RTOG Partial Breast Irradiation Workshop

- RTOG 0413/NSABP B-39 -

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Outline

- **Definition/Rationale for PBI**
- **RTOG/NSABP phase III protocol design**
- **RTOG/NSABP phase III scientific endpoints**

Partial Breast Irradiation

- Definition -

- **Delivery of larger doses/fraction of radiation therapy (RT) to the lumpectomy cavity (plus 1-2 cm margin) after breast conserving surgery in patients with early stage breast cancer using brachytherapy or external beam irradiation techniques**
- **Complete RT in < 4-5 days after lumpectomy instead of 6-7 weeks**

'Rationale' For Partial Breast Irradiation

- **↓ Time and Inconvenience Of BCT**
- **Improve Documented Underutilization Of Breast Conserving Therapy (BCT)?**
- **Potentially Reduce Acute and Chronic Toxicity**
- **Improve Quality Of Life Of Patients**
- **Eliminate Scheduling Problems With Systemic Chemotherapy (?)**

Scientific Rationale

- Partial Breast Irradiation -

- **Major Effect Of Post-Lumpectomy RT:**
  - ***Reduce Risk Of Recurrence In Tumor Bed Region***

Scientific Rationale

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  - ***Reduce Risk Of Recurrence In Tumor Bed Region***
- **Recurrences Away From Tumor Bed ('Elsewhere' Failures-New Primary cancers):**
  - ***Similar After Lumpectomy Alone Or Followed By Whole Breast RT***

Scientific Rationale

- Partial Breast Irradiation -

- **Major Effect Of Post-Lumpectomy RT:**
  - ***Reduce Risk Of Recurrence In Tumor Bed Region***
- **Recurrences Away From Tumor Bed ('Elsewhere' Failures-New Primary cancers):**
  - ***Similar After Lumpectomy Alone Or Followed By Whole Breast RT***
- **Whole Breast RT:**
  - ***May Not Be Needed In 'Appropriately' Selected Patients***

Partial Breast Irradiation

- Supporting Data -

- **Catheter based brachytherapy**
- **MammoSite Balloon Device**
- **3D Conformal external beam radiation therapy**

Published PBI Results

- Catheter Based Brachytherapy -

Institution	*# Patients*	*Follow-Up (Months)*	*% Local Recurrence*
WBH - LDR Patients	120	**82**	**0.9**
Oschner Clinic	51	**75**	**2.0**
WBH - All Patients	199	**65**	**1.2**
NIO – Hungary	45	**60**	**4.4**
Tufts-Brown University	33	**58**	**6**
WBH - HDR Patients	59	**52**	**2.1**
Virginia Commonwealth University	59	**50**	**5.1**
RTOG 95-17	99	**44**	**3.0**
University Kansas	24	**37**	**0**
NIO-Hungary Phase III	181	**30**	**1.1**
Florence Italy	90	**27**	**4.4**
MGH	48	**23**	**0**
Totals	***1005***		**0-6%**

RTOG 95-17

- Brachytherapy Alone Trial-

- Robert Kuske, M.D.: Principal Investigator
- 99 patients enrolled
- Results updated at ASCO ‘04
- Median f/u 3.7 yrs (range 0.6-5.7)
- Actuarial 4-yr breast and nodal recurrence rate of 3%
  - Local failure - 3 pts
- Contralateral failure = 3 pts

MammoSite Data

- **Original FDA Trial Data**
- **ASBS MammoSite Registry trial**
- **Single Institution Experiences**

FDA Trial – 3-Yr Cosmetic Outcome

- 88% Excellent/Good & No Recurrences -

Courtesy M. Keisch, M.D. (ASTRO '04)

Variable Analyzed	*Cosmetic Result*					*p-value*
	Excellent	Good	Fair	Poor	Unknown	
# of pts (% of total)	17 (39.6)	21 (48.8)	4 (9.3)	0 (0)	1 (2.3)	--
Median Skin Spacing (mm)	12	8	6.5	---	---	0.0004[a]
≥ 5 ≤ 7 mm Skin Spacing (n=13)	1(8%)[b]	9(69%)[b]	3(23%)	---	---	0.0451[b]
≥ 7 mm Skin Spacing (n=30)	16(53%)[b]	12(40%)[b]	1(3%)	---	1(3%)	
Open Cavity Placement # (%)	10 (40)[c]	11 (44%)[c]	3 (12%)	---	1 (4%)	ns[c]
Closed Cavity Placement # (%)	7 (39%)[c]	10 (55%)[c]	1 (6%)	---	0	
Balloon Fill (cc) Mean ± Std	52.0 ± 13.2	47.9± 11.5	53.8 ± 13.8	---	61 ± 0	
Balloon Fill ≤ 50 cc	9 (34.6)[d]	15 (57.7)[d]	2 (7.7)	---	---	ns[d]
Balloon Fill > 50 cc	8 (50.0)[d]	6 (37.5)[d]	2 (12.5)	---	---	
Bra Size A+B	1 (10%)[e]	7 (70%)[e]	2 (20%)	---	---	ns[e]
Bra Size C+D	12 (48%)[e]	12 (48%)[e]	1 (4%)	---	---	
Median Follow-up (mos)	21	19	26	---	25	
Follow-up (Range mos)	1-31	1-30	19-31	---	25	

[a] Kruskall-Wallis Test

[b] Chi Square Test: p-value comparing Excellent/Good results between the skin distance groups

[c] Chi Square Test: p-value comparing Excellent/Good results between cavity groups

[d] Chi Square Test: p-value comparing Excellent/Good results between balloon/fill groups

[e] Chi Square Test: p-value comparing Excellent/Good results between bra size groups

ASBS MammoSite Registry Trial

- **Trial developed by manufacturer**
- **Started with clearance of device by FDA (May 2002)**
- **American Society of Breast Surgeons (ASBS) assumed management Nov 2003**
  - **Additional new data collected**
  - **Random chart checks (10%)**
  - **Additional follow-up**
- **Synergos, Inc. (Independent Contract Research Organization):**
  - **Data handling, management, statistics**

Background

- **Trial completed accrual/closed: Nov 2004**
  - **1500 patients enrolled**
  - ***87* Institutions**
  - ***233* Investigators**
  - **80%: IRB approved protocol**
- **<u>Current analysis</u>:**
  - **First *1419* patients enrolled**
  - **All patients signed informed consent**
  - **Follow-up complete through Nov 11, 2004**
  - **First analysis by ASBS**
  - **Results presented at San Antonio Breast Cancer Symposium**

ASBS Registry Trial

Characteristic	*Finding*
Median Age	65 Years (Range 35-93)
AJCC Tumor Stage	Number (%)
Tis (in-situ)	169 (13.7%)
Invasive Carcinoma	1068 (86.3%)
T1a ($\leq$ 0.5 cm)	144 (11.6%)
T1b (> 0.5 and $\leq$ 1.0 cm)	424 (34.3%)
T1c (> 1.0 and $\leq$ 2.0 cm)	423 (34.2%)
T2 (> 2.0 and $\leq$ 5.0 cm)	77 (6.2%)
Stage 0	169 (13.7%)
Stage I	991 (80.1%)
Stage II	77 (89.3%)
N0	977 (91.5)%
N(+)	33 (3.1)%
NX	58 (5.4)%

ASBS Registry Trial

- Cosmesis -

Visit	*N*	*Excellent/Good Cosmesis*	*Fair/Poor Cosmesis*
All Visits	1084	1030 (95.0%)	54 (5.0%)
3 Months	755	717 (95.0%)	38 (5.0%)
6 Months	555	526 (94.8%)	29 (5.2%)
9 Months	368	346 (94.0%)	22 (6.0%)
12 Months	248	229 (92.3%)	19 (7.7%)
18 Months	70	63 (90.0%)	7 (10.0%)
24 Months	19	18 (94.7%)	1 (5.3%)

ASBS Registry Trial- Cosmesis

Variable Analyzed	*Cosmetic Result*				*p-value*
	Excellent	**Good**	**Fair**	**Poor**	
# of pts (% of total)	598 (55.2%)	432 (39.9%)	45 (4.2%)	9 (0.8%)	
Median Skin Spacing (mm)	10.0	10.0	8.0	8.0	< 0.0001[a]
< 7 mm Skin Spacing (n=121)	46 (38.0%)	59 (48.8%)	14 (11.6%)	2 (1.6%)	0.0001[b]
≥7 mm Skin Spacing (n=964)	552 (57.3%)	373 (38.7%)	31 (3.2%)	7 (0.7%)	
Open Cavity Placement (n=488, 45%)	275 (56.4%)	185 (37.9%)	22 (4.5%)	6 (1.2%)	0.3275[c]
Closed Cavity Placement (n=586, 55%)	323 (54.2%)	247 (41.4%)	23 (3.9%)	3 (0.5%)	
Balloon Fill (cc) Mean + Std	56.6 ± 17.8	55.4 ± 17.8	54.3 ± 14.8	57.0 ± 14.4	
Balloon Fill ≤ 50 cc	262 (52.0%)	218 (43.2%)	21 (4.2%)	3 (0.6%)	0.7813[d]
Balloon Fill > 50 cc	336 (57.9%)	214 (36.9%)	24 (4.1%)	6 (1.0%)	
Bra Size A+B	124 (49.6%)	105 (42.0%)	17 (6.8%)	4 (1.6%)	0.0074[e]
Bra Size C+D	474 (56.8%)	327 (39.2%)	28 (3.4%)	5 (0.6%)	
Systemic Chemotherapy					
Yes[h]	55 (48.3%)	52 (45.6%)	7 (6.1%)	0 (0.0%)	0.4974[f]
No	543 (56.0%)	380 (39.2%)	38 (3.9%)	9 (0.9%)	
Wound infection					
Yes[i]	30 (34.1%)	49 (55.7%)	5 (5.7%)	4 (4.5%)	0.0349[g]
No	566 (57.0%)	382 (38.5%)	40 (4.0%)	5 (0.5%)	
Median Follow-up (mos)	6	4	5	13	

ASBS Registry Trial

- Infection Rates -

*Event**	*# Patients*	*%*
Breast Infection	52	4.6
Breast Abscess	19	1.7
Cellulitis	15	1.3
Mastitis	11	1.0
Infection (NOS)	4	0.4
Total Patients (evaluable patients n=1140)	92	8.1
Device Related (evaluable patients n=1140)	60	5.3
Cosmesis (At Last Follow-up)		
Excellent/Good	79	85.9
Fair/Poor	10	10.8

* As reported by investigator

ASBS Registry Trial

- Radiation Recall Reactions -

	# Patients	%
Total Cases Evaluable	***442***	***36***
Total Cases Reported	15	3.4
Chemo Given (n=74)		
Recall reaction (+)	10	13.5
Recall reaction (-)	64	87.5
No chemo given (n=367)		
Recall reaction (+)	5	1.4
Recall reaction (-)	363	98.6
Time to Chemo (Days)*		
< 14	3/19	15.8
≥ 14	7/43	16.3
< 21	5/25	20.0
≥ 21	5/37	13.5
< 28	6/34	17.6
≥ 28	4/28	14.3
Unknown	0/12	0.0
Skin spacing (<7 mm)		
Recall reaction (+)	3	6.0
Recall reaction (-)	47	94.0
Skin spacing (?7 mm)		
Recall reaction (+)	12	3.1
Recall reaction (-)	380	96.9

3D Conformal External Beam PBI

- Published Data -

- **William Beaumont Hospital**
- **USC/New York University**
- **RTOG 0319**
- **Massachusetts General Hospital**

3D Conformal External Beam Radiotherapy

Phase I/II PBI Trial

- William Beaumont Hospital -

- **62 patients treated:**
  - **During treatment**
    - **Minimal to no skin changes (All patients)**
  - **At initial 6 week follow-up visit**
    - **Faint hyperpigmentation (14 pt)**
    - **Mild breast discomfort not requiring analgesics (6 pt)**
    - **Isolated area (<2cm) dry desquamation (6 patients)**
  - **Median follow-up > 1 Year**
    - **Minimal to no observable/palpable RT effects**

Int J Radiat Oncol Biol Phys 2003

Formenti et al

- 47 patients treated in prone position at New York University
- Int J Radiat Oncol Biol Phys 2004
- 30 Gy in 6 fractions
- Minimal toxicity (median follow-up 18 months)

RTOG 0319

A Phase I/II Trial To Evaluate Three Dimensional Conformal Radiation Therapy (3D-CRT) Confined To The Region Of The Lumpectomy Cavity For Stage I/ II Breast Carcinoma: Initial Report of Feasibility and Reproducibility of Radiation Therapy Oncology Group (RTOG) Study 0319.

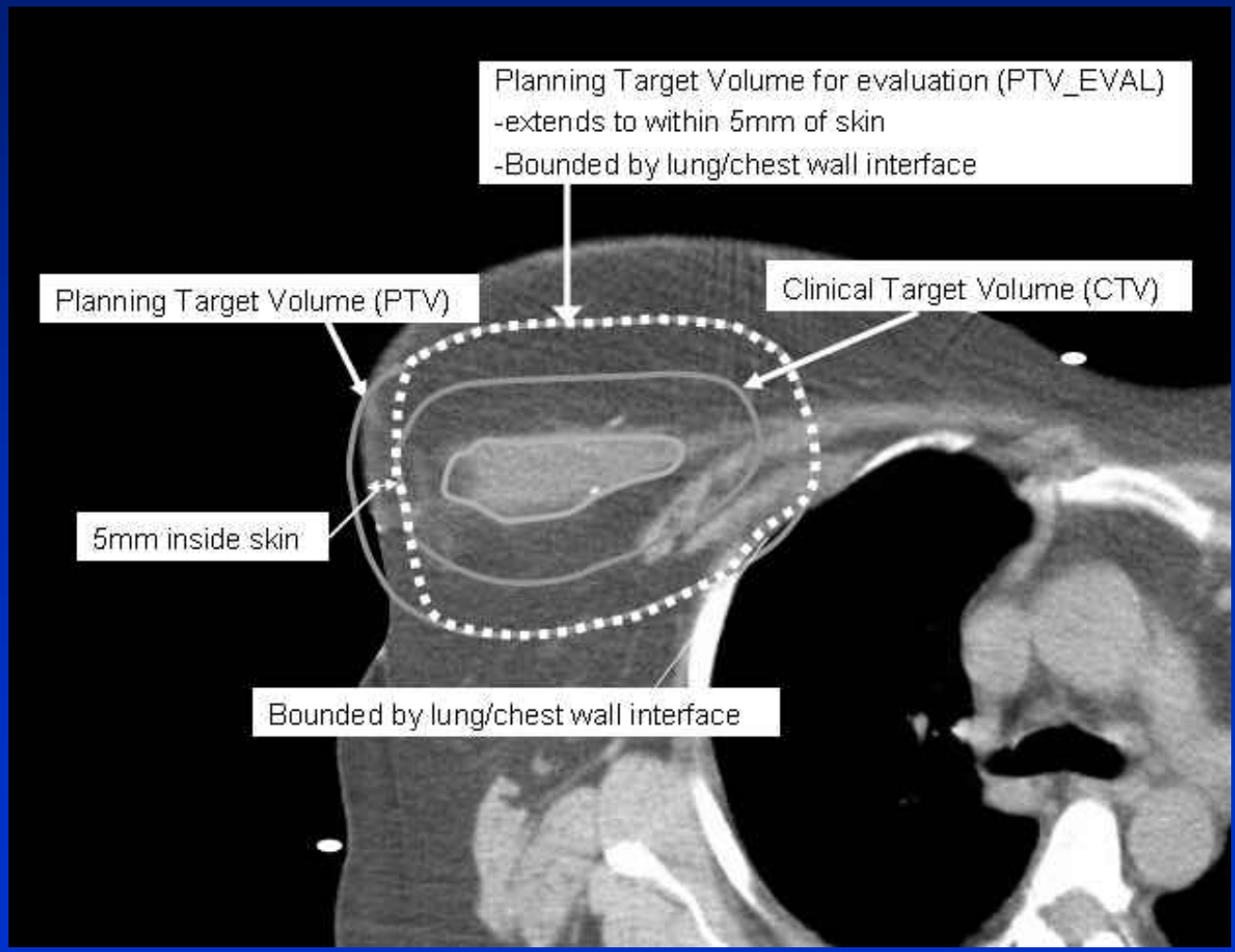
RTOG 0319

- **Accrual goal:**
  - **42 patients**
  - **Same as RTOG 95-17**
- **Participating Institutions**
  - **40 Sites Registered**
  - **24 Institutions Enrolled Patients**
- **Status:**
  - **52 patients treated (58 patients enrolled)**
  - **Trial opened August 15, 2003**
  - **Trial completed accrual: April 30, 2004**

3D-CRT Technique

- **Prescribed Dose:**
  - **3.85 Gy BID x 10 fractions in 5 days (current dose)**
- **Dosimetric Objectives:**
  - **Completely encompass CTV with 100% isodose line**
  - **Completely encompass PTV with 95% isodose line**
  - **Maintain a < 110% hot spot**
  - **Limit 50% of prescribed dose to ≤ 50% of breast**
  - **Irradiate less lung, heart, contralateral breast than whole breast tangents (or brachytherapy)**

Planning Volumes



Overall Accrual	
Study sample size	46
Total patients entered	58
Average monthly accrual	6.1

Accrual By Site	
Cross Cancer Institute - University of Alberta	8
University of Colorado Health Sciences Center	7
Medical College of Virginia Hospitals	6
Mayo Clinic	6
Medical College of Wisconsin	3
Yale Cancer Center	2
Foundation for Cancer Research and Education	2
Methodist Medical Center of Illinois	2
LDS Hospital	2
Memorial Sloan Kettering Cancer Center	1

RTOG 0319

- Patient/Tumor Characteristics -

Finding	*3D-RT (n=52)*	*3D-RT (n=42)*
Age		
Median	61	61
Range	38-89	38-83
Tumor dimension		
Median	0.90	0.85
Range	0.1-2.6	0.1-2.6
Less than 1cm	23 (44%)	20 (48%)
Between 1cm and 2cm	17 (33%)	14 (33%)
2cm or more	3 (6%)	2 (5%)
Missing	9 (17%)	6 (14%)
Histology		
Invasive ductal	45 (87%)	36 (86%)
Colloid	1 (2%)	1 (2%)
Tubular	5 (10%)	4 (10%)
Pending	1 (2%)	1 (2%)

RTOG 0319

- Results (First 42 Evaluable Patients) -

Variable	*Per Protocol (Acceptable)*	*Minor Variation (Marginally Acceptable)*	*Major Variation (Unacceptable)*
Overall Evaluation	6 (14%)	32 (76%)	4 (10%)
PTV Coverage	26 (62%)	16 (38%)	0 (0%)
Normal Tissues			
Contralateral Lung	37 (88%)	3 (7%)	2 (5%)
Ipsilateral Lung	33 (78%)	5 (12%)	4 (10%)
Heart	38 (91%)	3 (7%)	1 (2%)
Thyroid*	35 (85%)	6 (15%)	0
Contra Breast	22 (53%)	19 (45%)	1 (2%)
Ipsilateral Breast	28 (67%)	14 (33%)	0

*Note: One patient did not have a thyroid

RTOG 0319

- Results (All 51 Patients) -

Variable	*Per Protocol (Acceptable)*	*Minor Variation (Marginally Acceptable)*	*Major Variation (Unacceptable)*
Overall Evaluation	9 (18%)	37 (72%)	5 (10%)
PTV Coverage	32 (63%)	18 (35%)	1 (2%)
Normal Tissues			
Contralateral Lung	46 (90%)	3 (6%)	2 (4%)
Ipsilateral Lung	39 (76%)	8 (16%)	4 (8%)
Heart	45 (88%)	5 (10%)	1 (2%)
Thyroid*	44 (88%)	6 (12%)	0
Contra Breast	30 (59%)	20 (39%)	1 (2%)
Ipsilateral Breast	35 (69%)	16 (31%)	0

*Note: One patient did not have a thyroid

RTOG 0319

- **Results:**
  - **Data presented at San Antonio Breast Cancer Symposium**
  - **Technique shown to be reproducible**
  - **Image-Guided Radiation Therapy Center Used to submit images/data for analysis**

3D Conformal External Beam PBI

- Summary -

- 62 pts treated at William Beaumont Hospital using supine technique
- 52 patients successfully treated on RTOG 0319
- RTOG 0319: Data presented at San Antonio Breast Conference (December 2004)
- 47 patients treated successfully in prone position at New York University (Fermenti et al)
- > 50 patients treated at MGH (Taghian)

NSABP B 39/RTOG 0413

A Randomized Phase III Study of Conventional Whole Breast Radiation Therapy (WBT) vs Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer

NSABP B 39/RTOG 0413

- Eligibility Criteria -

- **Stage 0, I, II**
- **Infiltrating Carcinoma**
- **< 3.0 cm**
- **Negative margins (NSABP Criteria)**
- **≤ 3 positive nodes**
- **EIC (+) with negative margins**
- **Age > 18**

Protocol Design

Eligible patient with lumpectomy

Randomized

Whole Breast Radiotherapy after adjuvant chemotherapy

45-50Gy in 25 fractions
electron boost of 60-66 Gy to surgical bed with margin

VS

Partial Breast Irradiation prior to adjuvant chemotherapy

34 Gy in 3.4 Gy bid x 5-7 days

Interstitial Brachytherapy or
Mammosite Balloon Catheter or
3D Conformal External Beam

NSABP B-39/RTOG 0413

- **Sample size - 3000 patients**
- **<u>Stratification</u>:**
  - **Disease Stage (DCIS only, invasive and node negative, invasive and node positive (1-3)**
  - **Menopausal Status (premenopausal, postmenopausal)**
  - **Hormone Receptor Status (ER-positive and/or PgR Positive; ER-negative and PgR negative)**
  - **Intention to Receive Chemotherapy (Yes/No)**

Endpoints

- **Primary: in-breast tumor recurrence**
- **Secondary:**
  - **Distant disease-free survival**
  - **Overall survival**
  - **QOL: Cosmesis, fatigue, symptoms, burden of care**
  - **Direct non-medical costs (e.g. lost income)**

Sample Size Considerations

- **Estimated 6.1% 10-year cumulative incidence of IBTR for WBT**
  - **(hazard of 7.8 IBTR/1000 pt-year,**
  - **based on 11 previous NSABP trials**
- **Accrual 2.5 years**
- **Analyze when 175 IBTRs (about 11 years after trial opens)**

Pathology Specimen Submission

Pathology specimens must be submitted for all patients who have consented to the storage and use of their samples. Tissue requirements for B-39/0413 are:

- **paraffin block of initial diagnostic core biopsy, if available.**
- **representative H&E slides from the index tumor.**
- **representative paraffin block of from index tumor.**
- **representative paraffin block containing normal lobule at lumpectomy margin.**
- **representative paraffin block from positive lymph node, if applicable.**

QOL Population and Assessments

The QOL and cosmesis population will include *the first 482 enrolled patients who have indicated the intention to receive chemotherapy, and the first 482 patients who have indicated the intention not to receive chemotherapy,* and who have completed the baseline QOL form (Form QLB). In addition to the baseline QOL assessment, there will be QOL assessments at the following 6 time points:

- **at the end of adjuvant (non-hormonal) therapy (Form QLT)**
- **at 4 weeks after the completion of adjuvant (non-hormonal) therapy (Form QLP)**
- **6 months, and 1, 2, and 3 years after completion of adjuvant (non-hormonal) therapy (Form QLF)**

Physician-Reported Cosmesis Assessment

In addition to the baseline physician-reported cosmesis assessment, the patient's radiation oncologist will complete physician-reported cosmesis assessments at years 1 and 3 after completion of adjuvant (non-hormonal) therapy. If it is not possible for the patient's radiation oncologist to complete the assessments, the assessments may be completed by the patient's surgeon. ***It is preferred that the 3 physician-reported cosmesis assessments be completed by the same radiation oncologist.***

Quality Assurance

- **Cases submitted digitally to the ITC, processed and reviewed, second review by Investigators**
  - **Rapid review**
    - **First case for each PBI technique from each facility**
    - **Submitted-reviewed-feedback prior to treatment start**
  - **Timely review**
    - **Subsequent 4 cases of each PBI tech. will be reviewed with feedback**
    - **Patient may be treated prior to review and feedback.**
  - **Approval for accrual**
    - **Following completion of 5 cases for each PBI technique, all 5 will be reviewed together with feedback**
    - **Judgment on quality - repeat QA or approved for accrual**
    - **Facility can continue accruing during this period**
  - **Random case monitoring**

RTOG 0413/NSABP 0413

- **Protocol Availability for IRB Submission**
- **Credentialing (Date of Activation)**
- **Trial Activation**