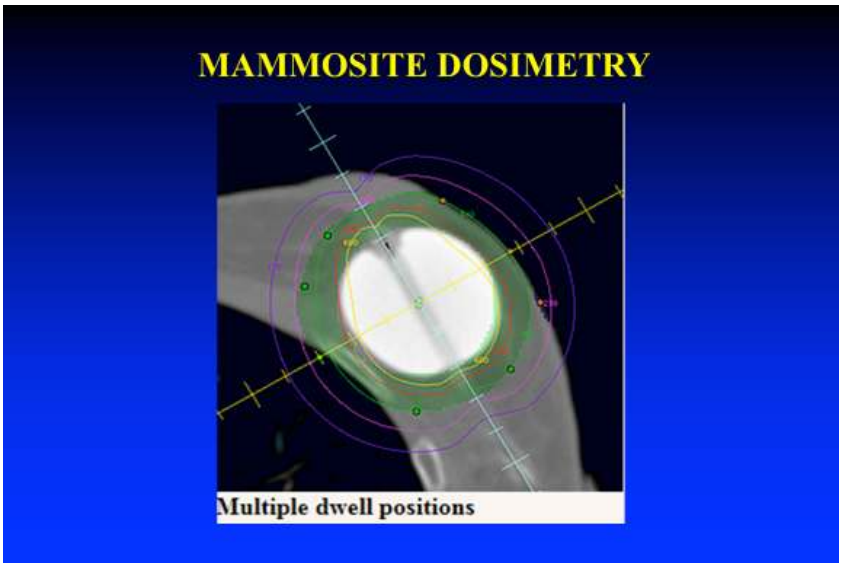

Figure 4

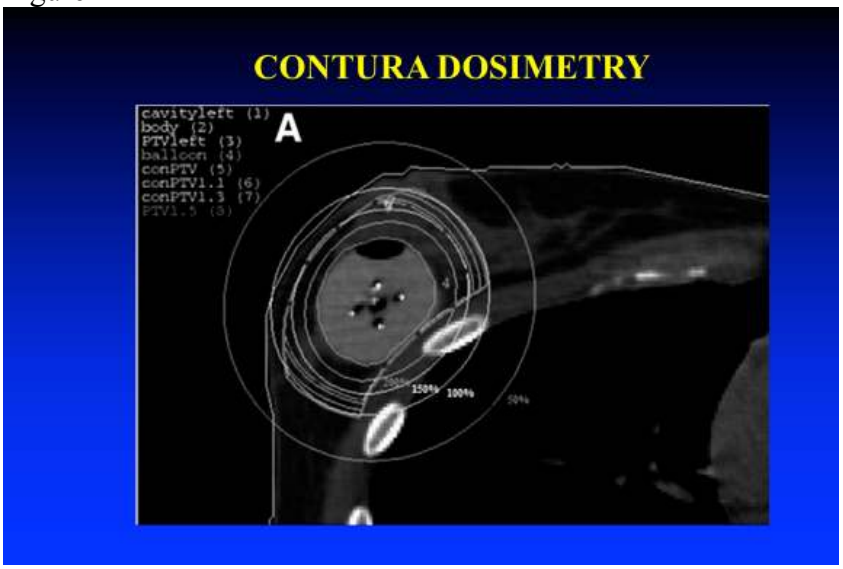

Figure 5

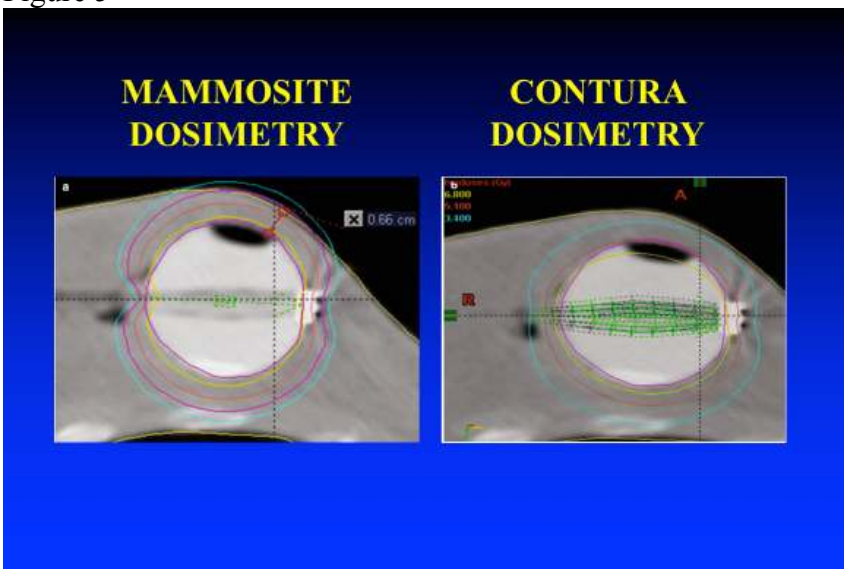

Figure 6

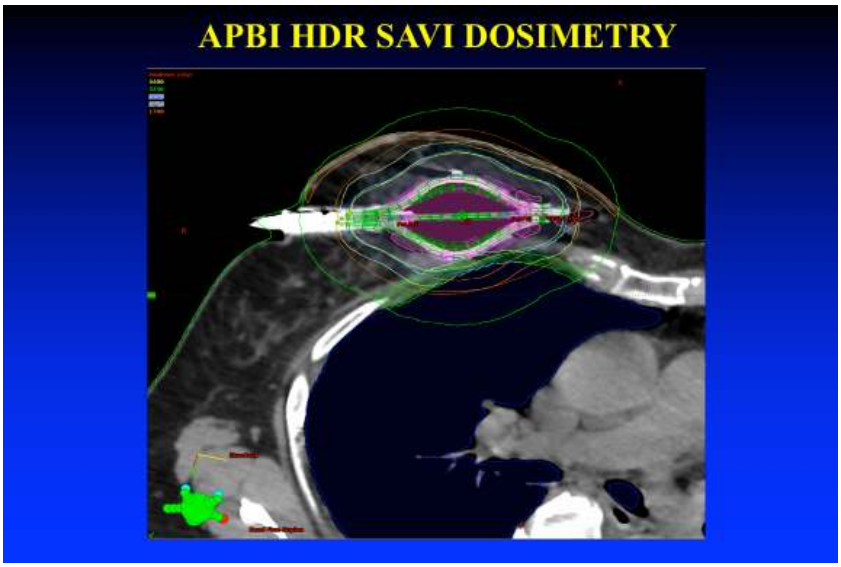

Figure 7

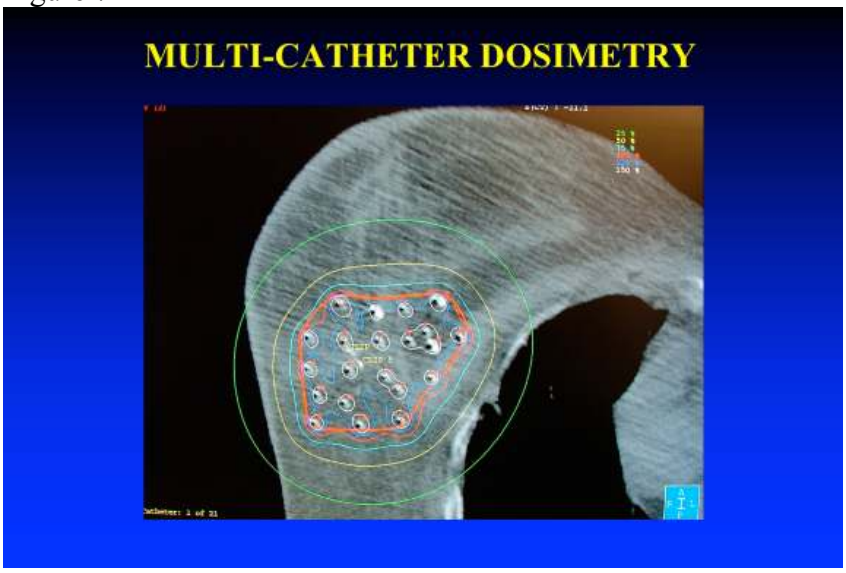

Figure 8

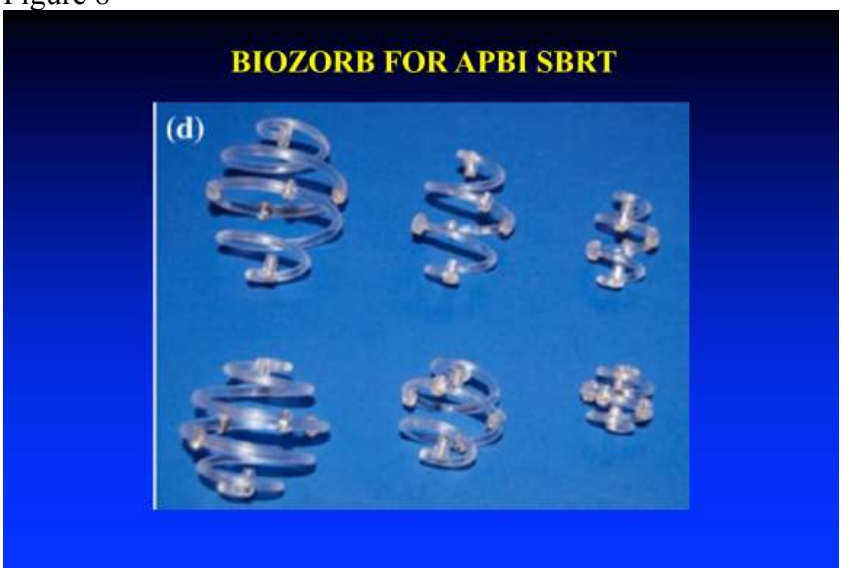

Figure 9

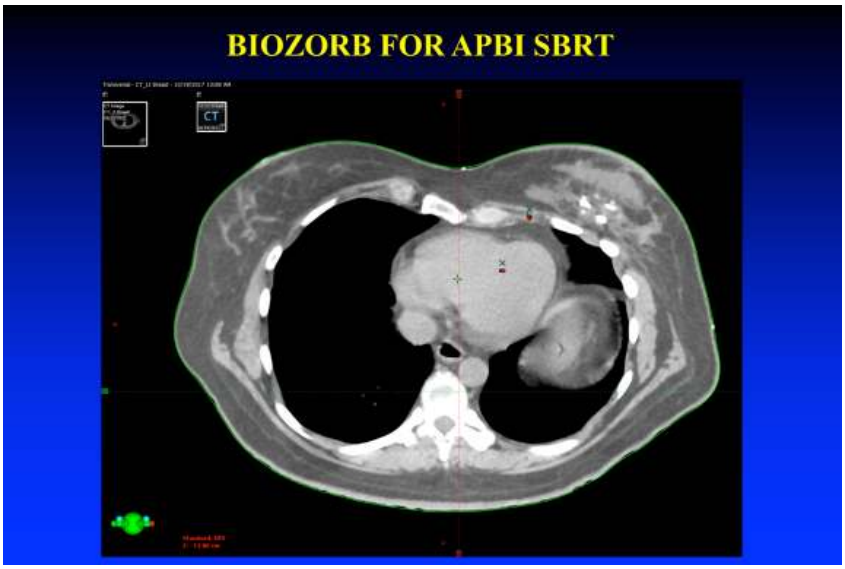

Figure 10

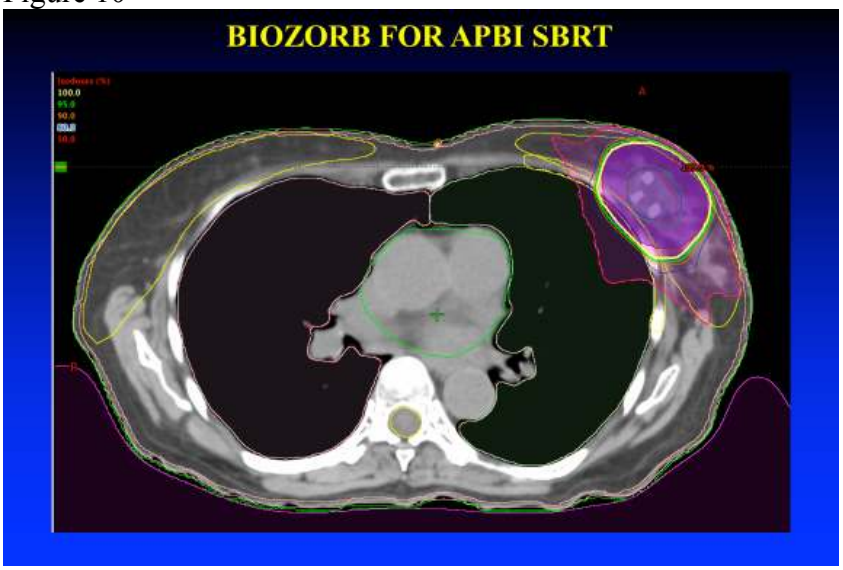

Figure 11

Figure 12

Figure 13

Figure 14

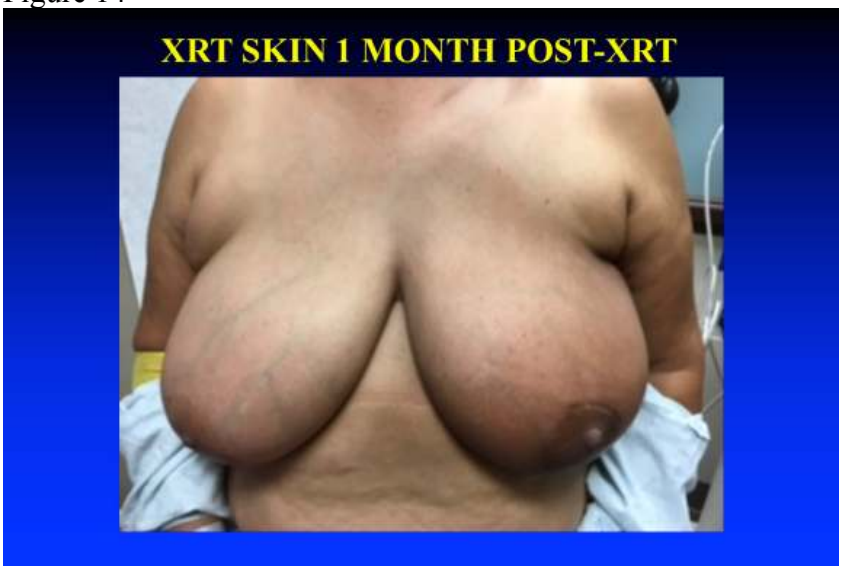

Figure 15

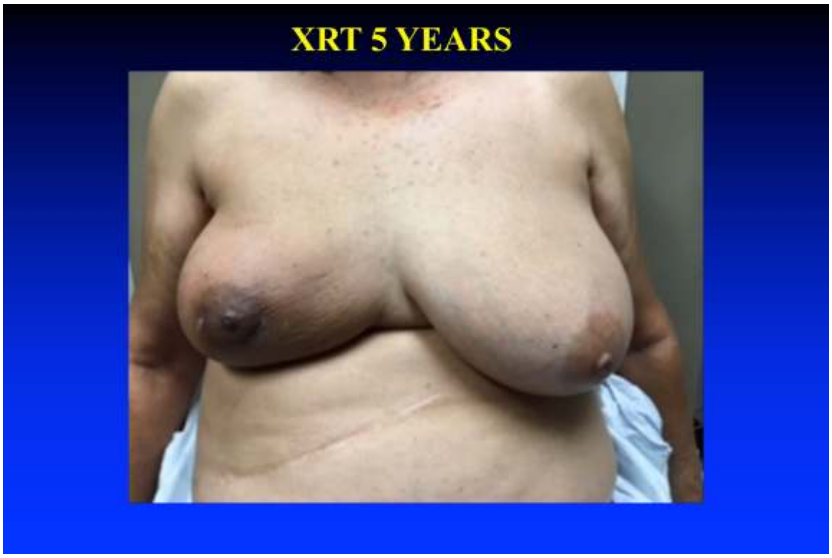

Figure 16

Figure 17

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