Overview of APBI Phase III Trials: Validation of the APBI Concept According to the Irradiation Technique Used

Atif J. Khan, MD
Department of Radiation Oncology
The Cancer Institute of New Jersey
New Brunswick, NJ

Disclosure

Atif J. Khan, MD, does not have any financial relationships or products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months.

Standardization must not, however, be allowed to create a fixed belief that no further improvement is possible and that any suggested change is necessarily to be regarded with disapproval. Most surgeons who have taken the trouble to follow up their patients after performing the radical operation for cancer of the breast are indeed gravely dissatisfied with their results. I have described elsewhere (Keynes, 1929, 1932) the earlier stages of an attempt to find out whether irradiation with interstitial radium needles might be used to mitigate or possibly abolish the necessity for so drastic a form of treatment as the radical operation. The present communication embodies the late results obtained in a longer series of patients treated with interstitial radium than has hitherto been recorded. Encouragement is to be obtained from a survey of the present treatment of cancer

recently at St. Bartholomew's and University College Hospitals by J. H. Gray (1936, 1936a) under the inspiration of Professor H. H. Woollard. By the use of thorotrast and barium lymphatics have been made visible and their course traced more accurately than before, and it has been shown that there are no lymphatic plexuses in the deep fascial layers. Thus the lymphatic system of the breast lies in the gland and on its surface, the main lymphatic trunks passing round the fold of the axilla to the axillary nodes. No evidence whatever has been discovered in support of the theory of centrifugal permeation. On the other hand normal lymphatic channels are found to connect a carcinoma with infected nodes, the only possible inference being that carcinoma cells pass to the nodes as emboli, usually without forming intermediate points of growth. The supposed permeated

- "Most surgeons who have taken the trouble to follow up their patients after performing the radical operation for cancer of the breast are indeed gravely dissatisfied with their results"
- "…an attempt to find out whether irradiation with interstitial radium needles might be used to mitigate or possibly abolish the necessity for so drastic a form of treatment as the radical operation."
- "At the present time the whole breast area is treated with long needles, each containing 3 mg. radium element, placed in parallel series from each side and overlapping in the centre. The axilla is irradiated with from four to seven needles, two of which can be introduced into the apex of the axilla through the pectoral muscles. Care is taken to avoid placing a needle in too close proximity to the neurovascular bundle. Three shorter needles are introduced into the area above the clavicle, and, lastly, one of the shorter needles is placed in each of the upper three or four intercostal spaces."

APBI: Concept?

- Patterns of failure data within the breast…
- Pathological data demonstrating extent of residual…

"The APBI Concept"

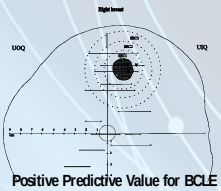
Patterns of failure data within the breast..

Study	N	Median f/u (mo)	IBTR (%) No WBI	IBTR (%) WBI	True Recurrence (%) No WBI	True Recurrence (%) WBI
Milan 3	579	109	20.5	5.4	17.6	3.7
Ontario	837	43	25.7	5.5	22.1	4.5
Uppsala-Oreboro	381	33	5.7	2.2	4.1	1.6

What about the Holland data??

"The APBI Concept"

Patterns of failure data within the breast…



Breast Carcinomas of Limited Extent

Frequency, Radiologic-Pathologic Characteristics, and Surgical Margin Requirements

Daniel R. G. Faverly, M.D.[1,2]
Jan H. C. L. Hendriks, M.D.[2,3]
Roland Holland, M.D.[1,2]

CANCER February 15, 2001 / Volume 91 / Number 4

Positive Predictive Value for BCLE Based on Both Mammographic and Pathologic Characteristics in a Hypothetical Surgical Excision with a Macroscopically Free Margin of 2 cm

Variable	Frequency in the study group (%)	Sensitivity of the variable[a] (%)	Positive predictive value for BCLE[b] (%)	Frequency of false-positive BCLE[c] (%)	*P* value[d]
Absence of tumor beyond the edge of index tumor on mammography and absence of tumor in SEC2 on pathology[e]	72/135 (53)	64/72 (89)	64/72 (89)	8/72 (11)	< 0.001

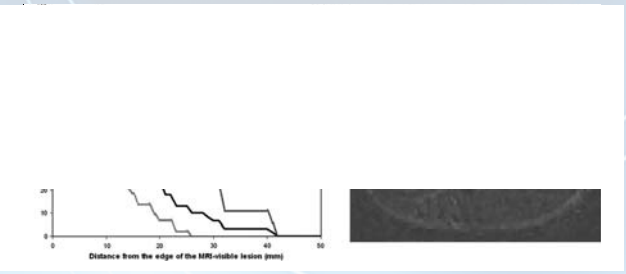
BCLE: breast carcinoma of limited extent; SEC2: sector 2, tissue sector of 1 cm thickness between 1 and 2 cm from the edge of index tumor.
[a] Proportion of tumors associated with the variable in the BCLE group.
[b] No. of rightly identified BCLE cases vs. the no. of suspected BCLE cases based on the given variable.
[c] No. of erroneously suspected BCLE cases.
[d] Level of statistical significance: *P* value < 0.05.
[e] Absence of DCIS, invasive carcinoma, and lymphatic emboli in sector 2.

"The APBI Concept"

Magnetic resonance imaging

Precise correlation between MRI and histopathology – Exploring treatment margins for MRI-guided localized breast cancer therapy

Annemarie C. Schmitz [a,b], Maurice A.A.J. van den Bosch [b], Claudette E. Loo [a], Willem P.Th.M. Mali [b], Harry Bartelink [c], Maria Gertenbach [d], Roland Holland [†], Johannes L. Peterse [f,*], Emiel J.Th. Rutgers [g], Kenneth G. Gilhuijs [a,*]



"Given a theoretical 10-mm uniform excision margin, the results of the current study suggest that irradiation of an additional 10 mm around the excision cavity using, e.g., brachytherapy with the MammoSite catheter may cover microscopic disease in up to 75% of the patients. When only EIC tumors are considered, disease coverage may increase up to 93%."

A Prospective Pathologic Study to Define the Clinical Target Volume for Partial Breast Radiation Therapy in Women With Early Breast Cancer

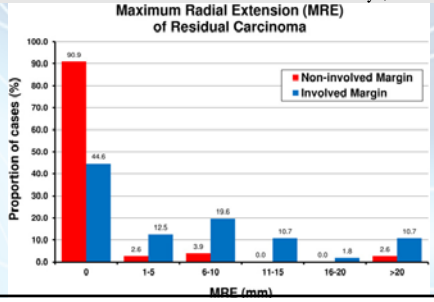
Brandon T. Nguyen, MBBS(Hons),*,# Siddhartha Deb, MBBS,†,§ Stephen Fox, DPhil,† Prudence Hill, PhD,‖ Marnie Collins, BSci(Hons),‡ and Boon H. Chua, PhD*,¶

Table 4 Incidence of residual disease in the re-excision or completion mastectomy specimens stratified by width of the nearest initial radial surgical margin

Initial nearest radial margin	Total patients	Patients with residual disease	Percent with residual disease	95% CI
Negative (>1 mm)	56	4	7.2%	2.3-16.9
Close (>0 mm and ≤1 mm)	21	3	14.3%	4.0-34.0
Involved (0 mm)	56	31	55.4%	41.5-68.7
Total	133	38	28.6%	21.1-36.5

Abbreviation: CI = confidence interval.

Int J Radiation Oncol Biol Phys, Vol. 84, No. 5, pp. 1116–1122, 2012



DEFINING THE CLINICAL TARGET VOLUME FOR PATIENTS WITH EARLY-STAGE BREAST CANCER TREATED WITH LUMPECTOMY AND ACCELERATED PARTIAL BREAST IRRADIATION: A PATHOLOGIC ANALYSIS

Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 3, pp. 722–730, 2004

FRANK A. VICINI, M.D.,* LARRY L. KESTIN, M.D.,* AND NEAL S. GOLDSTEIN, M.D.†

Departments of *Radiation Oncology and †Anatomic Pathology, William Beaumont Hospital, Royal Oak, MI

		Reexcision specimen findings					
		Extension distance from edge of initial excision site (mm)					
Initial excision specimens margins	No.	Negative	>0–<5 mm	5–<10 mm	10–<15 mm	≥15 mm	*p* valu
Negative	18 (100%)	13 (72.2%)	1 (5.6%)	2 (11.1%)	2 (11.1%)	0	<0.00
Near: least amount	59 (100%	39 (66.1%)	11 (18.6%)	7 (11.9%)	1 (1.7%)	1 (1.7%)	
Near: intermediate amount	34 (100%)	23 (67.7%)	5 (14.7%)	5 (14.7%)	0	1 (2.9%)	
Near: greatest amount	23 (100%)	8 (34.8%)	3 (13.0%)	4 (17.4%)	5 (21.7%)	3 (13.0%)	
Positive	199 (100%)	36 (18.1%)	47 (23.6%)	65 (32.7%)	26 (13.1%)	25 (12.6%)	
NSABP criteria							
Negative	134 (100%)	83 (61.9%)	20 (14.9%)	18 (13.4%)	8 (6.0%)	5 (3.7%)	<0.00
Positive	199 (100%)	36 (18.1%)	47 (23.6%)	65 (32.7%)	26 (10.2%)	25 (9.0%)	
Carcinoma: specimen dimension ratio							
<0.30	137 (100%)	70 (51.1%)	24 (17.5%)	27 (19.7%)	11 (8.0%)	5 (3.6%)	<0.00
0.30–<0.60	102 (100%)	33 (32.2%)	24 (23.5%)	26 (25.5%)	11 (10.8%)	8 (7.8%)	
≥0.60	93 (100%)	15 (16.1%)	19 (20.4%)	30 (32.3%)	12 (12.9%)	17 (18.3%)	
Totals	333 (100%)	119 (35.7%)	67 (20.1%)	83 (24.9%)	34 (10.2%)	30 (9.0%)	

Abbreviation: NSABP = National Surgical Adjuvant Breast and Bowel Project.

Summary: "The APBI Concept"

- Available clinical and pathological data suggest microscopic residual disease may not extend to the whole breast!

Reported clinical data support the "APBI concept" in terms of treatment efficacy…

Published APBI Results — Multicatheter-Based Brachytherapy

Institution	*# Patients*	*Follow-Up (Months)*	*% Local Recurrence*
NIO-Hungary (phase II)	45	**136**	**9.3***
WBH	199	**113**	**5***
Orebro University	50	**86**	**4+**
MGH	48	**84**	**2**
Tufts/Brown University	33	**84**	**9**
NIO-Hungary (phase III)	128	**81**	**4.7**
Oschner Clinic	51	**75**	**2.0**
RTOG 95-17	99	**74**	**4.0**
Tufts-Brown University	33	**58**	**6**
VCU	59	**50**	**5.1**
University of Wisconsin	247	**48**	**3****
Joe Arrington Cancer Center	136	**48**	**3.7**
German-Austrian MC Trial	274	**38**	**0.4**
University Kansas	24	**37**	**0**
Florence Italy	90	**27**	**4.4**
Totals	***1516***	***27-136***	***0-9%***

*12-year rate, += 7-year rate
** High-risk patients

Published APBI Results – Balloon Applicator

Institution	*# Cases*	*Follow-Up (Months)*	*% Local Recurrence*
FDA Trial	43	**66**	**0%**
University of Wisconsin	26	**48.5**	**3%***
ASBS Registry Trial	1449	**51**	**2.6%**
MUSC	99	**46**	**3.1%**
Rush	70	**26**	**6%**
WBH	80	**24**	**2.9%**
VCU	483	**24**	**1.2%**
Texas Cancer Center	234	**21**	**0.8%**
Tufts/VCU/NEMC	28	**19**	**0%**
Single Institution Experiences	1000	**2-12**	**0-3%**
Totals	***3512***	***2-66***	***0-6%***

*High-risk patients

But do we have Phase III data on APBI?

10 Phase III Trials

- Ten Phase III Trials
- Four PBI Techniques:
  - Brachytherapy RT (Interstitial/MammoSite)
    - NSABP B-39/RTOG 0413
    - GEC-ESTRO Working Group
    - National Institute of Hungary
  - Single-Fraction Intra-Operative RT
    - European Institute of Oncology
    - University College of London
  - Fractionated External Beam RT
    - NSABP B-39/RTOG 0413
    - National Institute of Hungary
    - Canadian Phase III trial
    - Medical Research Council-UK
    - Barcelona
    - Florence
    - Spain

Reported Phase III Trials of Brachytherapy

HDR Multicatheter Interstitial APBI

BREAST-CONSERVING TREATMENT WITH PARTIAL OR WHOLE BREAST IRRADIATION FOR LOW-RISK INVASIVE BREAST CARCINOMA—5-YEAR RESULTS OF A RANDOMIZED TRIAL

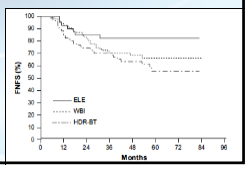
CSABA POLGÁR, M.D., PH.D.,* JÁNOS FODOR, M.D., PH.D., D.SC.,* TIBOR MAJOR, M.SC., PH.D.,* GYÖRGY NÉMETH, M.D., PH.D., D.SC.,* KATALIN LÖVEY, M.D.,* ZSOLT OROSZ, M.D., PH.D.,† ZOLTÁN SULYOK, M.D.,‡ ZOLTÁN TAKÁCSI-NAGY, M.D., PH.D.,* AND MIKLÓS KÁSLER, M.D., PH.D.*

- 258 patients, T1N0-1mic, non-lobular, no EIC randomized to WBI or PBI (2 Gy/25F/n=40) electrons or HDR (5.2 Gy/7F Gy/n=88)
- Median follow-up of 66 months, median 9 catheters
- 5-year LR: 4.7% vs 3.4%
- Symptomatic fat necrosis: 11.4% HDR vs 8.5% WBI

Table 5. Cosmetic outcome

Harvard cosmetic score	PBI-HDR BT ($n = 85$)*	PBI-EB ($n = 40$)*	WBI-photons ($n = 93$)*	WBI-cobalt ($n = 23$)*
Excellent	21 (24.7)	5 (12.5)	11 (11.8)	2 (8.7)
Good	48 (56.5)	23 (57.5)	50 (53.8)	10 (43.5)
Fair	14 (16.5)	12 (30.0)	24 (25.8)	10 (43.5)
Poor	2 (2.3)	0	8 (8.6)	1 (4.3)

Abbreviations: PBI = partial breast irradiation; HDR BT = high-dose-rate brachytherapy; EB = external beam; WBI = whole breast irradiation.
Data presented number of patients (percentage).
* n = patient number with data available on cosmetic outcome.



National Institute of Oncology
- Budapest, Hungary -

- **Results/New Data:**
  - Presented at ESTRO 2012
  - 10-year update (median follow-up, 120 months)
  - No differences noted in local failure
    - –5.9% vs 5.1%
  - 81% E/G cosmesis with APBI vs 63% with WBI

Radiother Oncol 2013
Jun 3
S0167-8140(13)00220-X

Results From GEC-ESTRO Randomized Phase III Trial

(Brachytherapy 12 (2013) S15)

(n=1193)	APBI	WBI+boost	P-value
Acute skin grade 2	2.1 %	35.7 %	
Acute skin grade 3	0.2 %	7.0 %	P<0.0001
Hematoma grade 1	18.8%	1.8%	P<0.0001
No late skin	77.8%	72.3%	P=0.0182
No late hyperpigment.	78.5%	72.7%	P=0.0126
No differences in breast pain, hematoma, infection, fibrosis, fat necrosis.			

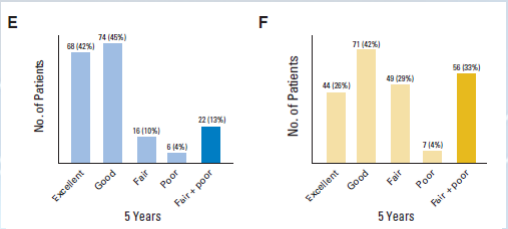
Reported Phase III Trials of EBRT APBI

Interim Cosmetic and Toxicity Results From RAPID: A Randomized Trial of Accelerated Partial Breast Irradiation Using Three-Dimensional Conformal External Beam Radiation Therapy

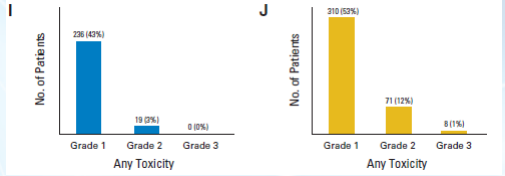
Ivo A. Olivotto, Timothy J. Whelan, Sameer Parpia, Do-Hoon Kim, Tanya Berrang, Pauline T. Truong, Iwa Kong, Brandy Cochrane, Alan Nichol, Isabelle Roy, Isabelle Germain, Mohamed Akra, Melanie Reed, Anthony Fyles, Theresa Trotter, Francisco Perera, Wayne Beckham, Mark N. Levine, and Jim A. Julian

Published Ahead of Print on July 8, 2013 as 10.1200/JCO.2013.50.5511
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.50.5511

Cosmesis



Toxicity



Interim Results

Adverse Cosmetic Outcome (Fair or Poor)
Nurse and Panel Assessment
at 3 Years

	WBI	APBI	Difference APBI – WBI (95% CI)	p-value
Nurse (n=850)	19%	32%	13% (7 – 19%)	< 0.0001
Panel (n=766)	17%	35%	18% (12 – 24%)	< 0.0001

Spain-Phase III Trial

- **102 patients:**
  - 51 WBI : 48 Gy +/- 10 Gy boost)
  - 51 APBI: 37.5 Gy (10 fractions bid)
- **Median follow-up: 5 years**
- **Results:**
  - No difference in IBTR (0% in both arms)
  - % Good/excellent cosmesis: No difference
    - 75% APBI
    - 84% WBI
- **Conclusion:**
  - No differences in efficacy/toxicity
  - Similar treatment used in NSABP B39/RTOG 0413

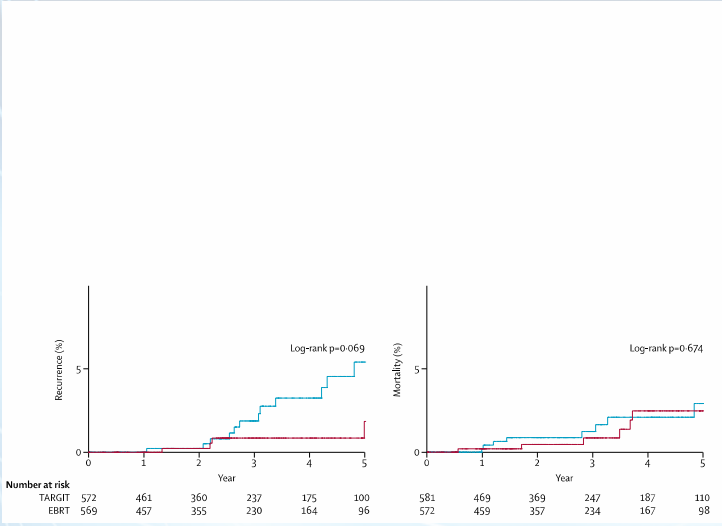
Reported Phase III Trials of Intraoperative APBI

Update on the TARGIT-A Trial

www.thelancet.com Vol 382 Published online November 11, 2013 http://dx.doi.org/10.1016/S0140-6736(13)61950-9

- 3451 randomized patients, median follow-up: 2.5 years; 2020 with 4-year follow-up, 1222 with 5-year follow-up
- Pre- vs post-pathology strata (pre-path: 21% received whole breast RT)
- **5-year ipsilateral breast recurrence: 3.3% vs 1.3% (*P* = 0.042)**
- Absolute difference: 2%
  - Absolute difference in pre-path strata: 1% (2.1% vs 1.1%)
  - Absolute difference in post-path strata: 3.7% (5.4% vs 1.7%)

Update on the TARGIT-A Trial



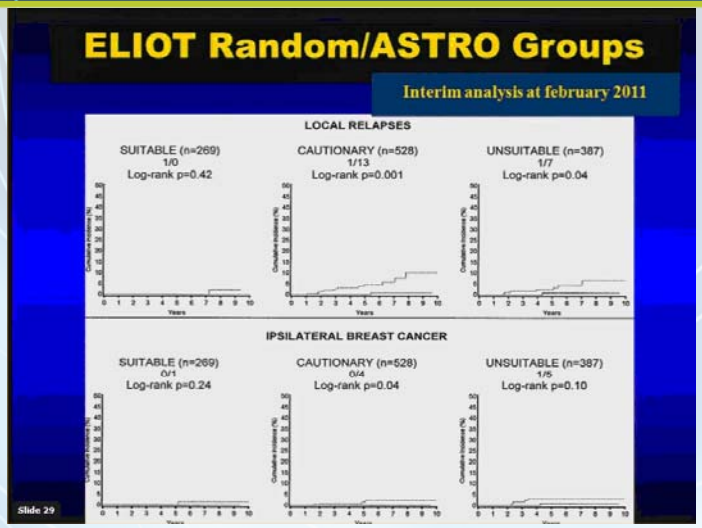
Does TARGIT Work?

- Reported prematurely
- Microscopic cells don't lie as far away as 1 cm
- When treating with a single fraction, much lower doses are needed than previously thought
- Perioperative radiotherapy has an effect on the microenvironment
- Whole breast contamination overwhelms signal

Update on the ELIOT Trial

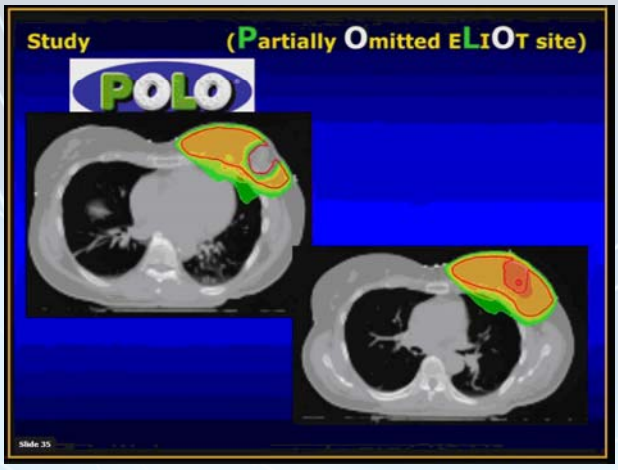
www.thelancet.com/oncology Published online November 11, 2013 http://dx.doi.org/10.1016/S1470-2045(13)70497-2

- 1184 randomized women; median follow-up, 6 years
- No "remedial" whole breast RT
- **5-year ipsilateral breast recurrence: 4.4% vs 0.4% (*P* < 0.0001)**
- Fat necrosis rate: 14.5% (vs 2%–3% with device-based 5-day APBI)
- Only 23% of patients "suitable" for APBI, 33% (387/1184) "unsuitable"

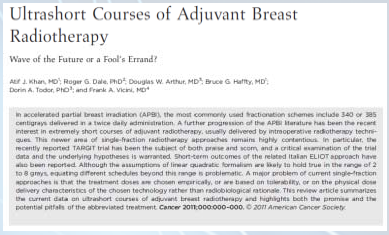


ESTRO meeting proceedings, 2012

ELIOT Successor Trial…



Limitations of Intraoperative APBI



Ultrashort Courses of Adjuvant Breast Radiotherapy

Wave of the Future or a Fool's Errand?

Atif J. Khan, MD[1], Roger G. Dale, PhD[2], Douglas W. Arthur, MD[3], Bruce G. Haffty, MD[1], Donn A. Todor, PhD[1], and Frank A. Vicini, MD[4]

In accelerated partial breast irradiation (APBI), the most commonly used fractionation schemes include 340 or 385 centigrays delivered in a twice daily administration. A further progression of the APBI literature has been the recent interest in extremely short courses of adjuvant radiotherapy, usually delivered by intraoperative radiotherapy techniques. This newer area of single-fraction radiotherapy approaches remains highly contentious. In particular, the recently reported TARGIT trial has been the subject of both praise and scorn, and a critical examination of the trial data and the underlying hypotheses is warranted. Short-term outcomes of the related Italian ELIOT approach have also been reported. Although the assumptions of linear quadratic formalism are likely to hold true in the range of 2 to 8 grays, equating different schedules beyond this range is problematic. A major problem of current single-fraction approaches is that the treatment doses are chosen empirically, or are based on tolerability, or on the physical dose delivery characteristics of the chosen technology rather than radiobiological rationale. This review article summarizes the current data on ultrashort courses of adjuvant breast radiotherapy and highlights both the promise and the potential pitfalls of the abbreviated treatment. **Cancer 2011;000:000–000.** © 2011 American Cancer Society.

- Treatment triage occurs before permanent path review (no margin/LN evaluation)
- 20% of patients selected for intraop got additional WBI (TARGIT-A, but not ELIOT)
- Logistics (increase OR time, coordinate schedules (surgeon/radiation oncologists dedicated path to do intraop assessment)
- Treatment planning is NOT image based
- Dosimetry/radiobiology not validated

Summary: Reported experiences from Canadian RAPID Trial and UK/Italian Intraop Trials do NOT affect the "APBI Concept" but may tell us something about those particular APBI techniques!

PENDING Phase III Trials of Intraoperative APBI

NSABP B-39/RTOG 0413 Phase III APBI Trial

Eligible Patients with Lumpectomy

RANDOMIZED

Whole Breast Irradiation after Adjuvant Chemotherapy

50 Gy (2.0 Gy/fraction) or
50.4 Gy (1.8 Gy/fraction) to whole breast, followed by optional boost to ≥60 Gy

Partial Breast Irradiation prior to Adjuvant Chemotherapy

For a total of 10 treatments given on 5 days over 5 to 10 days:

34 Gy in 3.4 Gy fractions
Interstitial Brachytherapy or
MammoSite balloon catheter
or
38.5 Gy in 3.85 Gy fractions
3D Conformal External Beam

NSABP B-39/RTOG 0413

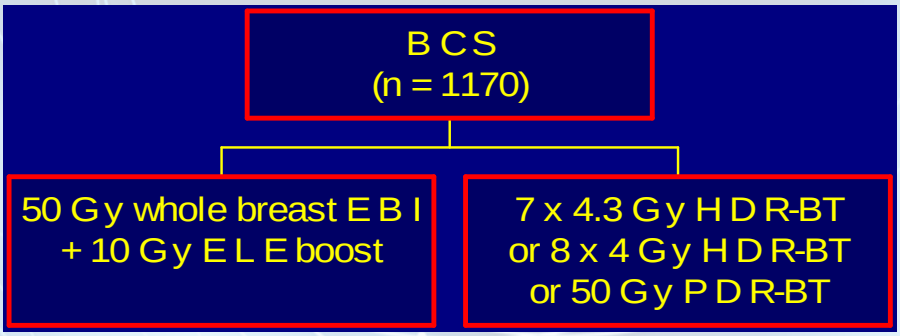
- **Open**:
  - March 21, 2005
- **Accrual**:
  - Completed May 2013: *4216*
- **Participating Sites**:
  - 78 – NSABP
  - 142 – RTOG/CTSU
- **PBI Technique:**
  - 71.0%: 3D Conformal
  - 23.3%: MammoSite
  - 5.7%: Interstitial
  - 0.2%: SAVI (5 cases)
  - 0.1%: Contura (3 cases)

NSABP B-39/RTOG 0413

- **Toxicity**:
  - Adverse events, including toxicities, second primary cancers and deaths monitored continuously (q/month)
  - Progress reports presented to Data Monitoring Committee (DMC) at 6-month intervals (reviewed internally monthly)
    - To date, DMC has found no reason for concern
    - Majority of dermatologic toxicities, pain, fibrosis-cosmesis, infection, etc., have been Grade 1 and 2 (<2% grade III)
- Int J Radiat Oncol Biol Phys. 2010 May 1;77(1):317

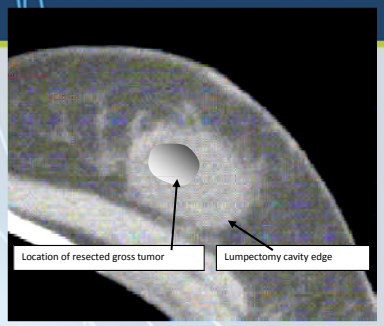
- Toxicity data from 1458 patients randomized to 3-D CRT APBI were reviewed
- 1076 patients in their third year of follow-up
- Median time on study of 49.8 months
- No significant toxicity-related issues have been noted
- For the 3D-CRT used in this trial rates of fibrosis-cosmesis and fibrosis-deep connective tissue toxicities are:
  - Grade 2: ≤13%
  - Grade 3: ≤3%
  - Grade 4 or more: 0%
- Median follow-up (all patients): 7 years

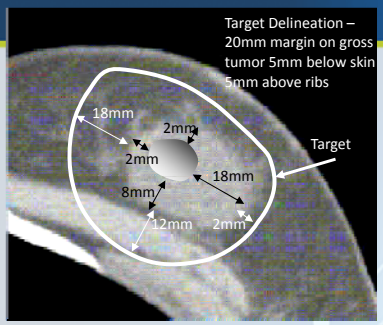
GEC-ESTRO
- Multicenter Phase III Trial -



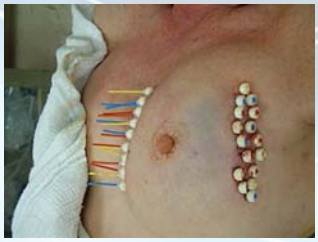
Status:
Activated May 2004

Accrual:
1195 enrolled, 2009 (closed)





GEC-ESTRO Target Definition



DW

GEC-ESTRO
- Multicenter Phase III Trial -

Presented at ESTRO 2012

- No differences in toxicity at 1 year!
- Outcome data not yet reported

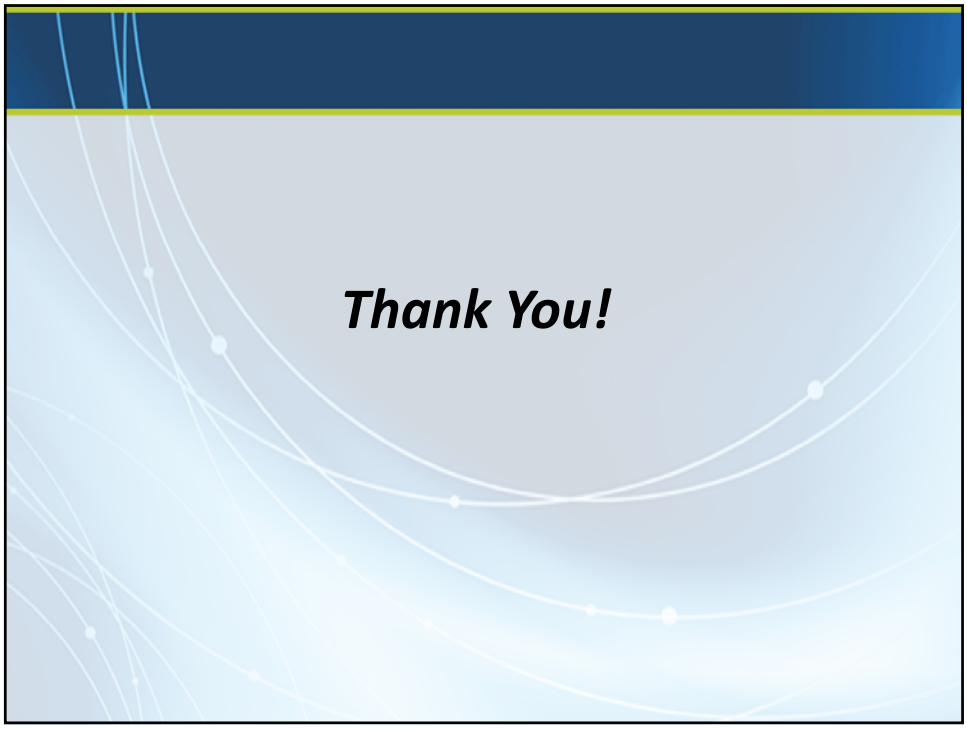
Results should be available on efficacy in 2014

Medical Research Council-UK

- IMPORT Low Trial
- **Arm I:**
  - WBI - 2.67 Gy x 15
  - Accelerated whole breast RT
- **Arm II:**
  - (1): WBI - 2.4 Gy x 15 plus
  - Concurrent PBI: 2.67 Gy x 15
  - (2): PBI: 2.67 Gy x 15
- Enrollment goals: 1935 cases

Conclusions

- APBI concept is based on sound rationale
- Phase I and II and Registry Trial data support APBI concept
- Phase III trials currently pending…deluge of data anticipated
- Hungarian randomized trial demonstrates equivalence
- Early results from GEC-ESTRO support better toxicity with brachy-APBI


Thank You!