IceCure

IceCure ProSense™ Cryoablation System

General and Plastic Surgery Devices Panel Meeting

November 7, 2024

Introduction and Company Overview

Shay Levav

Vice President of Quality Assurance,
Regulatory Affairs and Clinical Application

IceCure Medical

Introducing IceCure Medical

IceCure

FOUNDED IN 2006

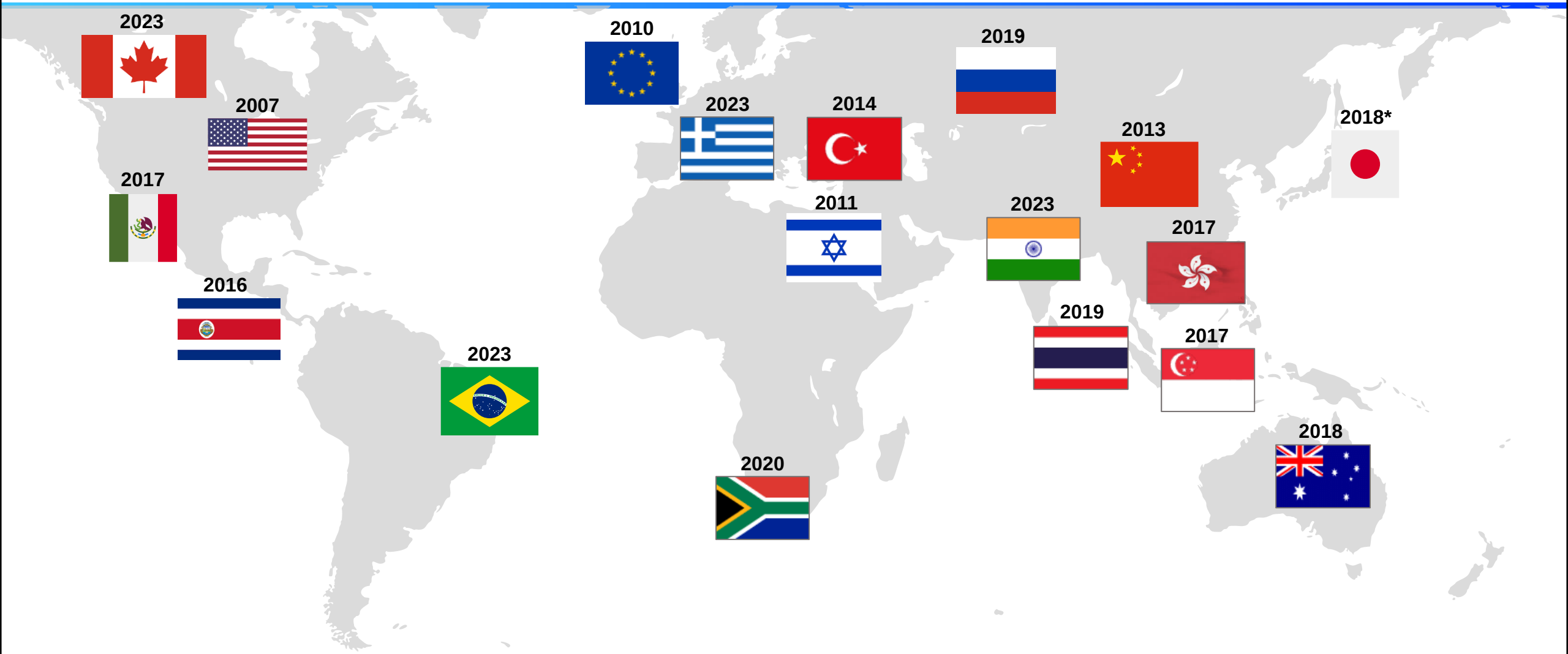
Bringing advanced minimally invasive cryoablation solutions

IceCure's flagship product, ProSense™, is a cryosurgical tool for treatment of tumors in women's health and interventional oncology fields

ProSense™ utilizes Liquid Nitrogen (LN2) for optimal tumor destruction

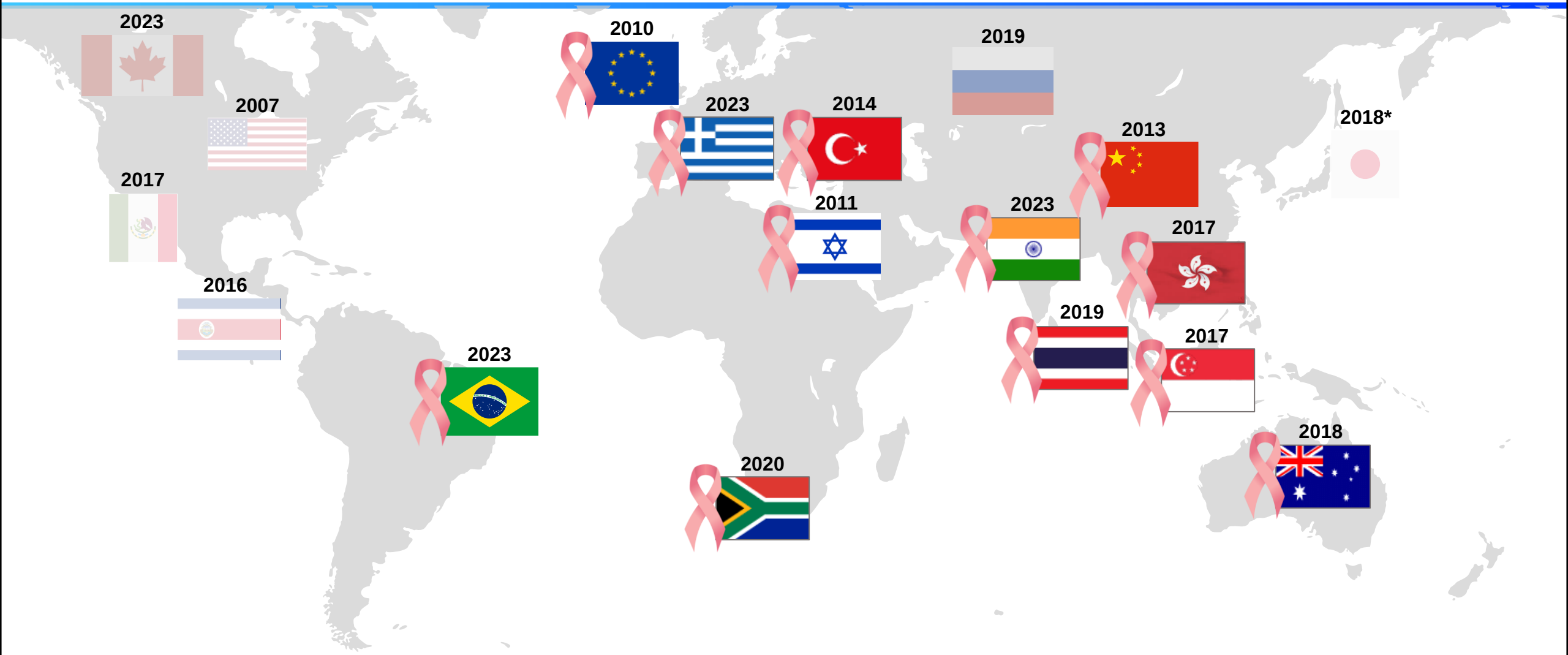
Freezing tumors quickly with minimal pain, rapid recovery, and great cosmetic results

ProSense™ Cryoablation System Approvals



*Under Private License Importation

ProSense™ Cryoablation System Approvals



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ProSense™ Cryoablation System

- FDA cleared since 2007 for tumor ablation (including breast fibroadenomas)
- ICE3 clinical study, initiated in 2014, is the largest clinical trial to evaluate cryoablation without excision for treatment of breast cancer
- FDA granted ProSense™ Breakthrough Device Designation in March 2021

Expands patient choice with minimally invasive alternative to standard-of-care lumpectomy

Proposed Indication

The ProSense™ is indicated for use in the treatment of patients with early stage, low-risk breast cancer* for the treatment of breast cancer with adjuvant endocrine therapy

*Patients ≥60 years of age with prognostic stage 1A defined as unifocal tumor size ≤1.5 cm, ER+/PR+/-, HER2-, histological grade 1-2 infiltrating ductal carcinoma (excluding lobular carcinoma, extensive intraductal component, or evidence of lymphovascular invasion), and clinically negative lymph node (N0)

ICE3 Study Conclusions

ICE3 Study Shows Benefits of Cryoablation Outweigh Risks

IBTR-free patients

>95% through 5 years follow-up

>96% through 5 years when treated with adjuvant endocrine therapy

- Near immediate recovery to normal activity – median 1 day
- >99% of patients were satisfied with cosmetic results at 5-years
- Risks are sufficiently mitigated through training and real-time visualization of tumor ablation during treatment and routine annual mammography

ICE3 demonstrates ProSense™ is safe and effective for the treatment of early stage, low-risk breast cancer

IBTR=Ipsilateral Breast Tumor Recurrence

Agenda

Patient Selection & Treatment Options	**Nathalie Johnson, MD, DHL, FACS** Sr. Medical Director Legacy Cancer Institute – Portland, Oregon
Principles of Cryoablation & Prior Studies	**Robert Carlton Ward, MD** Associate Professor of Diagnostic Imaging Warren Alpert Medical School of Brown University
ICE3 Study Design & Results	**Richard E. Fine, MD, FACS** Breast Program Director & Director of Education & Research Margaret West Comprehensive Breast Center, WCC & RI
FDA-Requested Post-Hoc Analyses	**Margeaux Rogers, MS, RAC** Vice President, Regulatory Affairs MCRA, LLC, an IQVIA Business
Clinical Perspective	**Richard E. Fine, MD, FACS**

Patient Selection & Treatment Options

Nathalie Johnson, MD, DHL, FACS

Senior Medical Director, Legacy Cancer Institute

Portland, Oregon

Breast Cancer Background

>300,000

NEW CASES

will be diagnosed in women in 2024[1]

Heterogeneous complex of diseases, a spectrum of many subtypes with distinct biological features

Biological features determine response patterns to various treatment modalities and clinical outcomes

1. American Cancer Society. *How common is breast cancer?* https://www.cancer.org/cancer/types/breast-cancer/about/how-common-is-breast-cancer.html.

Early Stage, Low-risk Breast Cancer Tumor Characteristics

Lowest Risk ← → **Highest Risk**

Tumor Size (T)	**T1:** Tumor size ≤2 cm	**T2:** Tumor size 2-5 cm	**T3:** Tumor size >5 cm	**T4:** Tumor extends to skin or chest wall
Lymph Nodes (N)	**N0:** No lymph node metastasis	**N1:** Metastasis to ipsilateral, movable axillary LNs	**N2:** Metastasis to ipsilateral fixed axillary, or IM LNs	**N3:** Metastasis to infraclavicular/supra-clavicular LN, or to axially and IM LNs
Metastasis (M)	**M0:** No distant metastasis	**M1:** Distant metastasis		

Early stage, low-risk breast cancer patients are most appropriate for de-escalation of care

Early Stage, Low-risk Breast Cancer Tumor Characteristics

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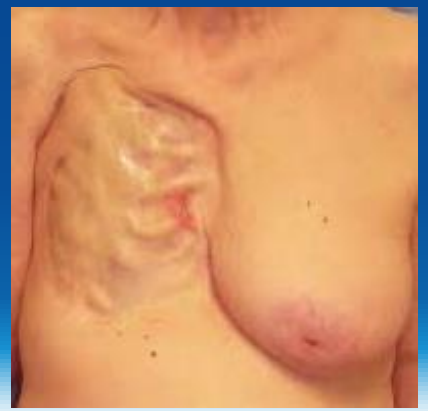
Metastasis (M)	**M0:** No distant metastasis	**M1:** Distant metastasis		
Subtype	Luminal A			
Nottingham Grade	1 or 2			
Receptor	ER+, PR+			
Her2 Status	Her2neu-			

Early stage, low-risk breast cancer patients are most appropriate for de-escalation of care

Specific Patient Selection Based on Tumor Risk

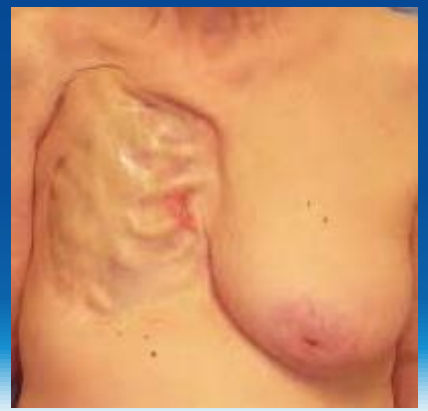
Risk Factor	ICE3 Selected / Indicated Population
Prognostic Stage	1A
Size	≤2 cm (further reduced to ≤1.5 cm)
Lymph Node Involvement	No lymph node metastases
Metastases	No distant metastases
Age	≥60 years
Receptor Status	ER+/PR+/-
HER2/neu	HER2-
Histological Grade (Nottingham) Subcomponents: nuclear, mitotic, tubule	Composite Grade 1/2

De-escalation Trends in Breast Cancer “Removal” Surgery



Radical Mastectomy
Halstead 1890’s

De-escalation Trends in Breast Cancer “Removal” Surgery



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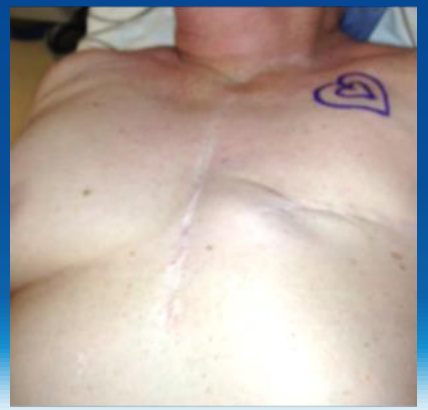

Modified Radical Mastectomy
Dyson & Patey 1948

Total Mastectomy + Radiation
McWhirter 1948

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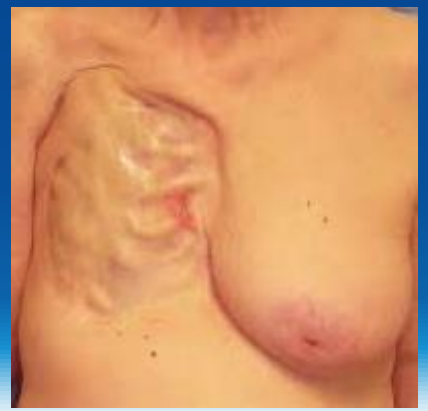

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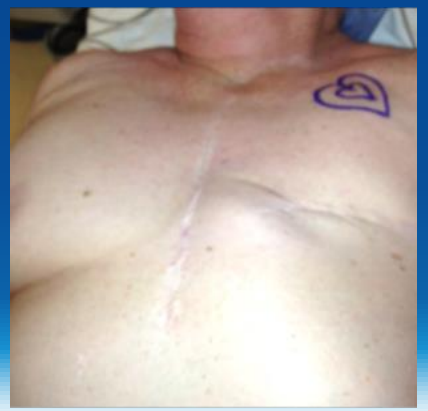

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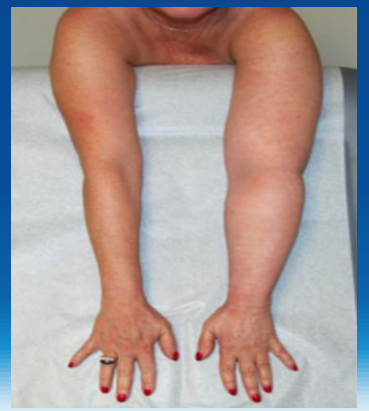
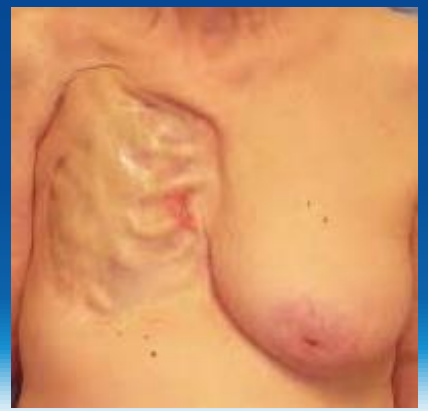


Lumpectomy, Axillary Dissection, Radiation
late 1980’s/1990’s

De-escalation Trends in Breast Cancer “Removal” Surgery



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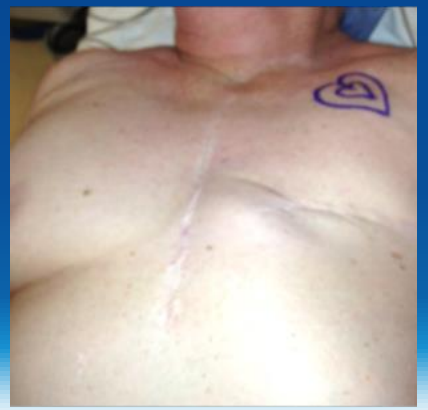

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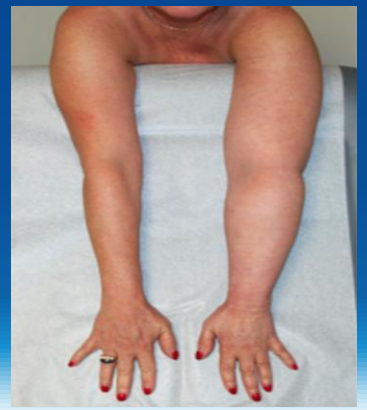

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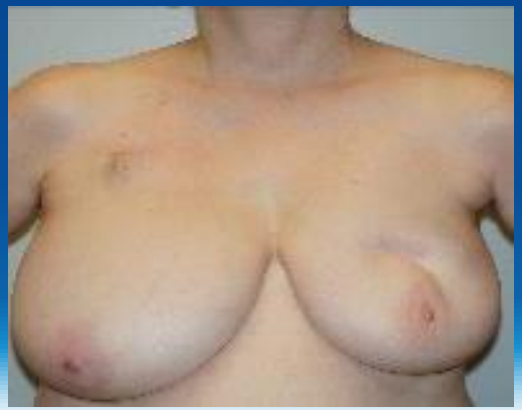
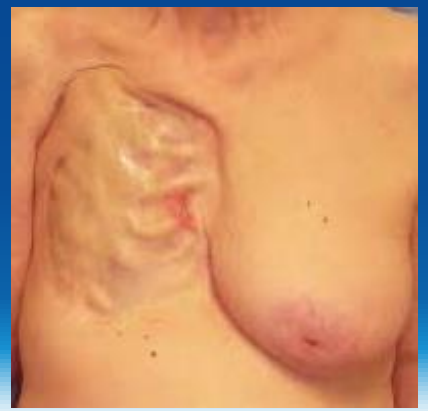


Lumpectomy/ Sentinel Lymph Node Biopsy

De-escalation Trends in Breast Cancer “Removal” Surgery



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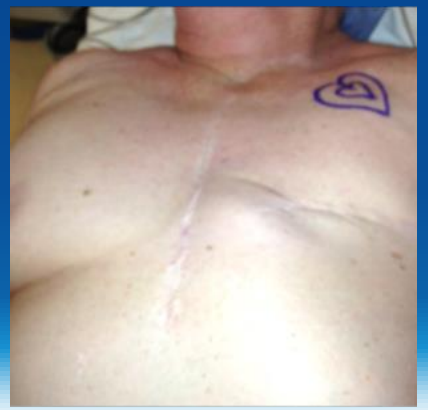

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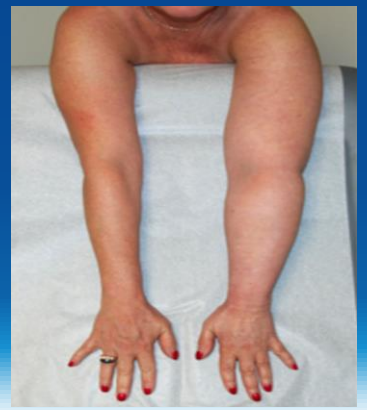

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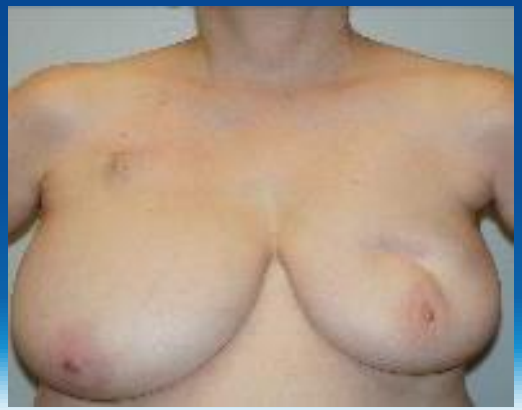
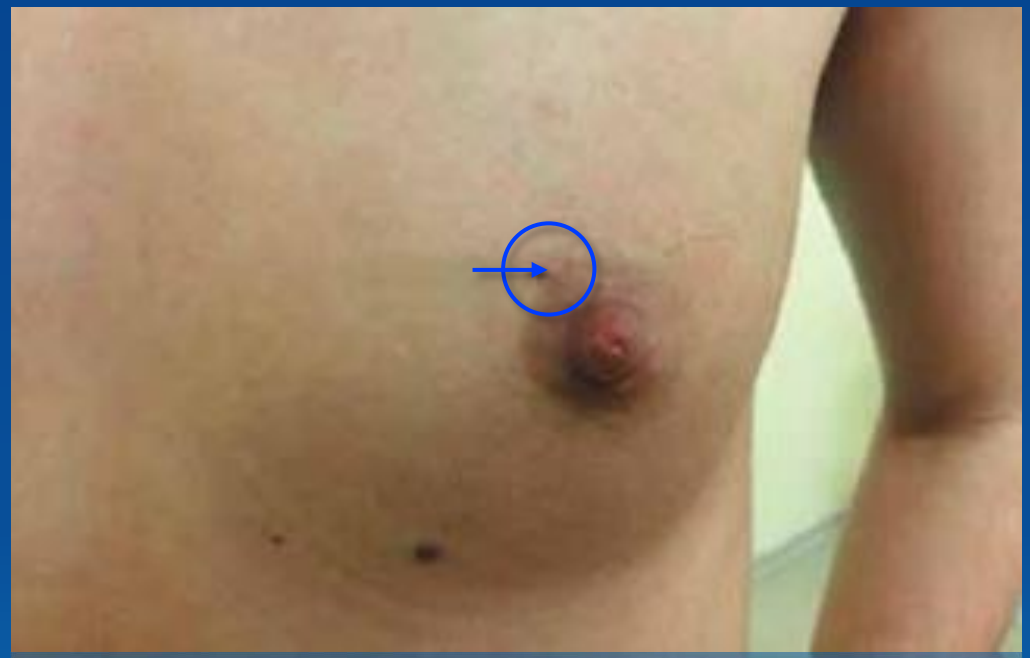


Lumpectomy/ Sentinel Lymph Node Biopsy

CAN WE DO LESS?

Cryoablation of Breast Tumors



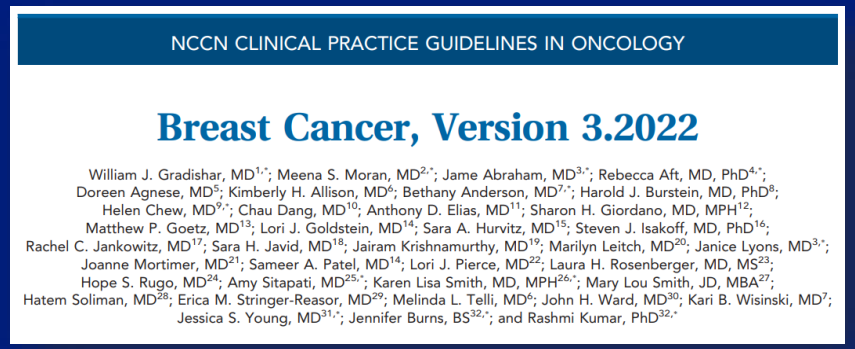
Cryoablation

1985 to present

De-escalation of Care – Omission of Radiotherapy

CALGB 9343:
- RT vs. No RT: 3% difference at 5 years and 8% at 10 years, in IBTR
- 1% difference in overall survival

PRIME II:
- RT vs. No RT: 3% difference at 5 years and 9% at 10 years, in IBTR
- No differences in distant metastases, contralateral breast cancer, overall survival, new breast cancers


NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY

Breast Cancer, Version 3.2022

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Despite differences in local recurrence rate, no meaningful difference in overall survival

2022/2024 National Comprehensive Cancer Network (NCCN) guidelines updated in 2024:
Consider omitting RT following BCS in women aged 65 years and older with Stage I, ER+ breast cancer who receive adjuvant endocrine therapy

Despite differences in local recurrence rate, the clinical community is recommending de-escalation of care

IBTR=Ipsilateral Breast Tumor Recurrence

De-escalation of Care – Less Axillary Surgery, Less Radiation

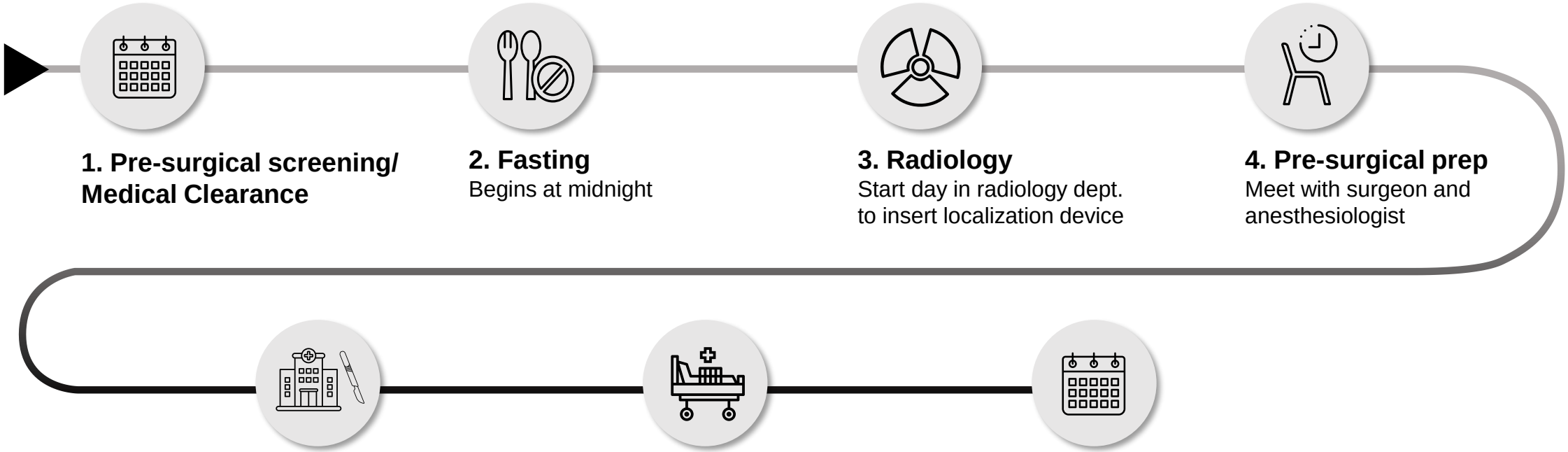
Choosing Wisely®

5 QUESTIONS to Ask Your Doctor Before You Get Any Test, Treatment, or Procedure

1. Do I really need this test or procedure?
2. What are the risks and side effects?
3. Are there simpler, safer options?
4. What happens if I don't do anything?
5. How much does it cost, and will my insurance pay for it?

CAN WE DO LESS? Are there even simpler, safer options?

Patient Experience: Lumpectomy



1. Pre-surgical screening/ Medical Clearance

2. Fasting
Begins at midnight

3. Radiology
Start day in radiology dept. to insert localization device

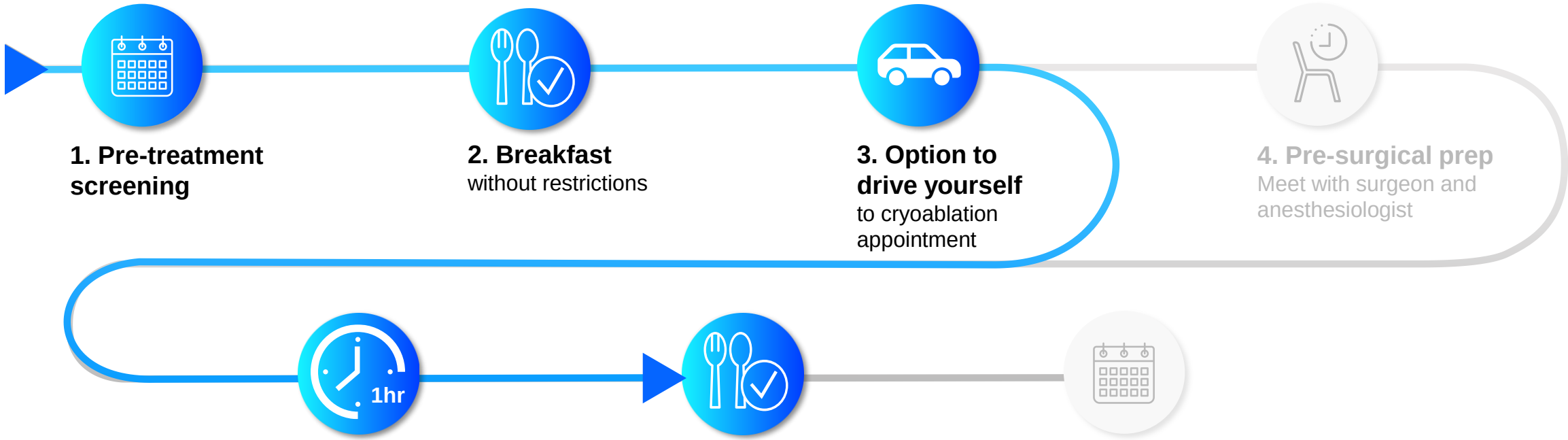
4. Pre-surgical prep
Meet with surgeon and anesthesiologist

5. Full anesthesia
Lumpectomy procedure lasts 1-2 hours, tumor is surgically excised

6. Recovery room
1 hour in recovery, waiting for anesthesia to wear off.
May experience pain, nausea.
Need to be driven home

7. Recovery at home
Pain control, Potential continued nausea from anesthesia, Higher risk of post-operative bleeding or seroma

Patient Experience: Cryoablation



1. Pre-treatment screening

2. Breakfast
without restrictions

3. Option to drive yourself
to cryoablation appointment

4. Pre-surgical prep
Meet with surgeon and anesthesiologist

4. Cryoablation
- **Local anesthesia**
- **Small bandage** placed on insertion site
- **One hour** start to finish

5. Resume normal activities
start your journey **towards being a breast cancer survivor**

7. Recovery at home
Pain control, Potential continued nausea from anesthesia, Higher risk of post-operative bleeding or seroma

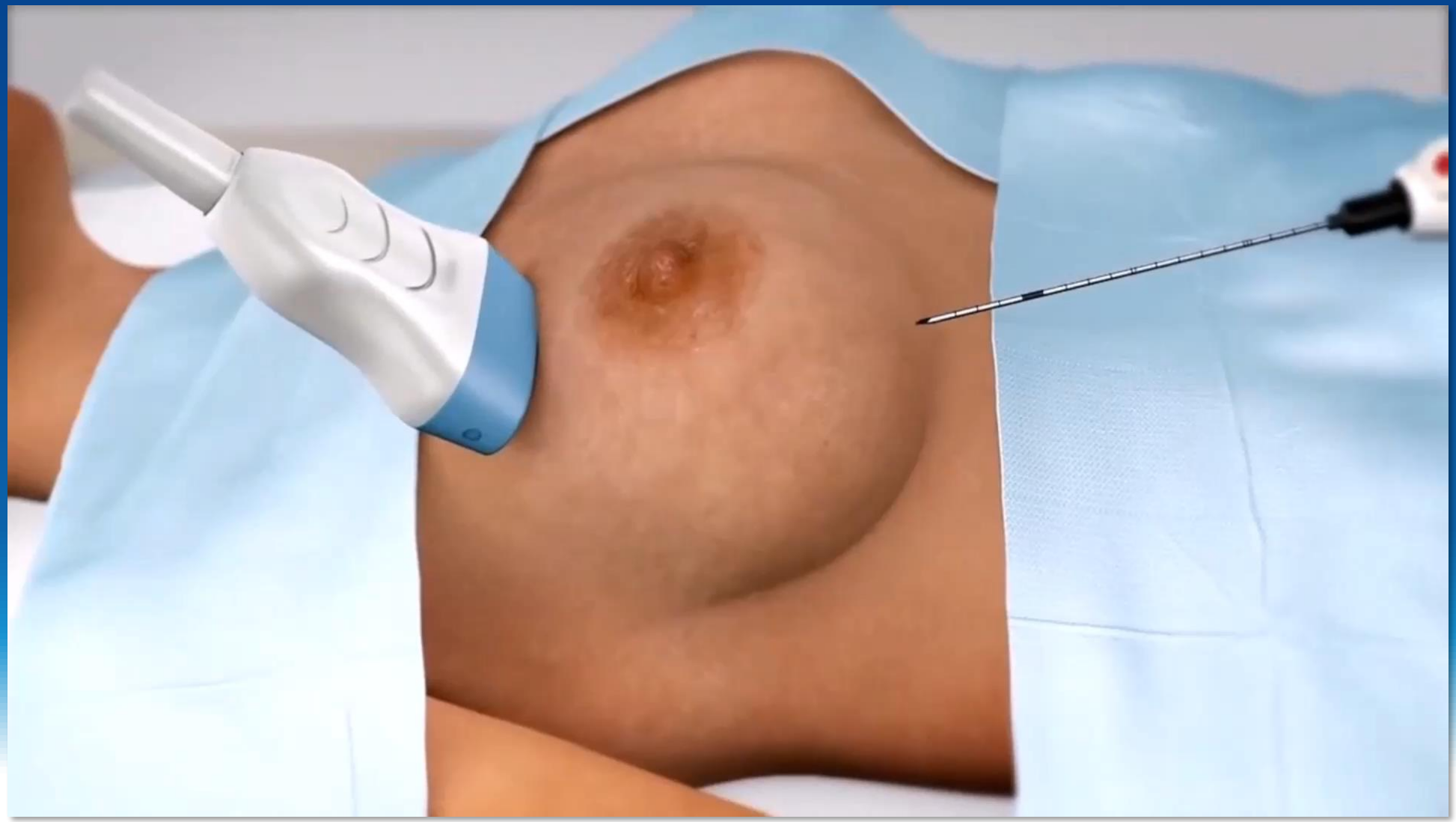
Principles of Cryoablation & Prior Studies

Robert C. Ward, MD

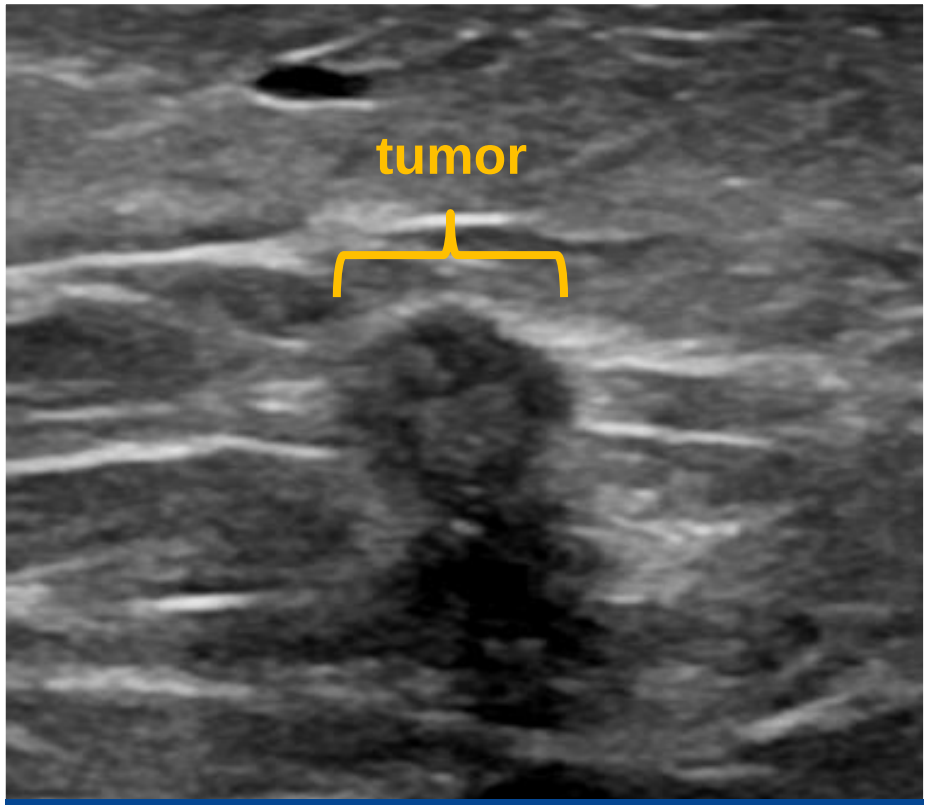
Associate Professor of Diagnostic Imaging

Warren Alpert Medical School of Brown University

Cryoablation, a Basic Ultrasound-guided Procedure



Real-time Ultrasound Needle Placement



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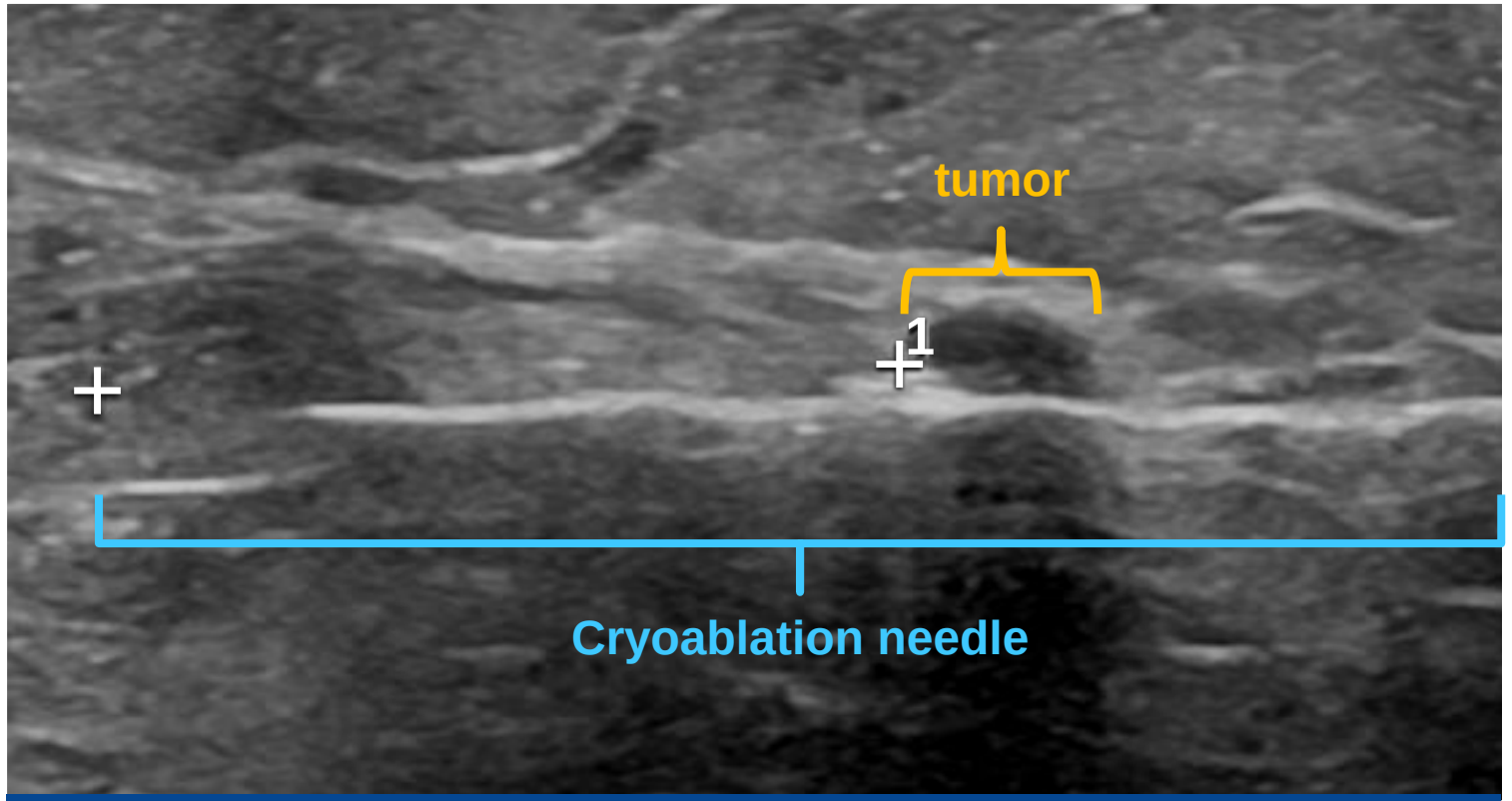
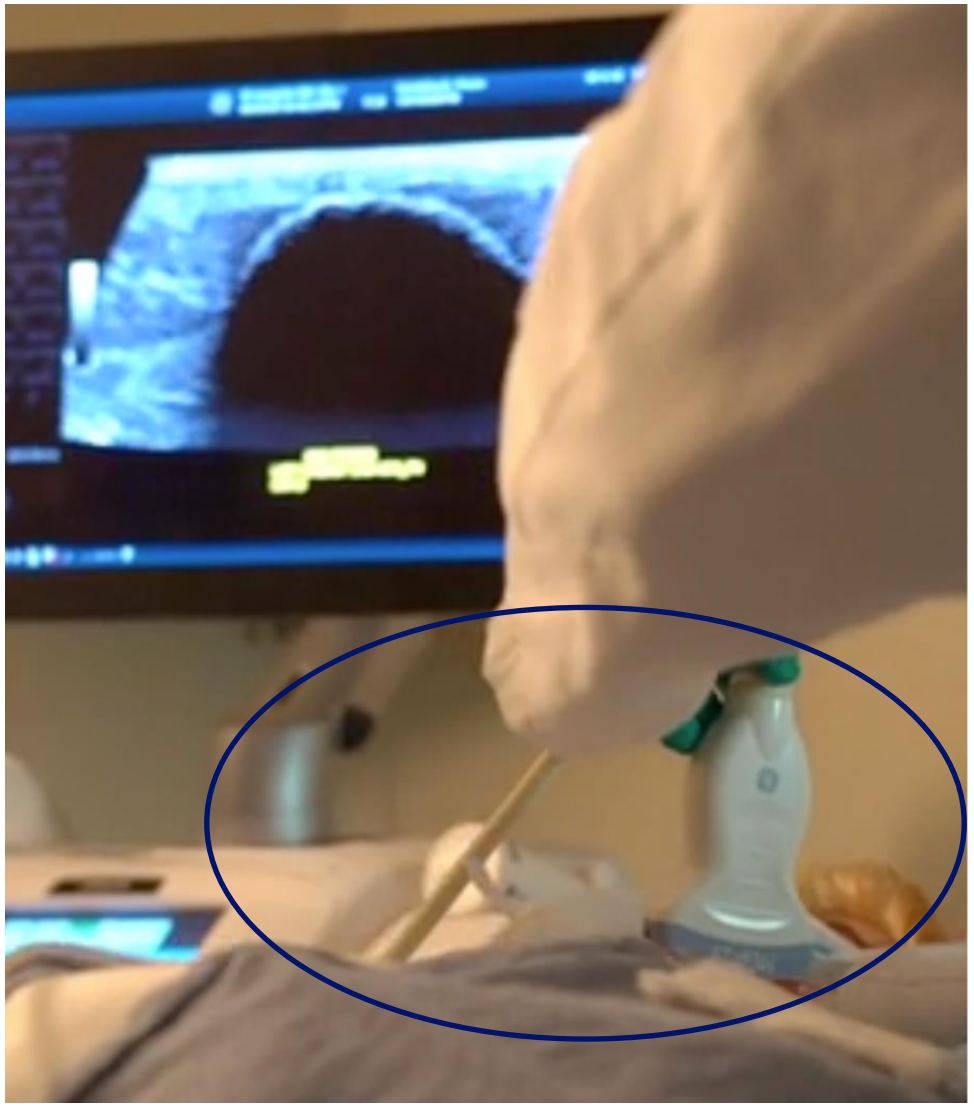
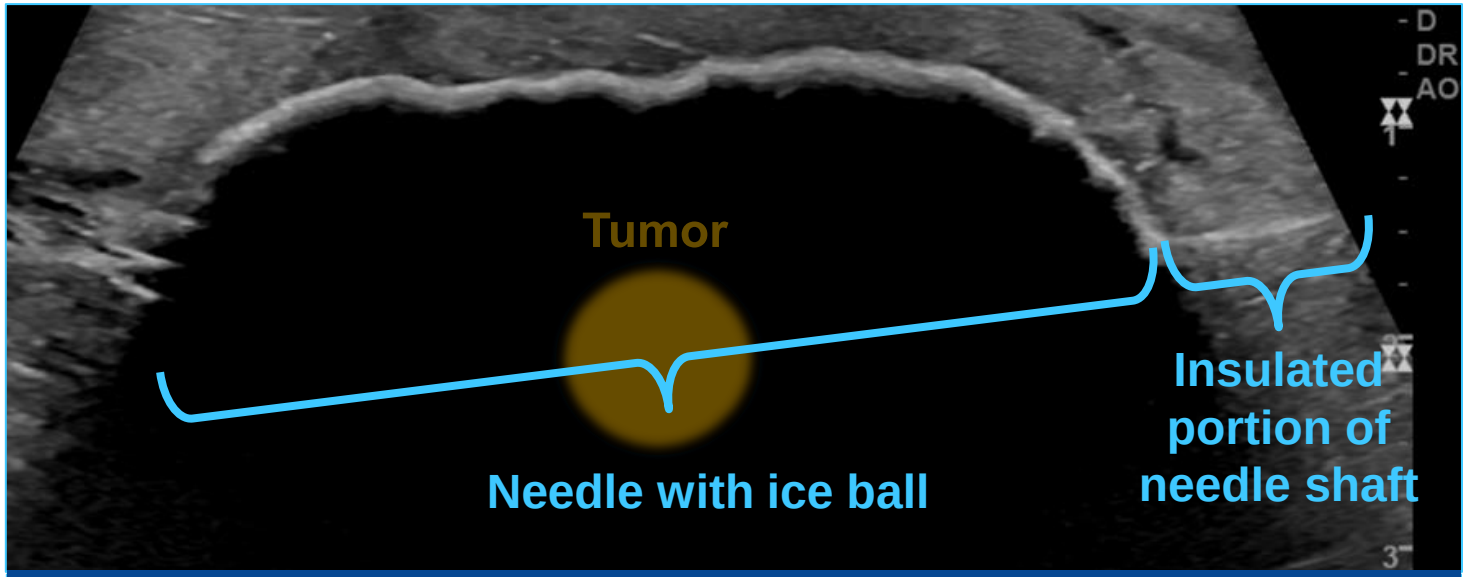


Needle Placement

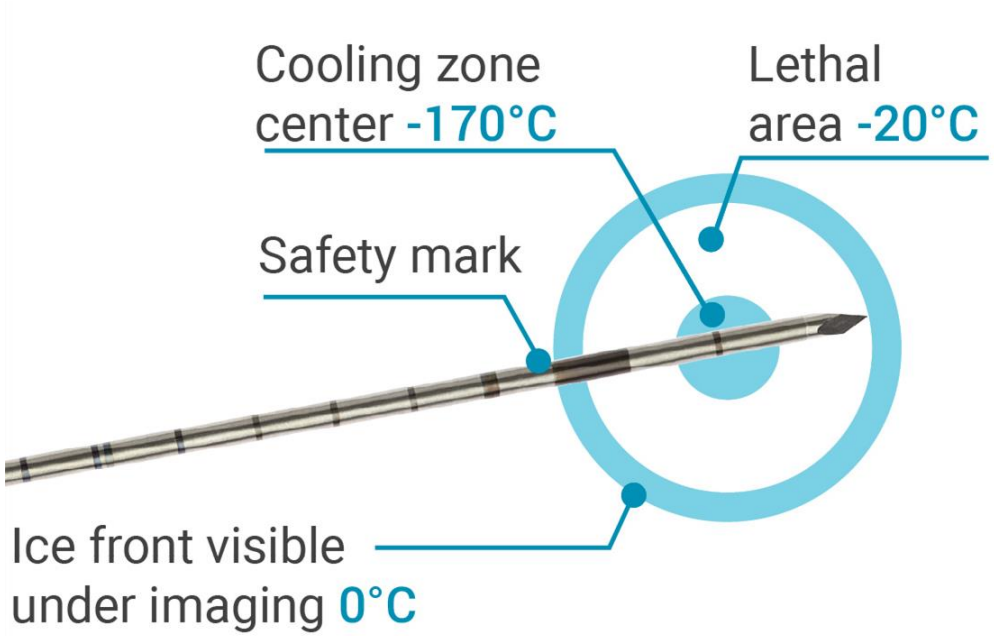
Real-time Ultrasound Procedural Monitoring

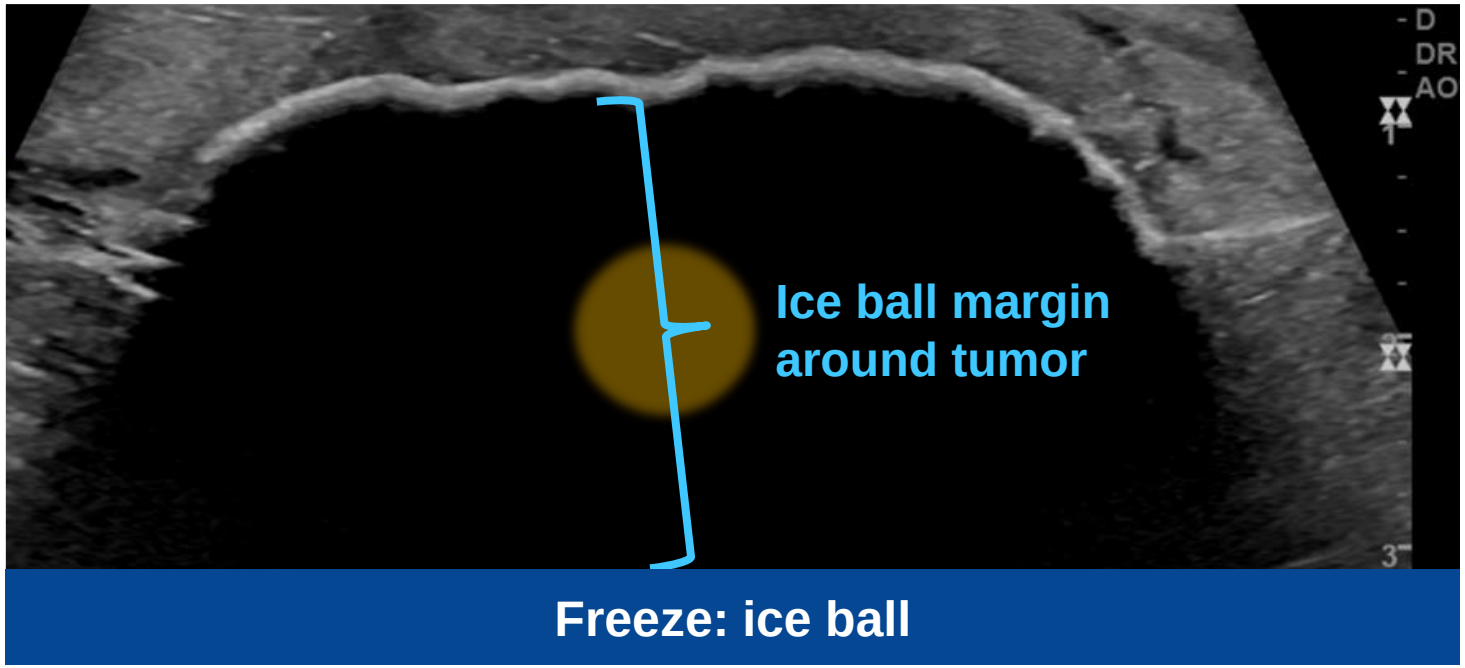




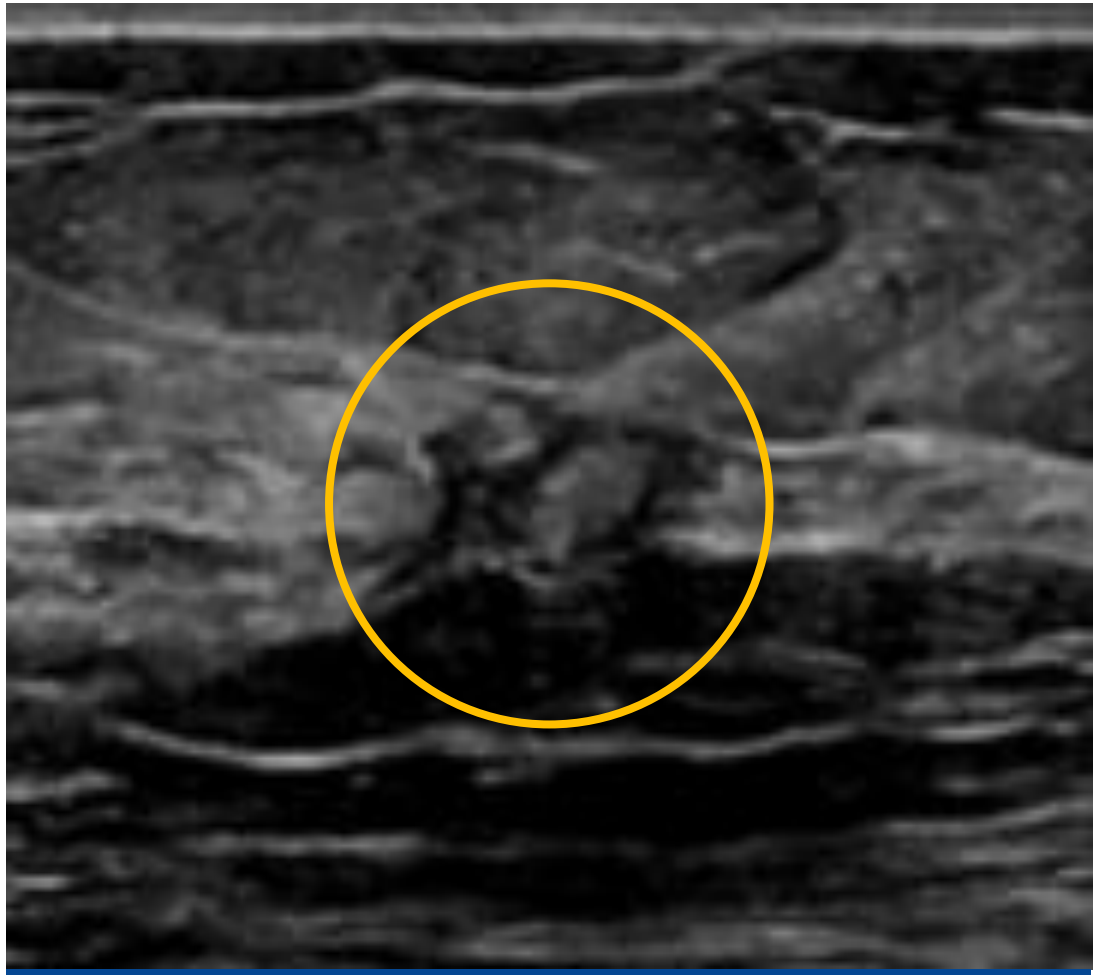
Freeze: ice ball

Real-time Ultrasound Margin Assessment





Follow-up Imaging: Ultrasound



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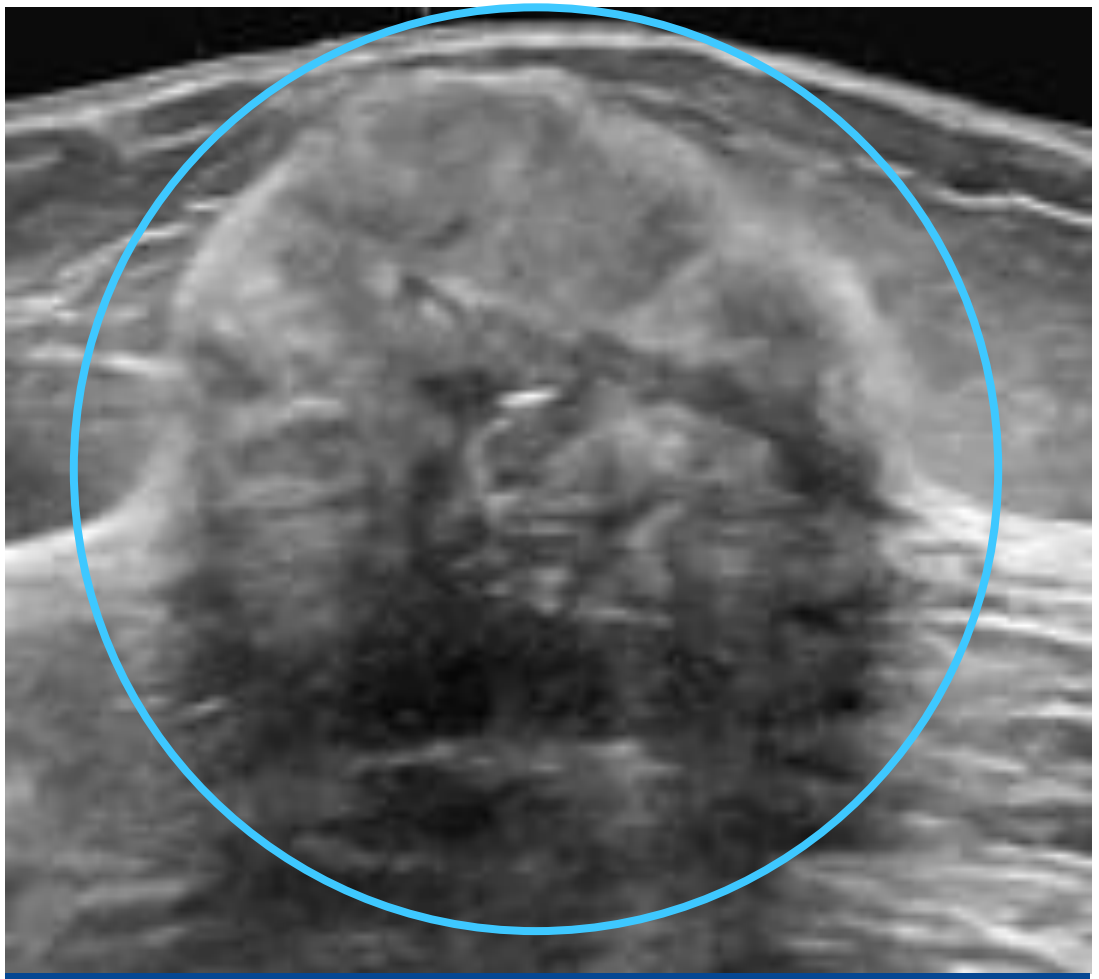
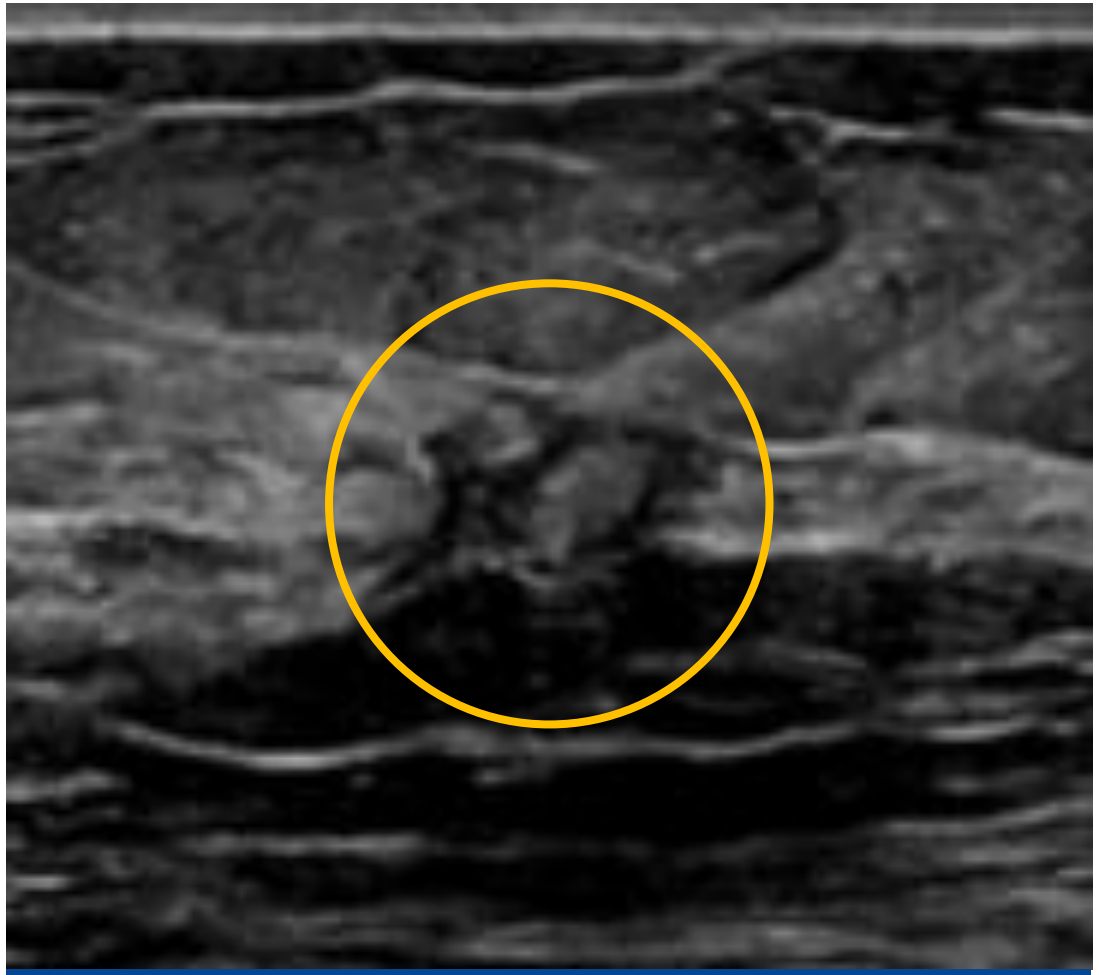


6 Months

Follow-up Imaging: Ultrasound



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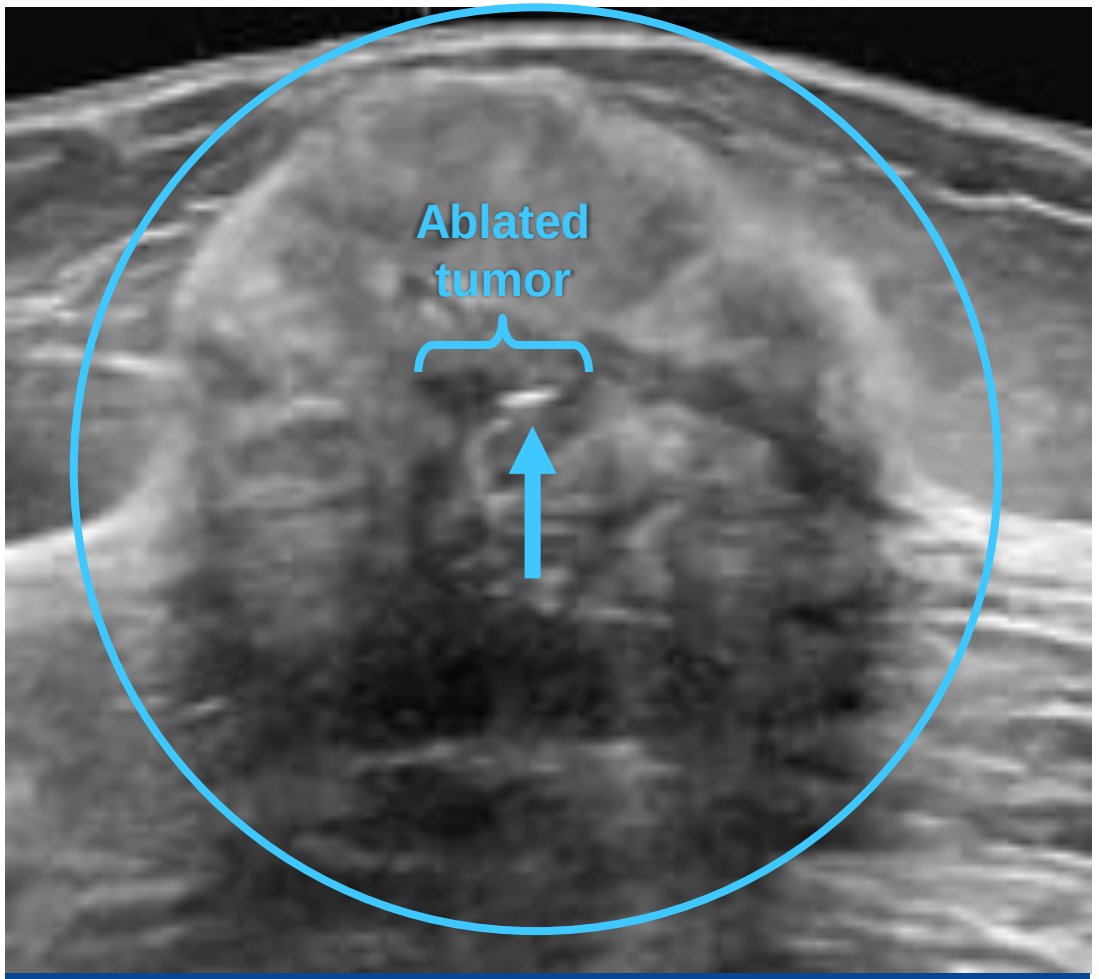
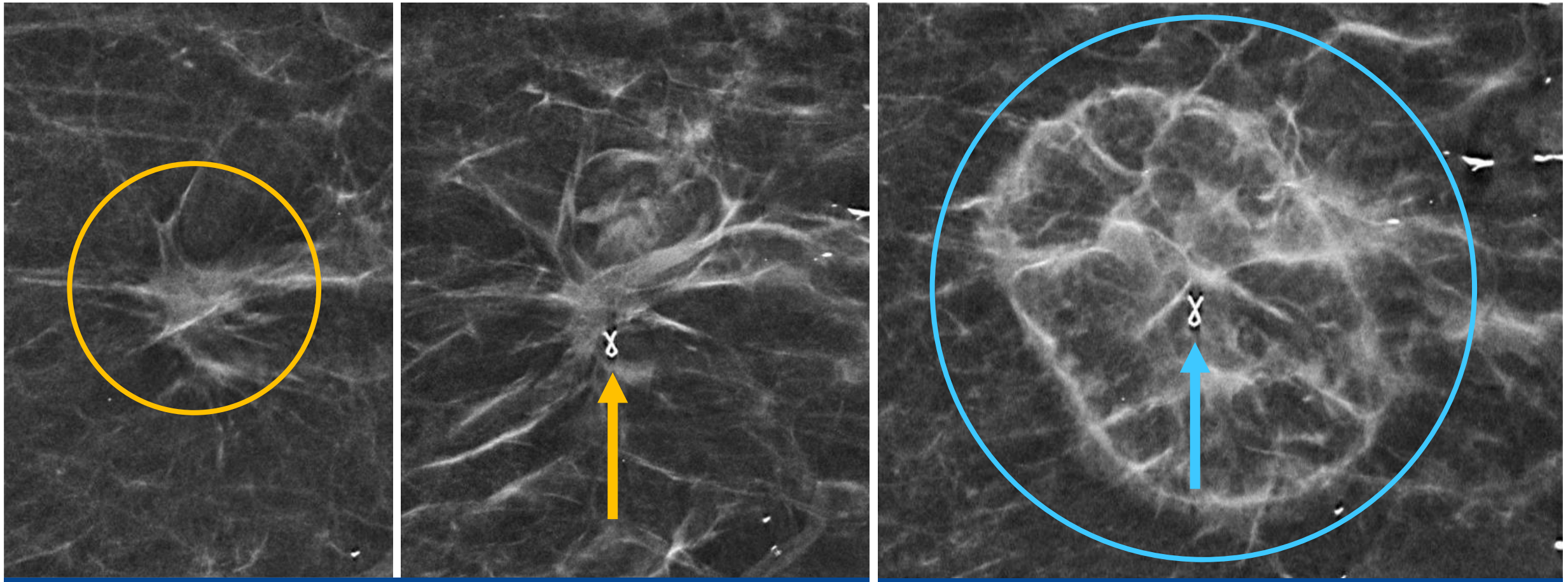
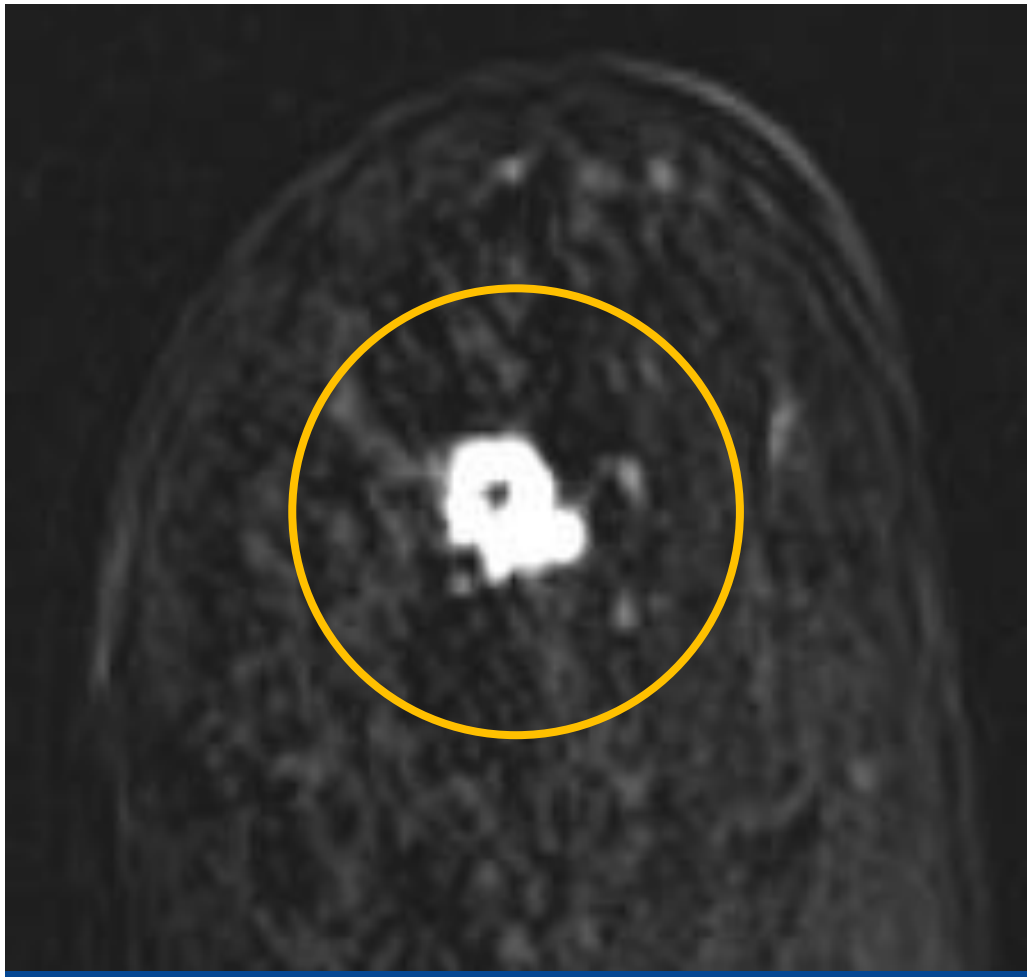


6 Months

Follow-up Imaging: Mammogram



Follow-up Imaging: MRI



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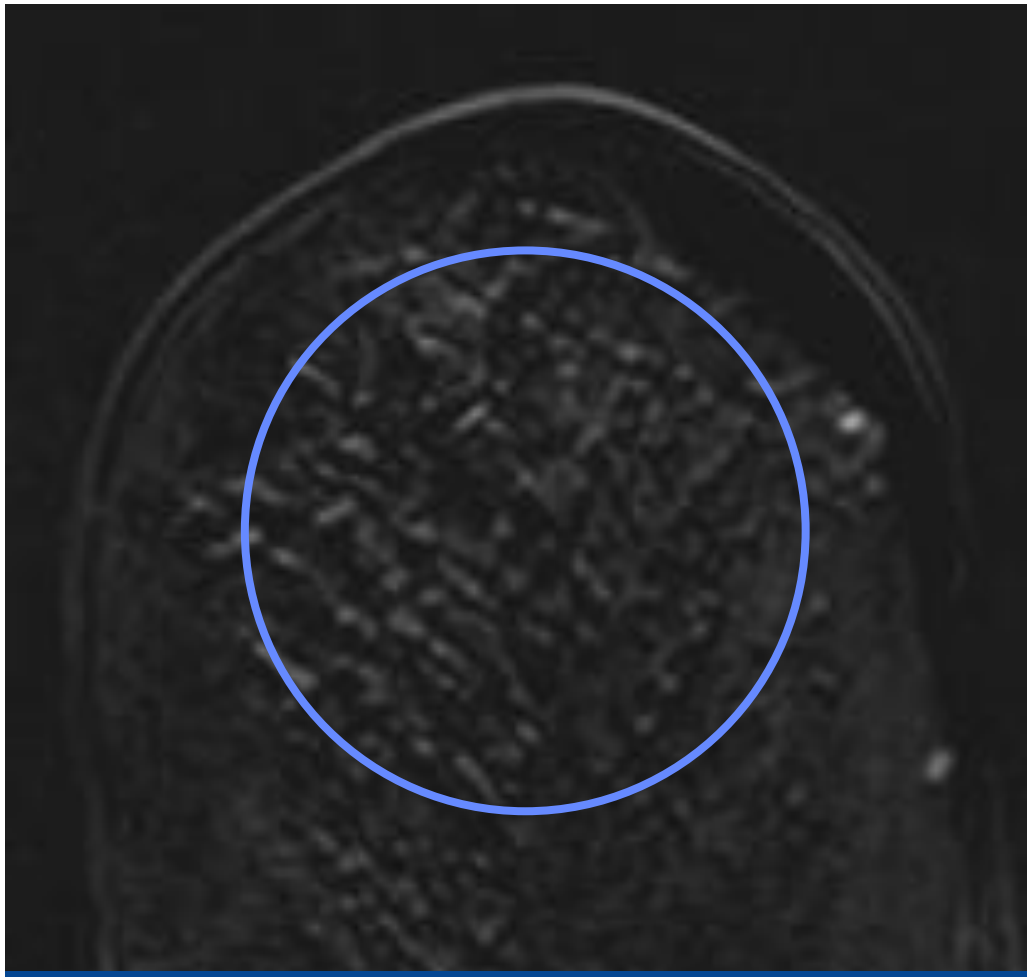
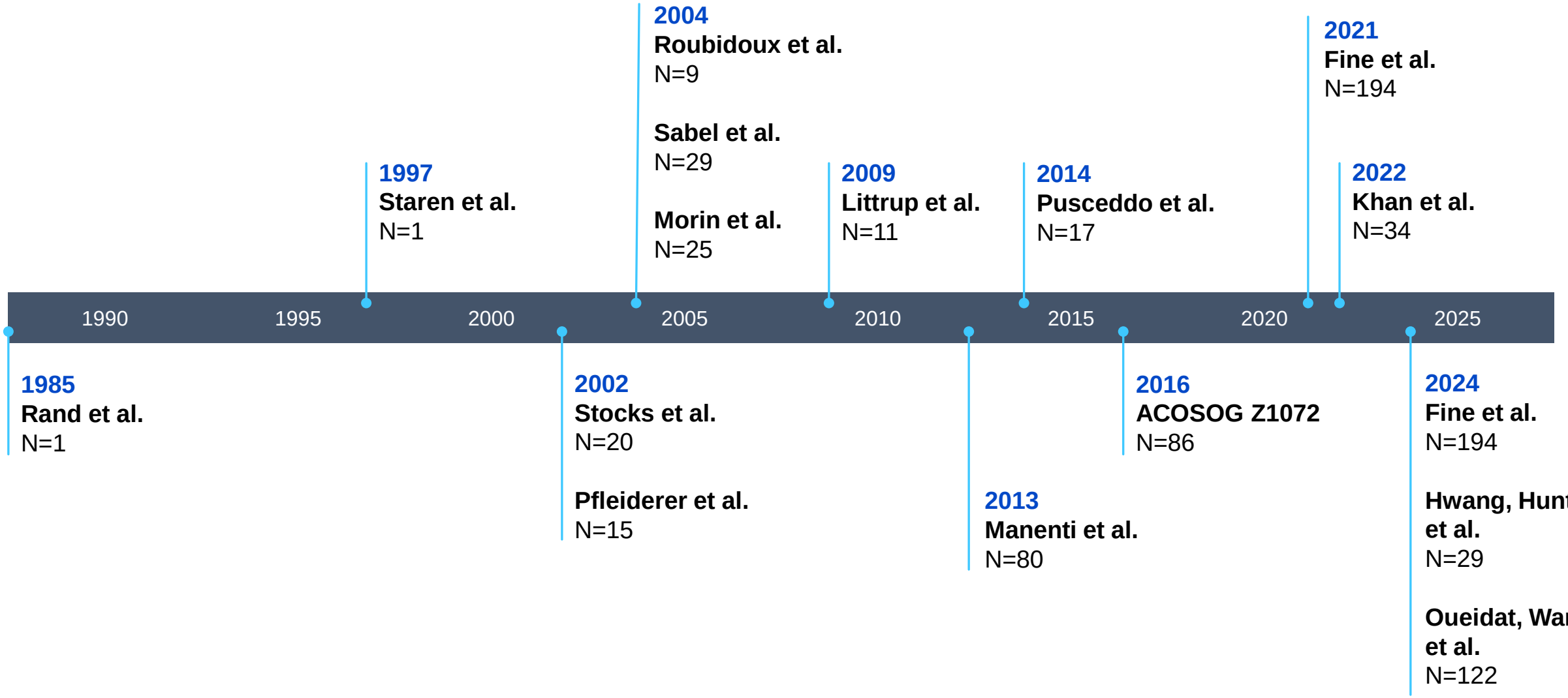


6 Months

Decades of Research and Prior Studies on Cryoablation in Treatment of Breast Cancer



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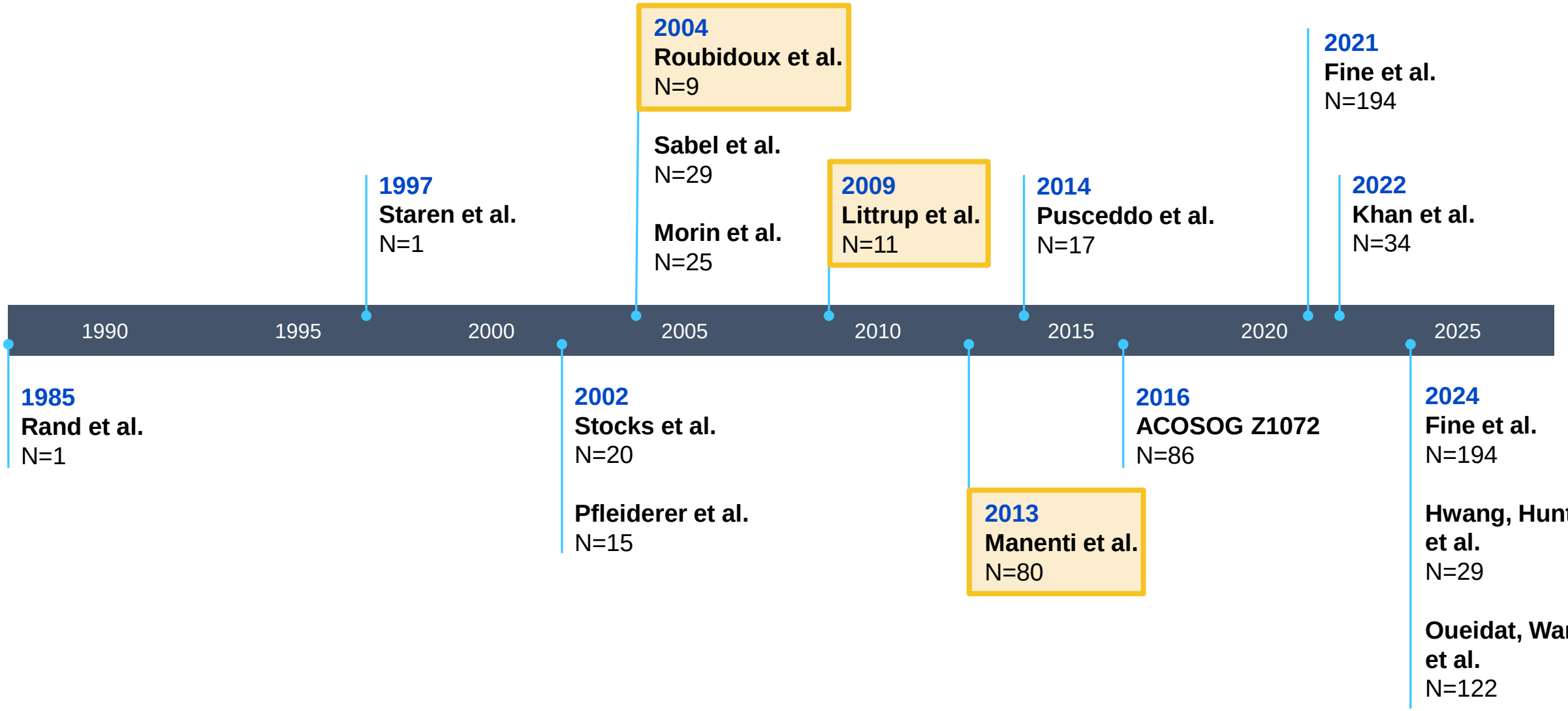


Roubidoux 2004

Study of **9 patients** treated with US-guided cryo and exision

No residual invasive cancer in tumors 1.7 cm or smaller or in cancers without spiculated margins at US

US=ultrasound

Roubidoux, Marilyn A., et al. "Small (< 2.0-cm) breast cancers: mammographic and US findings at US-guided cryoablation—initial experience." *Radiology* 233.3 (2004): 857-867.

Littrup 2009

Study of **11 patients** treated with US or US+CT-guided cryoablation

100% procedural success with mean tumor size 1.7 cm

No significant complications, retraction, or scarring were noted

Safely achieved 1 cm visible ice beyond tumor margins with **minimal discomfort, good cosmesis, no short-term tumor recurrences**

US=ultrasound

Littrup, Peter J., et al. "Cryotherapy for breast cancer: a feasibility study without excision." *Journal of Vascular and Interventional Radiology* 20.10 (2009): 1329-1341.

Manenti 2013

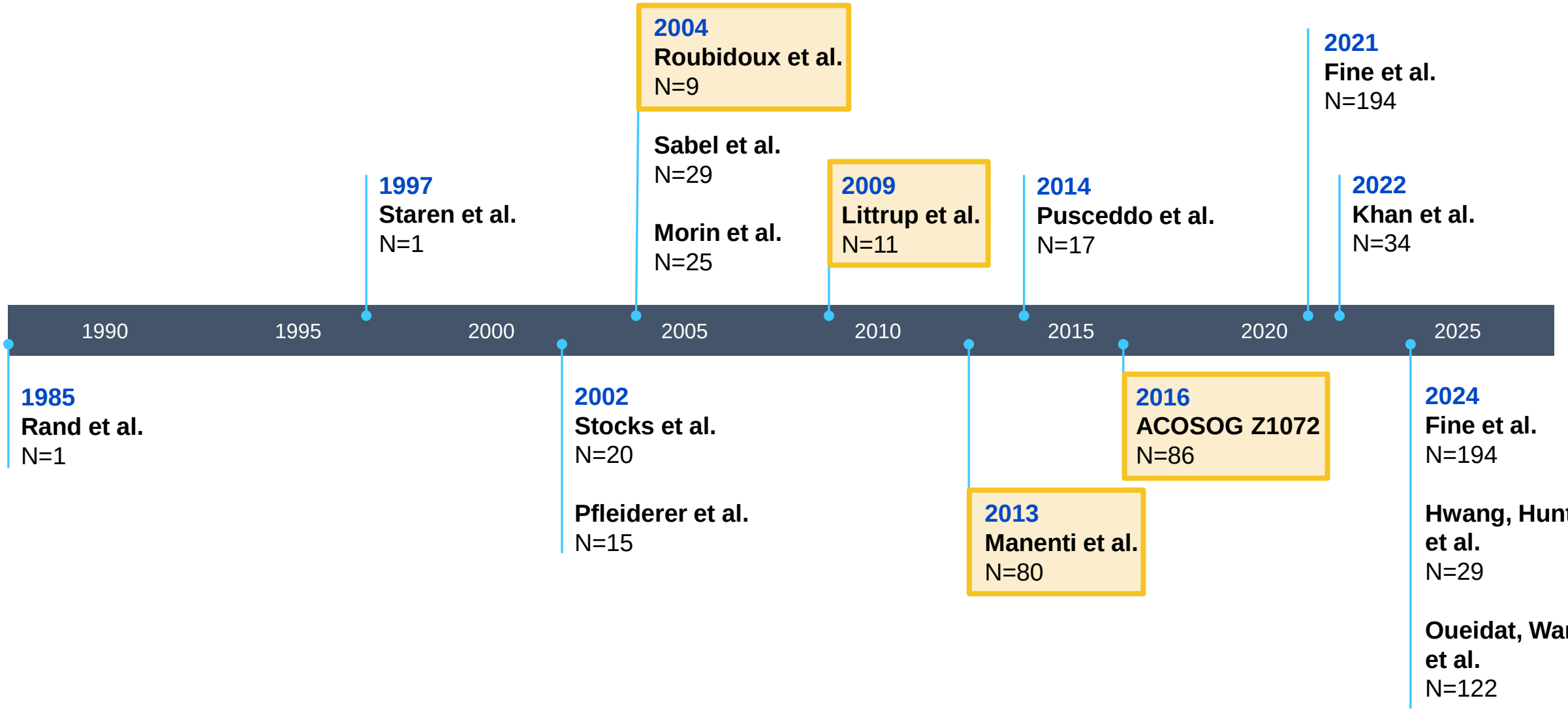
Study of **80 patients** comparing **RFA vs. cryoablation** in treatment of early breast cancer

Both resulted in **good clinical and cosmetic outcome**

Cryotherapy is the **preferred method** because of analgesic effect of freezing with better patient experience

Manenti, Guglielmo, et al. "Subclinical breast cancer: minimally invasive approaches. Our experience with percutaneous radiofrequency ablation vs. cryotherapy." *Breast care* 8.5 (2013): 356-360.

Decades of Research and Prior Studies on Cryoablation in Treatment of Breast Cancer



2016 ACOSOG Study

Ann Surg Oncol (2016) 23:2438–2445
DOI 10.1245/s10434-016-5275-3

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

A Phase II Trial Exploring the Success of Cryoablation Therapy in the Treatment of Invasive Breast Carcinoma: Results from ACOSOG (Alliance) Z1072

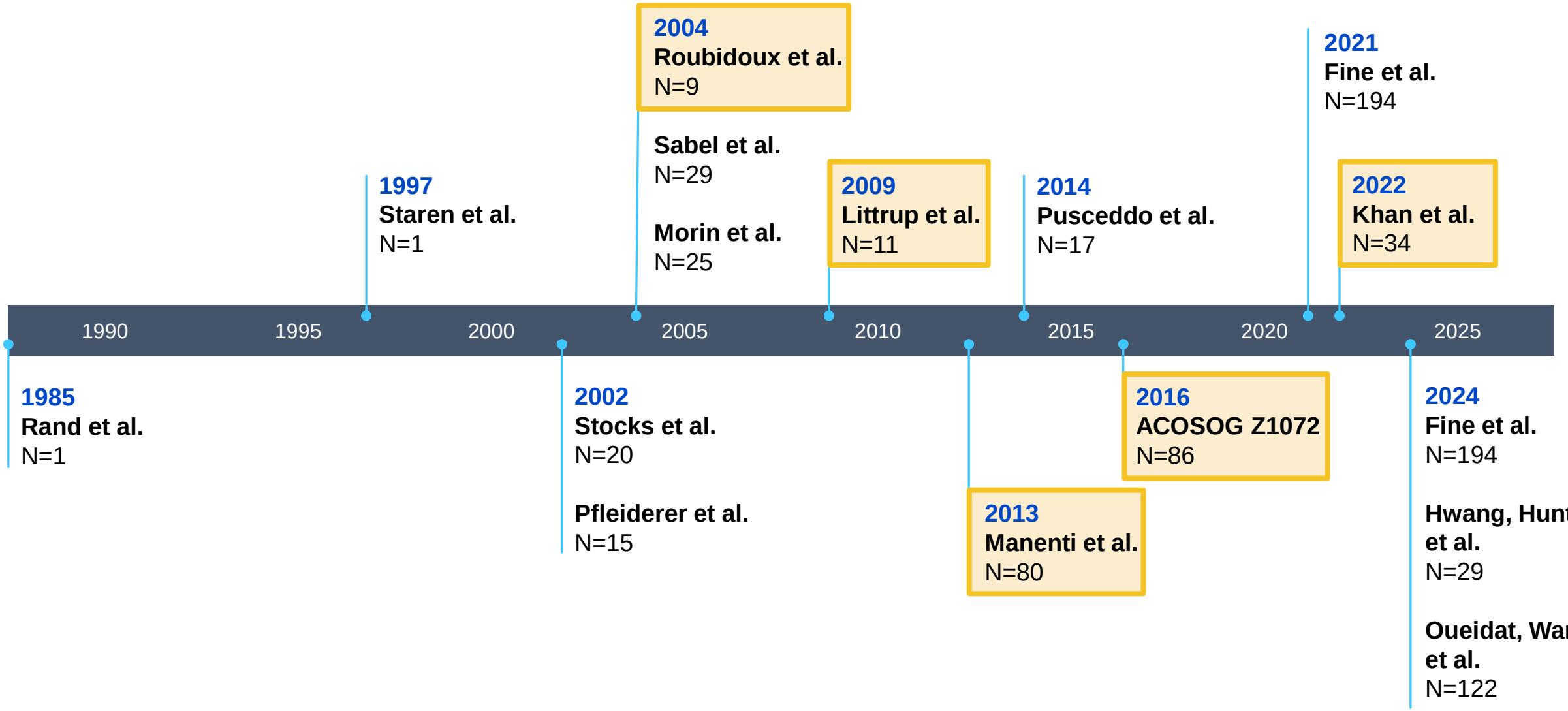
Rache M. Simmons, MD[1], Karla V. Ballman, PhD[2], Charles Cox, MD[3], Ned Carp, MD[4], Jennifer Sabol, MD[4], Rosa F. Hwang, MD[5], Deanna Attai, MD[6], Michael Sabel, MD[7], David Nathanson, MD[8], Andrew Kenler, MD[9], Linsey Gold, MD[10], Cary Kaufman, MD[11], Linda Han, MD[12], Aaron Bleznak, MD[13], J. Stanley Smith, MD[14], Dennis Holmes, MD[15], Bruno Fornage, MD[16], Carisa Le-Petross, MD[16], Syed Hoda, MD[17], Linda McCall, MS[18], Kelly K. Hunt, MD[5], and on behalf of the ACOSOG investigators

KEY CONCLUSIONS

- If 1 cm below, **100% success**
- Excluding multifocal disease **92% success** in tumors ≤2 cm
- No cases of ineffective ablation

Prospective *ablate and resect*, proved effectiveness of cryoablation
Led directly to the ICE3 trial without need for resection

Decades of Research and Prior Studies on Cryoablation in Treatment of Breast Cancer



Cost of Cryoablation vs. Lumpectomy

Ann Surg Oncol
https://doi.org/10.1245/s10434-022-12570-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

The Role of Cryoablation in Breast Cancer Beyond the Oncologic Control: COST and Breast-Q Patient-Reported Outcomes

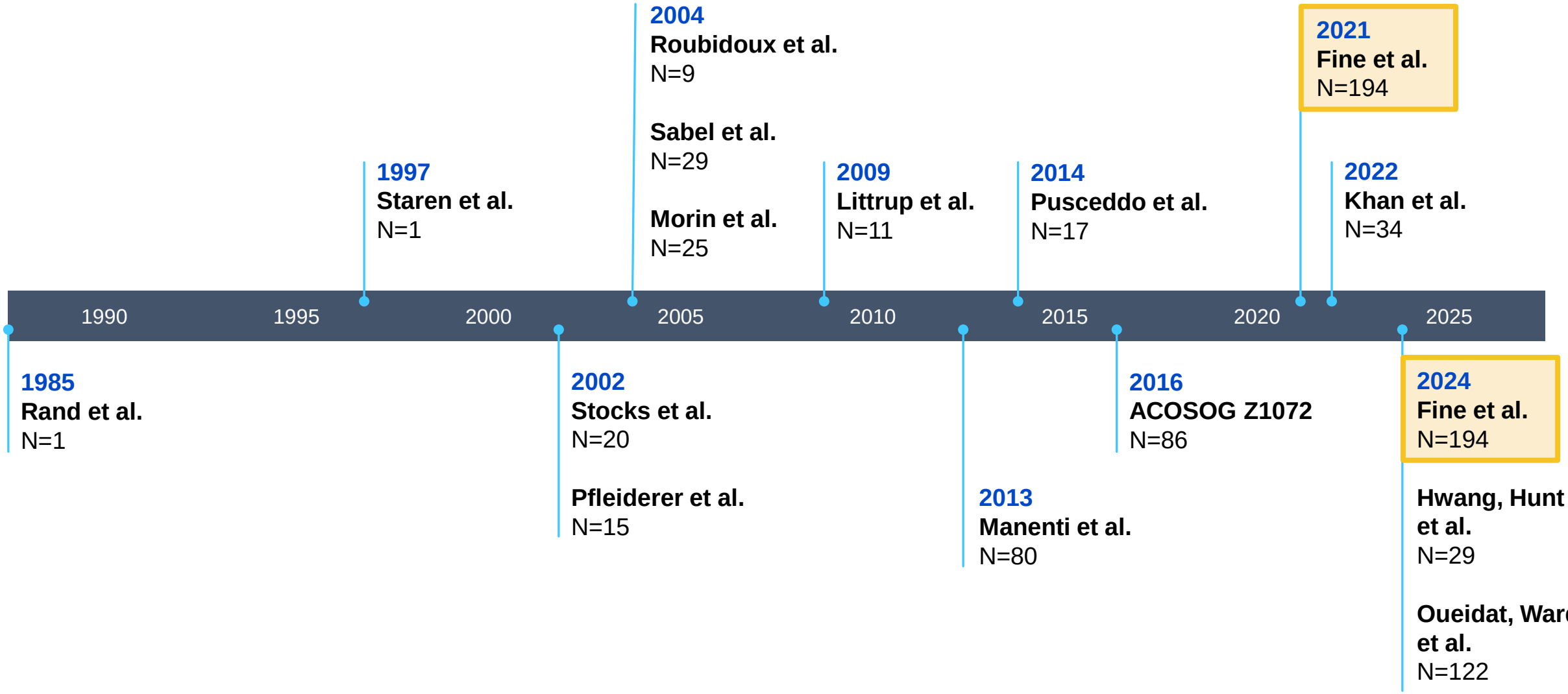
Sonia Y. Khan, BS[1,2], Annie Snitman, MD[1], Zaina Habrawi, MD[1,2], Sybil Crawford, PhD[3], Michael W. Melkus, PhD[1,2], and Rakhshanda Layeequr Rahman, MD[1,2]

KEY CONCLUSIONS

- Better psychosocial well-being
- Cryoablation significantly associated with better physical, sexual, and cosmetic satisfaction outcomes
- Lower financial toxicity

Better short-term psychosocial well-being, lower financial toxicity with cryoablation vs. lumpectomy procedures

Decades of Research and Prior Studies on Cryoablation in Treatment of Breast Cancer



ICE3 Study Design & Results

Richard E. Fine, MD, FACS

Breast Program Director & Director of Education & Research

Margaret West Comprehensive Breast Center, WCC & RI

Germantown, TN

Overall Study Design

IRB Approved, multi-centered (19 U.S. sites), single-arm, prospective study

Study Population

Early stage, low-risk breast cancer

Women ≥60 with unifocal histologic grade 1 or 2, invasive ductal carcinoma, ≤1.5 cm, ER+, PR +/-, Her2-, clinically lymph node neg

Intervention

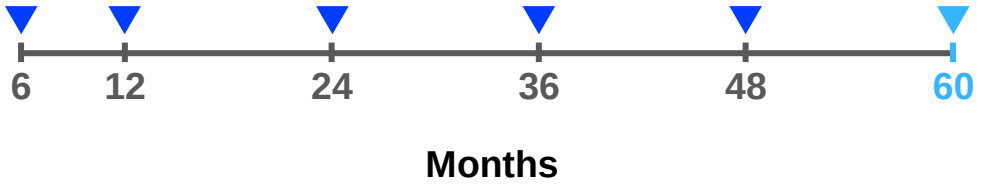
Cryoablation

US-guided precise tumor engulfment with an ice ball

Adjuvant treatment per physician discretion

Follow-up

Mammography (MRI optional*)



Outcome

Ipsilateral Breast Tumor Recurrence (IBTR)

5 years post-cryo

All patients enrolled in the ICE3 study had early stage, low-risk breast cancer

US=ultrasound
*Breast MRI optional or if lesion not visible on mammogram

Study Design Considerations

Single-arm design

- **Unable to conduct a blinded study**
  - Cryoablation vs. surgical excision
- **Inherent difficulties in conducting a randomized controlled study**
  - Performed by both surgeons and radiologists

Literature performance goal

- **Primary outcome, IBTR, is objective**
- **Surgical lumpectomy is well-understood and outcomes well-documented in the published literature**
- **Published outcomes on thousands of patients more robust than a prospective control**

Sample size

- **ICE3 builds on a large body of prior work**
  - Data on ablate and resect demonstrate effectiveness in tumor destruction
- **Statistically justified sample size of 200 patients**

Key Inclusion/Exclusion Criteria

Key Inclusion Criteria

1. **Diagnosis of invasive ductal breast carcinoma by core needle biopsy, meeting the following criteria:**
   a. Unifocal primary disease
   b. Tumor size ≤1.5 cm in greatest diameter
   c. Histologic (Nottingham) grade 1-2
   d. Estrogen receptor positive, and/or progesterone receptor positive, HER2 negative
2. **Age ≥60 (WCG IRB), age ≥50 (Local IRB)**

Key Exclusion Criteria

1. **Lobular carcinoma**
2. **Luminal B pathology**
3. **Microinvasion or invasive breast carcinoma with extensive intraductal component (EIC)**
4. **Multifocal and/or multicentric in breast cancer, multifocal calcifications**
5. **Neoadjuvant chemotherapy for breast cancer**
6. **Prior en bloc open surgical biopsy and/or lumpectomy for the index breast cancer**

Primary Endpoint

- **Protocol Definition of Local Recurrence (IBTR):**
  - Evidence of invasive or in situ breast cancer in the ipsilateral breast or chest wall, including new primary confirmed by biopsy
  - Suspicious findings do not constitute criteria for breast cancer recurrence. Any recurrence of malignant disease should be proven by biopsy or excision
- **Independent DSMB Consideration of Local Recurrence (IBTR):**
  - Per clinical practice, local recurrence does not include new ipsilateral tumor in a different quadrant or at least 5 cm from original tumor. Instead, considered second primary breast cancer

1. Smith, T., et al. *Int. J. Radiat. Oncol. Biol. Phys,* (2000).
2. Yi, M, et al. *Ann. Surg*, (2011).
3. Huang, E., et al. *Cancer*, (2002).
4. Panet-Raymond, V, et al. *Int. J. Radiat. Oncol. Biol. Phys,* (2011).
5. Belkacemi Y, et al. *Front. Oncol,* (2018).

Protocol specified all recurrence events be confirmed by biopsy

Prespecified Literature-based Endpoint

Lumpectomy outcomes are well-established

Systematic literature review using PubMed and EBSCO yielded >1000 hits and resulted in selection of 4 papers reporting IBTR following breast conserving surgery at 2-5 years post-op

Performance goal determined to be <10%

- Literature supports 5-year reference rate of 5%
- Reference margin of 5% was clinically justified
- Performance goal determined by adding the reference margin to the reference rate

If the upper limit of the 95% CI at the 5-year time point is <10%, study will be considered successful

IBTR=Ipsilateral Breast Tumor Recurrence

Key Secondary Endpoints: Effectiveness

Regional Occurrence

Tumor in ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular, and/or ipsilateral axillary nodes or soft tissue of ipsilateral axilla

Distant Metastases

Tumor in any area of the body except those defined as local or regional

Disease Free Survival (Protocol Definition)

Freedom from disease events including local (DCIS or invasive), regional or distant breast cancer recurrence, second primary breast cancer, DCIS or invasive contralateral breast cancer, **second primary non-breast cancer and death due to any cause**

Disease Free Survival (NCI Definition)

Freedom from disease events including local (DCIS or invasive), regional or distant breast cancer recurrence, second primary breast cancer, DCIS or invasive contralateral breast cancer

Overall Survival

Freedom from death due to any cause

Breast Cancer Survival

Freedom from death due to breast cancer or unknown cause

Protocol specified all recurrence events be confirmed by biopsy

Patient Reported Outcomes & Safety

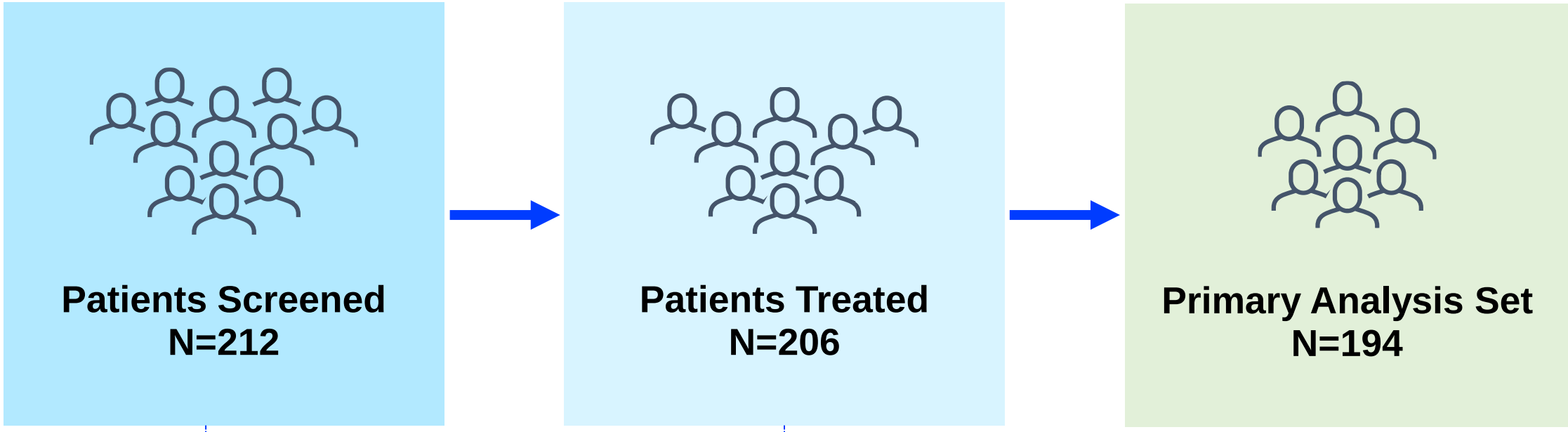
Patient and physician satisfaction
with breast cosmetic outcome

Safety: Adverse events
related to study device or procedure

Time to recovery
and resumption of normal activities

ICE3 Study Results

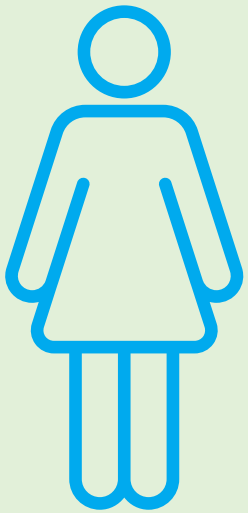
Analysis Population



DSMB=Data Safety Monitoring Board

Demographics

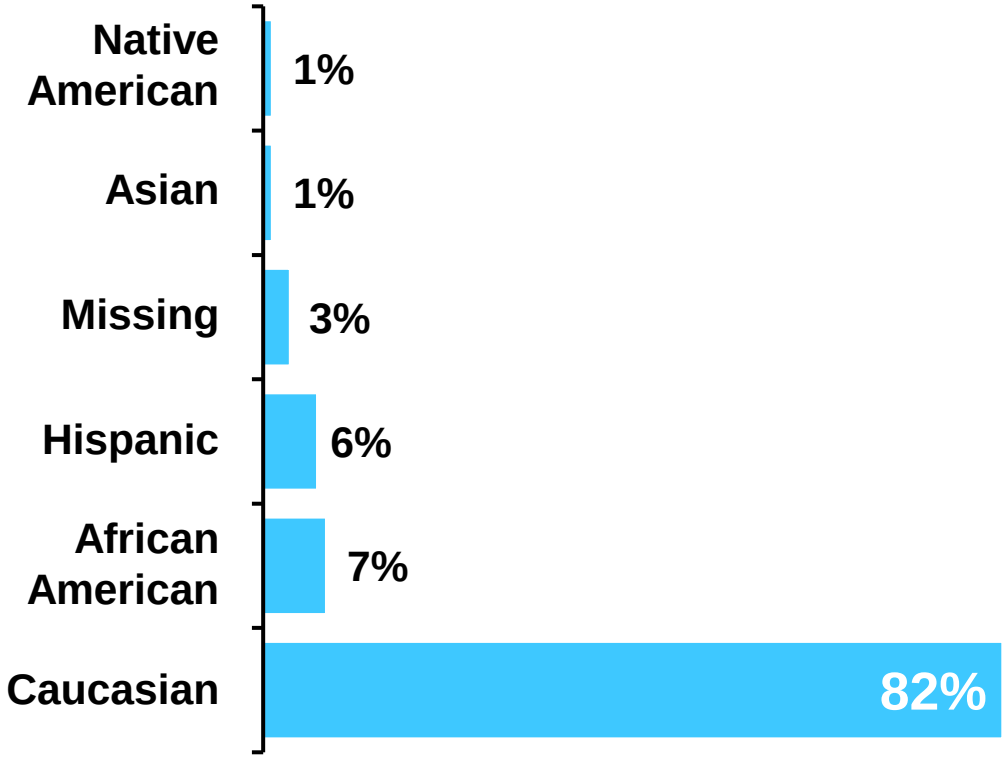
Primary Analysis Set (N=194)



Age:
74.9
(Range 55-94)

BMI:
28.8
(Range 15.0-47.6)

Gender:
100% female



Disease Characteristics

Primary Analysis Set

Baseline Characteristics	ICE3 N=194 n (%)
ER (Estrogen Receptor)	
Positive	194 (100)
Negative	0
PR (Progesterone Receptor)	
Positive	180 (93)
Negative	14 (7)
HER2/neu	
Positive	0
Negative	194 (100)
Histologic Grade	
1	96 (49)
2	98 (51)
3	0

Categorical Variables Primary Analysis Set

Disease Characteristics

Primary Analysis Set

Baseline Characteristics	ICE3 N=194 n (%)
ER (Estrogen Receptor)	
Positive	194 (100)
Negative	0
PR (Progesterone Receptor)	
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Categorical Variables Primary Analysis Set

Disease Characteristics

Primary Analysis Set

Baseline Characteristics	ICE3 N=194 n (%)
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Categorical Variables Primary Analysis Set

Disease Characteristics

Primary Analysis Set

Baseline Characteristics	ICE3 N=194 n (%)
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HER2/neu	
Positive	0
Negative	194 (100)
Histologic Grade	
1	96 (49)
2	98 (51)
3	0

Categorical Variables Primary Analysis Set

Cryoablation Procedure: Intra/periprocedural Data

Mean tumor size:
0.73 cm (0.1–1.49)

Procedure time:
30-40 mins

Anesthesia type:
100% local

Median time to resume normal activities:
1 day (0–8 days)

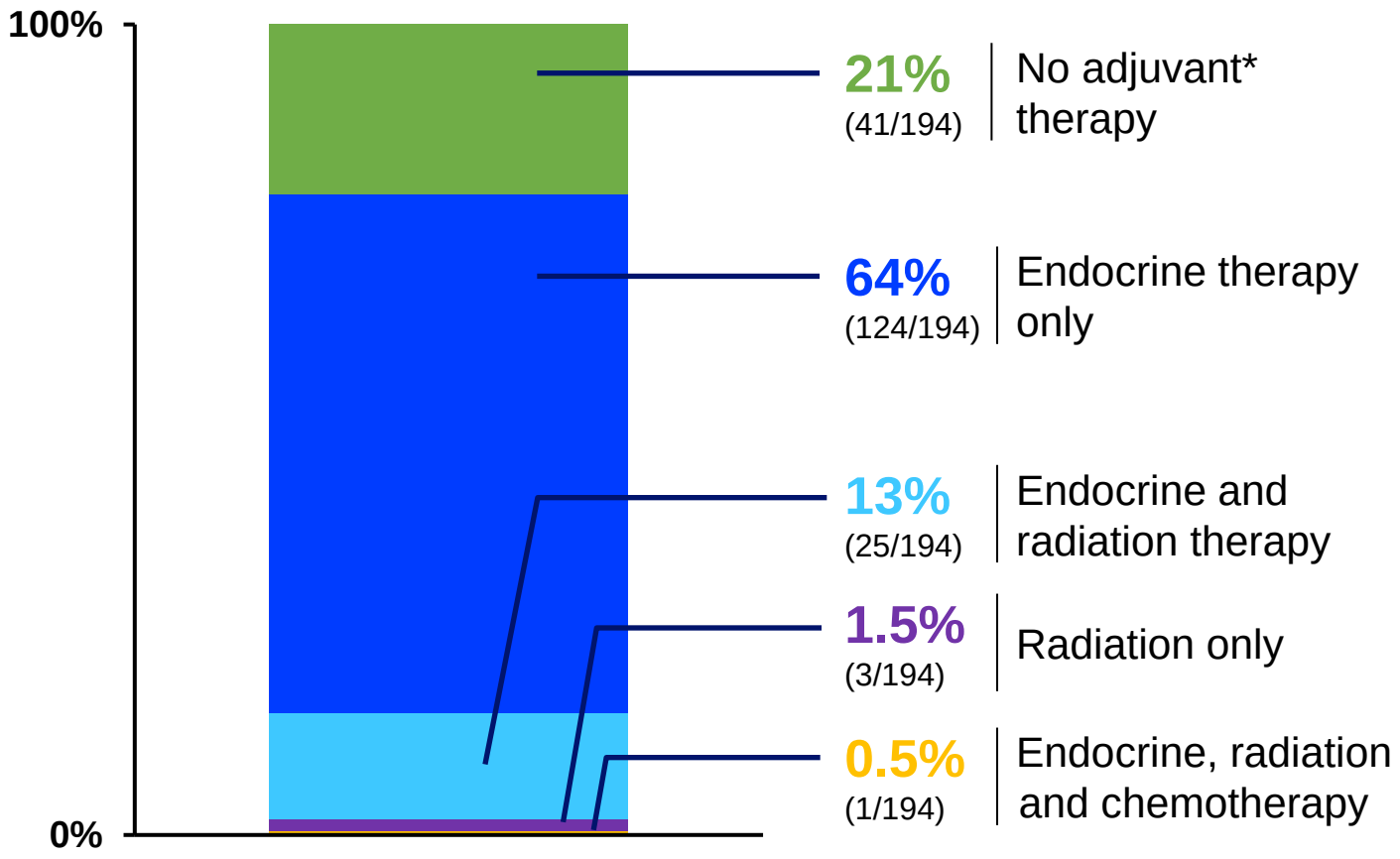
Procedure-related adverse events:

- **Bruising**
- **Pain**
- **Localized Edema**
- **Injection Site Reaction**
- **Hematoma**
- **Frost Injury**

Procedure-related adverse events were generally mild, occurred acutely, and resolved promptly without intervention

Adjuvant Treatment

Type of adjuvant treatment



*3 patients with unknown adjuvant therapy counted as none

Effectiveness

Primary Endpoint Met

Local IBTR Rate – Primary Analysis Set (N=194)

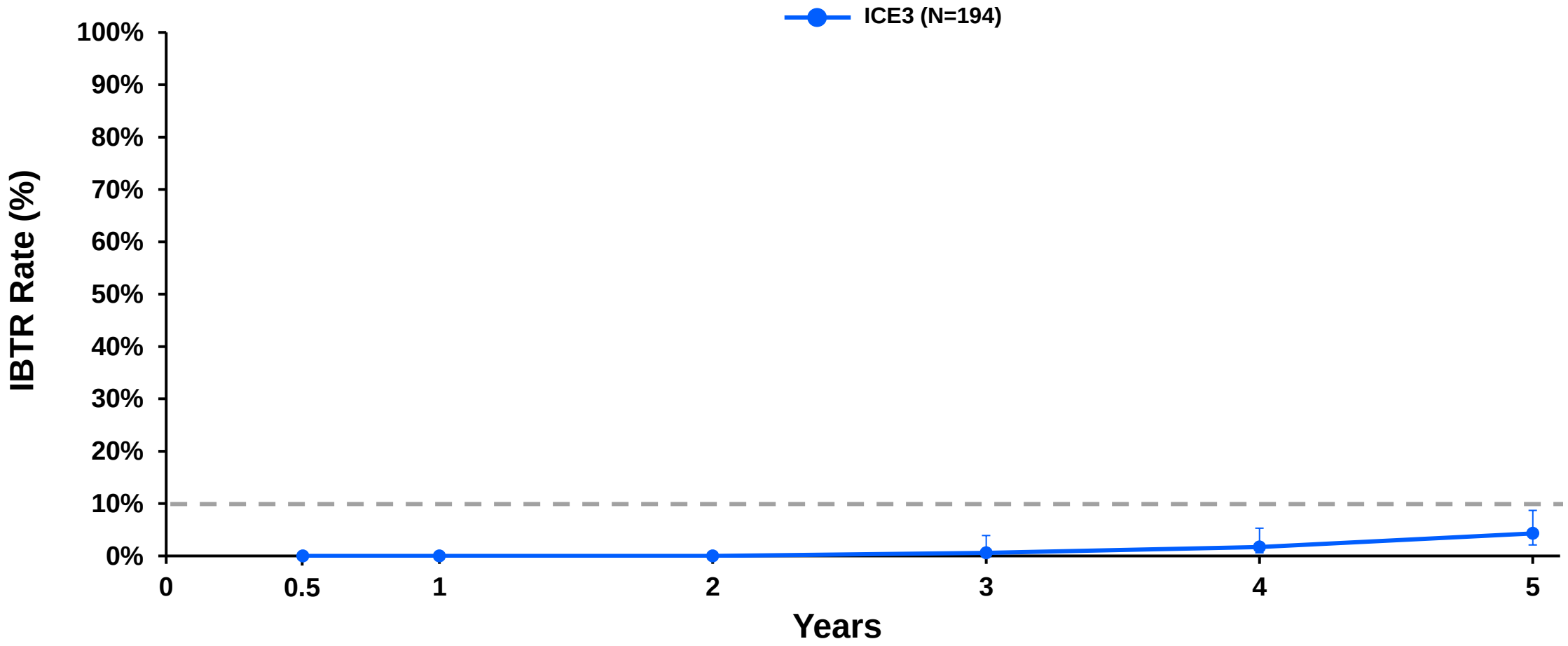
Time	At Risk*	Cumulative IBTR	IBTR Estimate†	2-sided 95% CI
Operative	194	-	-	-
Month 6	192	0	0.0%	-
Year 1	190	0	0.0%	-
Year 2	184	0	0.0%	-
Year 3	173	1	0.6%	0.1 - 3.9
Year 4	162	3	1.7%	0.6 - 5.3
Year 5	133	7	4.3%	2.1 - 8.7

ICE3 population met pre-specified <10% performance goal

*At risk: number of patients that completed the follow-up time interval with no IBTR event
†Kaplan-Meier (product-limit) estimate with 1-sided 95% CI upper bound (UB) and 2-sided 95% lower and upper bounds (LB and UB); IBTR=Ipsilateral Breast Tumor Recurrence

ICE3 Primary Endpoint

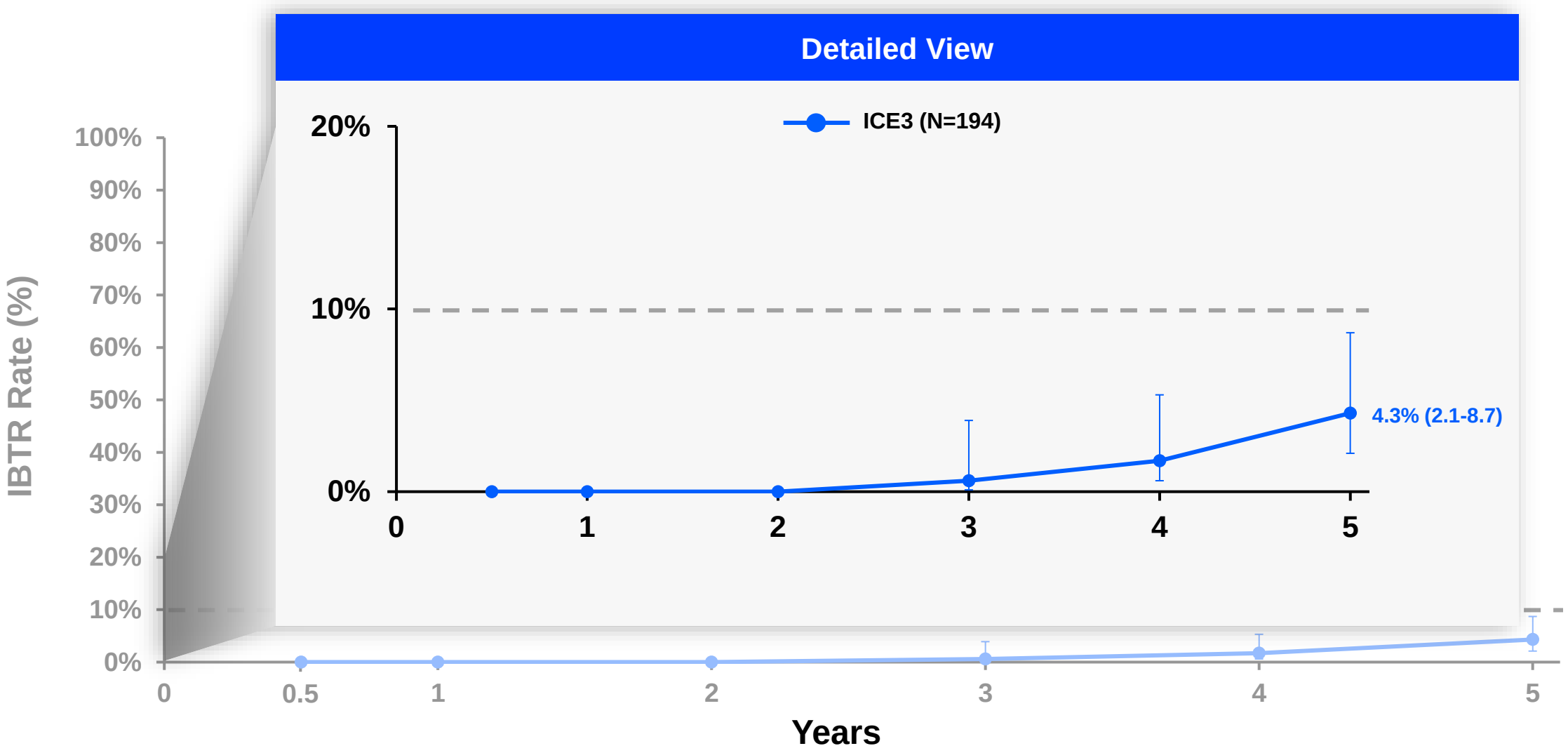
Primary Analysis Population (N=194)



Error bars=95% confidence intervals

ICE3 Primary Endpoint

Primary Analysis Population (N=194)



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Secondary Kaplan-Meier Analyses

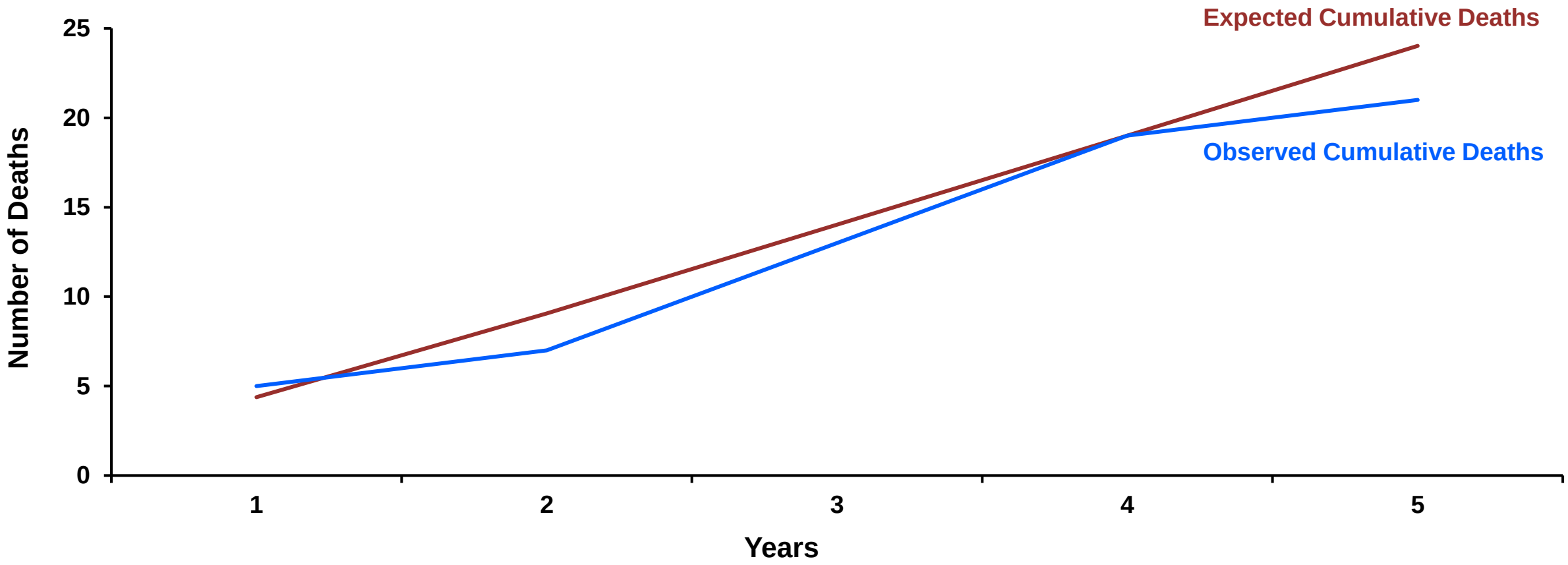
Primary Analysis Population (N=194)

Secondary Effectiveness Endpoint	Events	Year 5 KM Rate	2-sided 95% CI
Regional Recurrence Estimate	0	100.0%	-
Distant Metastases Estimate*	6	96.4%	92.2 - 98.4
Disease Free Survival - NCI Definition*	12	92.8%	87.6 - 95.8
Overall Survival Estimate	20	88.6%	82.9 - 92.5
Breast Cancer Survival Estimate	5	96.7%	92.2 - 98.6

99% of patients free from confirmed breast cancer-related death

*Includes events observed beyond 5-years; NCI Definition=In cancer, the length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer

Deaths Observed in ICE3 vs. Actuarial Survival



Fewer deaths observed in ICE3 than expected for 74-year-old population

Safety

Safety Overview

Primary Analysis Population (N=194)

	IceCure N=194		
	Events	Patients (n)	% (n/N)
Adverse Events			
All	517	140	72.2%
Procedure Related Adverse Events			
All	180	93	47.9%
Procedure Related Adverse Events by Severity			
Mild	158	83	42.8%
Moderate	18	15	7.7%
Severe	4	4	2.1%
Serious Adverse Events			
All	127	59	30.4%
Non-procedure Related	123	56	28.8%
Procedure Related	4	3	1.5%

Serious Adverse Events

Primary Analysis Population (N=194)

	IceCure N=194		
	Events	Patients (n)	% (n/N)
Serious Adverse Events			
All	127	59	30.4%
Non-procedure Related	123	56	28.8%
Procedure Related	4	3	1.5%

- **3 patients with SAEs possibly related to study procedure or device**
- **All determined to be due to physician error**
  - Probe mispositioning (1)
  - Suboptimal treatment (2)

Procedure-related Events Occurring in >2% of Patients

Primary Analysis Population (N=194)

	IceCure N=194		
	Events	Patients (n)	% (n/N)
Bruising	57	57	29.4
Pain	38	36	18.6
Localized Edema	37	35	18.0
Injection Site Reaction	11	10	5.2
Hematoma	9	9	4.6
Frost Injury	4	4	2.1

ICE3 study demonstrated no new device-related risks, all procedure-related events are known risks of cryoablation

Patient Reported Outcomes & Probable Benefits

Near immediate recovery

- **83%** of the ICE3 study population returned to **full daily activities 48 hours after procedure**
- **Days to resume activity on average:** median 1 day (0 to 8 days)

High percentage of patients and physicians satisfied with cosmetic results at 5 years

- **>99%** of patients ‘satisfied’ or ‘very satisfied’ (110/111)
- **97%** of physicians ‘satisfied’ or ‘very satisfied’ (99/102)

ICE3 Summary

Robust study with ~80% patient accountability at 5-years

- ICE3 clinical study met the pre-specified primary endpoint
- >95% of patients are IBTR-free through 5-years follow-up
- Near immediate recovery to normal activity (median 1 day recovery time)
- >99% of patients were satisfied with cosmetic results at 5-years

ProSense™ demonstrated to have low risk safety profile

- Non-serious procedure-related risks are common to all cryoablation systems, including ProSense™ System when used per the cleared indications
- All serious, procedure-related events are common to breast cancer treatment and can be mitigated by treatment according to proposed labeling

The totality of evidence demonstrates safety, effectiveness, and positive benefit/risk profile of the ProSense™ for treatment of early stage, low-risk breast cancer

IBTR=Ipsilateral Breast Tumor Recurrence

FDA-Requested Post-Hoc Analyses

Margeaux Rogers, MS, RAC
Vice President, Regulatory Affairs
MCRA, LLC, an IQVIA business

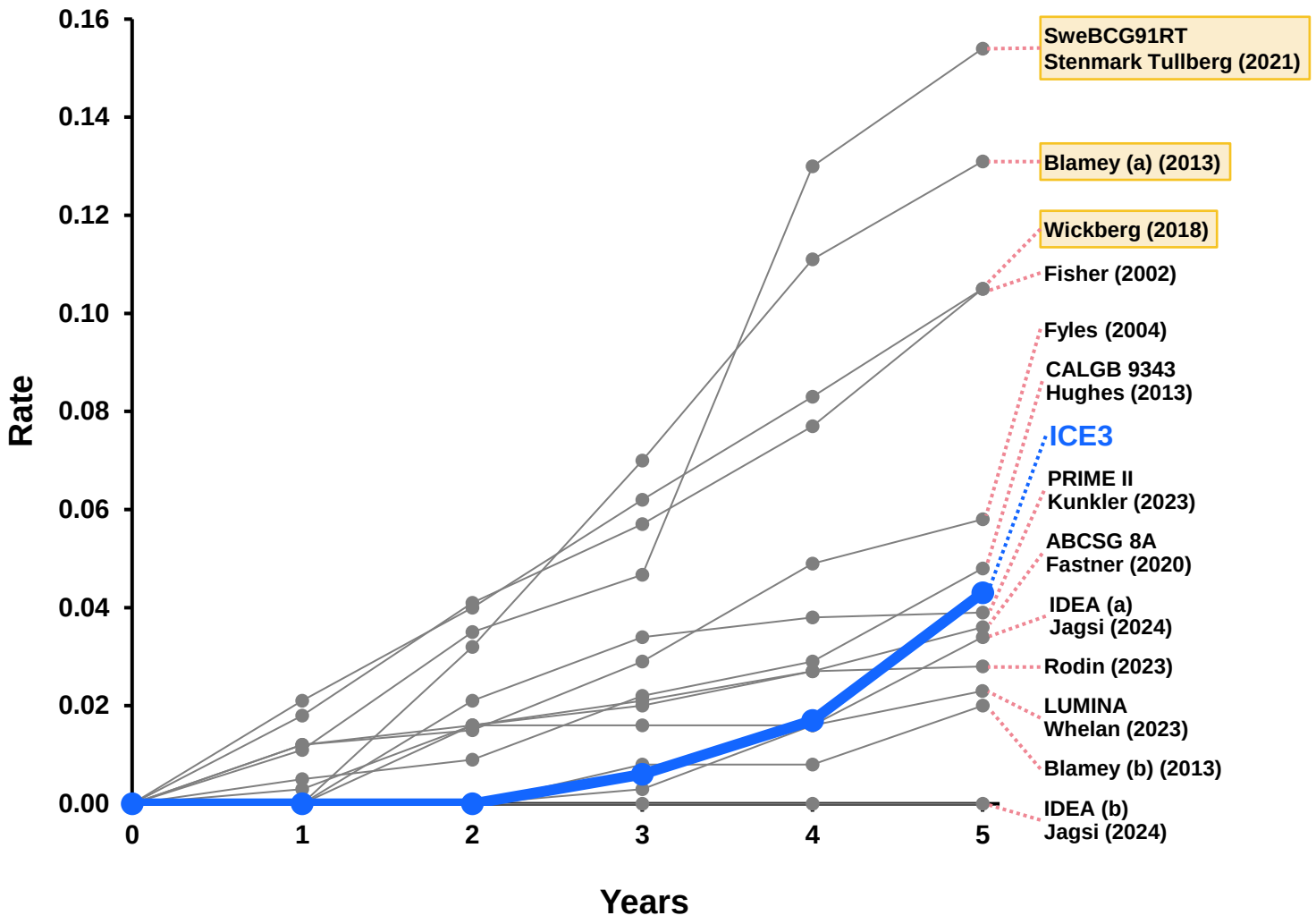
FDA-requested PRISMA Systematic Literature Review and Meta-analysis

- **FDA requested PRISMA systematic literature review and meta-analysis**
- **Designed to evaluate 5-year IBTR following lumpectomy without radiation**
- **Literature selection criteria were intentionally aligned with ICE3**
  - Anticipated differences in literature populations
  - Excluded unlike literature populations, excluded populations <100 patients
  - Pre-defined downweighting of data in cases where the literature were similar but not perfectly aligned as described in executive summary
- **Literature review protocol was submitted to FDA for input**
- **Search returned ~800 citations**
- **11 unique articles identified for data extraction**

IBTR=Ipsilateral Breast Tumor Recurrence

FDA-requested PRISMA Systematic Review and Meta-analysis

- **Overall PRISMA meta-analysis 5-year IBTR rate: 3.52%**
- **Range: 0% - 15.4%**
- **PRISMA meta-analysis 5-year IBTR rate with adjuvant endocrine therapy: 2.82%**
- **Range: 0% - 10.5%**



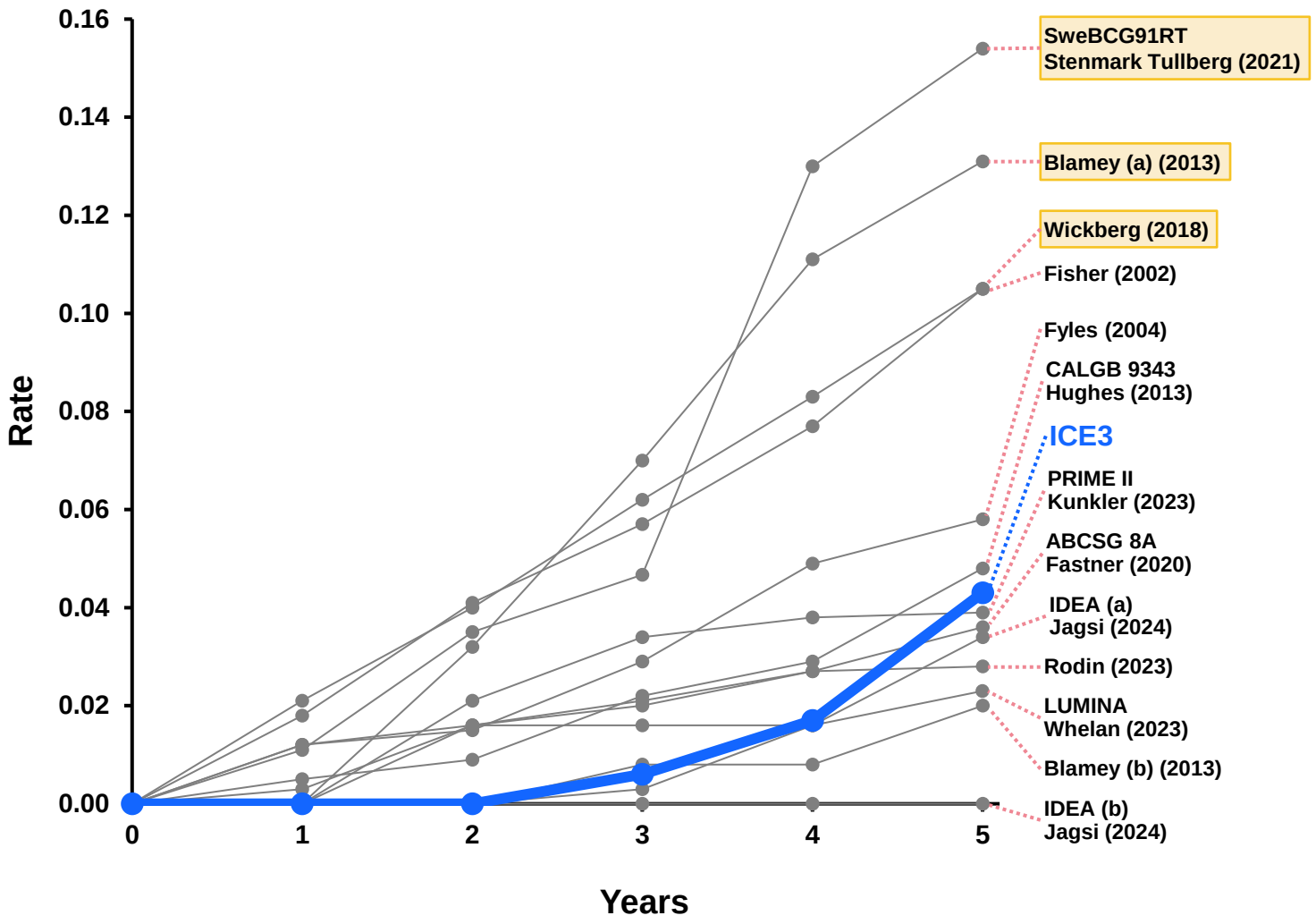
FDA-requested PRISMA Systematic Review and Meta-analysis

- **Overall PRISMA meta-analysis 5-year IBTR rate: 3.52%**
- **Range: 0% - 15.4%**

ICE3 5-year recurrence rate (N=194): 4.3%

- **PRISMA meta-analysis 5-year IBTR rate with adjuvant endocrine therapy: 2.82%**
- **Range: 0% - 10.5%**

ICE3 Indicated Population (N=147): 3.1%



FDA-requested Comparison to LUMINA Study

LUMINA Study: Explored omission of radiotherapy following treatment of breast-conserving surgery and endocrine therapy in patients with luminal A breast cancer

LUMINA Study Population (N=500)	ICE3 Study Population (N=194)
Luminal A subtype	2 patients determined to have luminal B type cancer, 2 unknown
Median age: 67.1 years	Median age: 74.9 years
Selected patients with good surgical outcomes	Prospective study design
All patients received adjuvant endocrine therapy	Only a subset of patients in ICE3 received adjuvant endocrine therapy

ICE3 expected to be worse case due to differences in adjuvant treatment

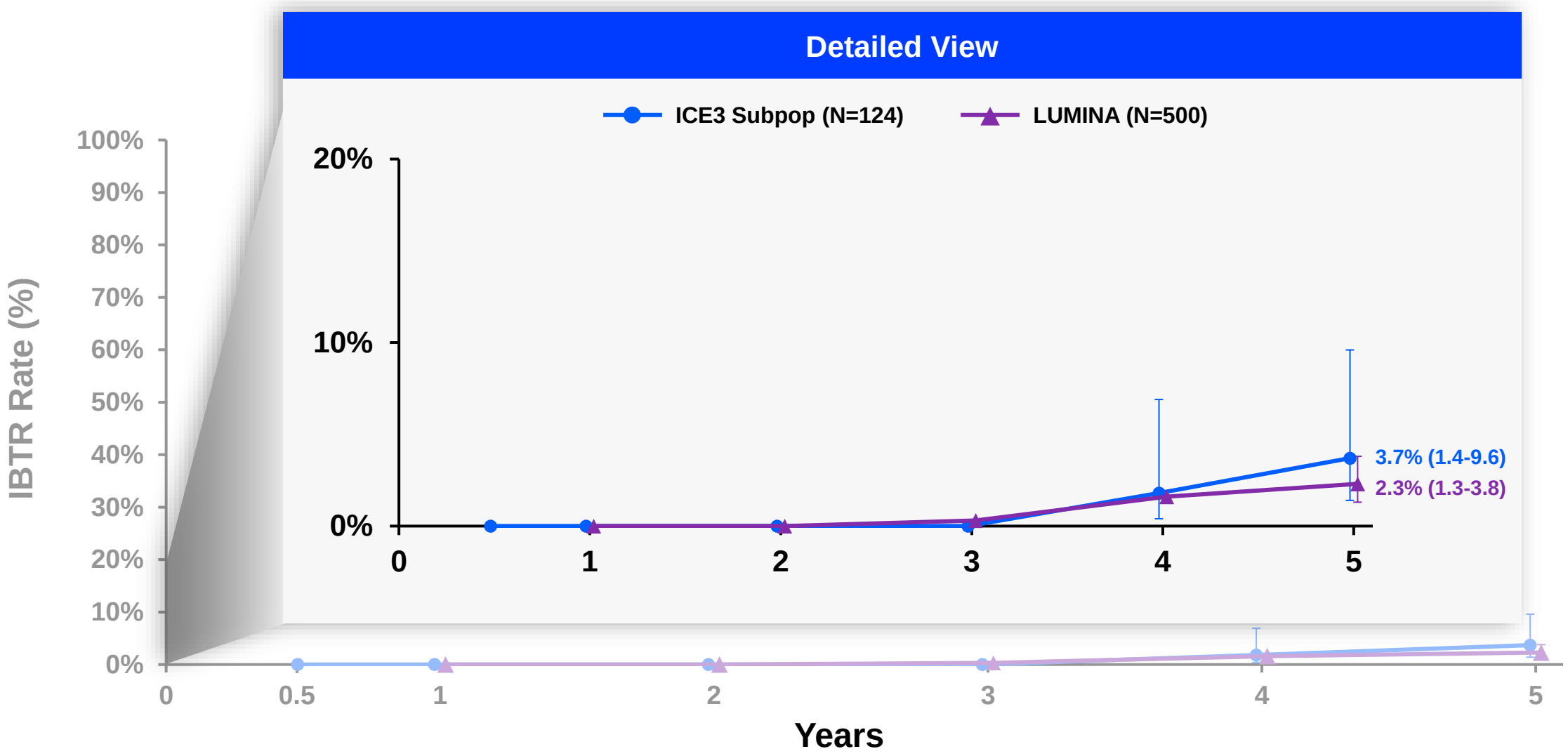
ICE3 Subpopulation for Comparison to LUMINA

ICE3 Primary Analysis Population
(N=194)

Subpopulation with Adjuvant Endocrine Therapy without Radiation
(N=124)

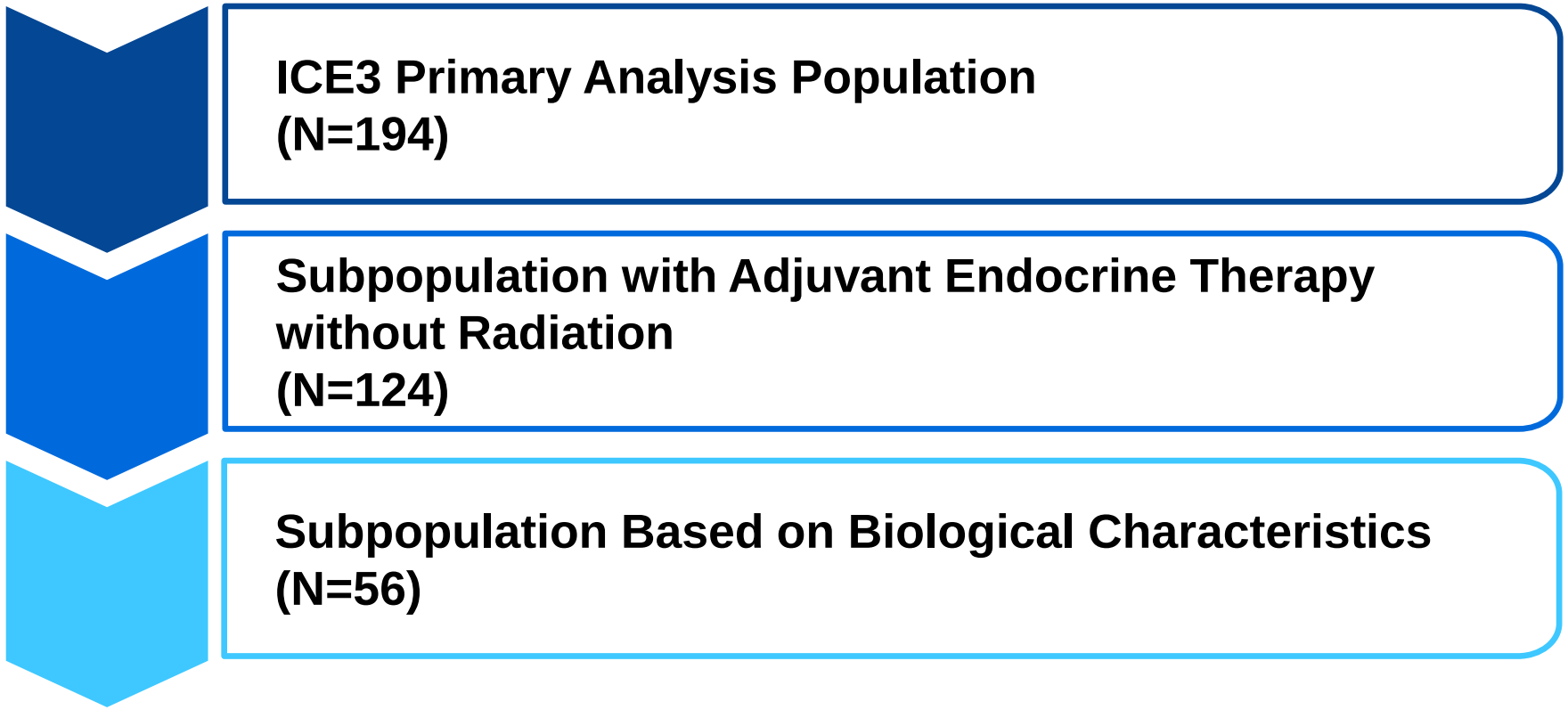
ICE3 Primary Endpoint

Adjuvant Endocrine Therapy Only (N=124) vs. LUMINA (N=500)



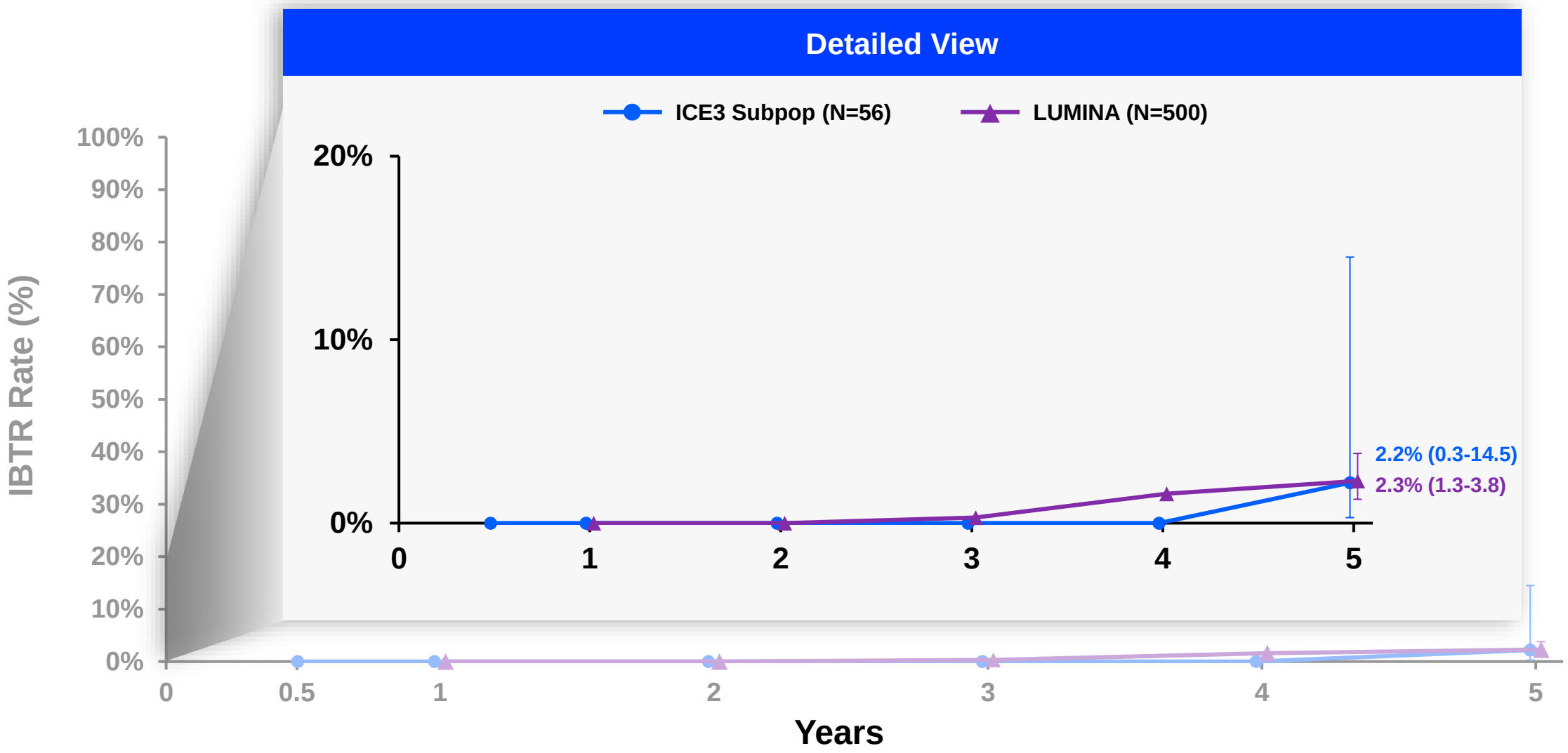
Error bars=95% confidence intervals

ICE3 Subpopulation for Comparison to LUMINA



ICE3 Primary Endpoint

Adjuvant Endocrine Therapy + Biological Characteristics (N=56) vs. LUMINA (N=500)



Error bars=95% confidence intervals

ICE3 Subpopulation for Comparison to LUMINA

ICE3 Primary Analysis Population
(N=194)

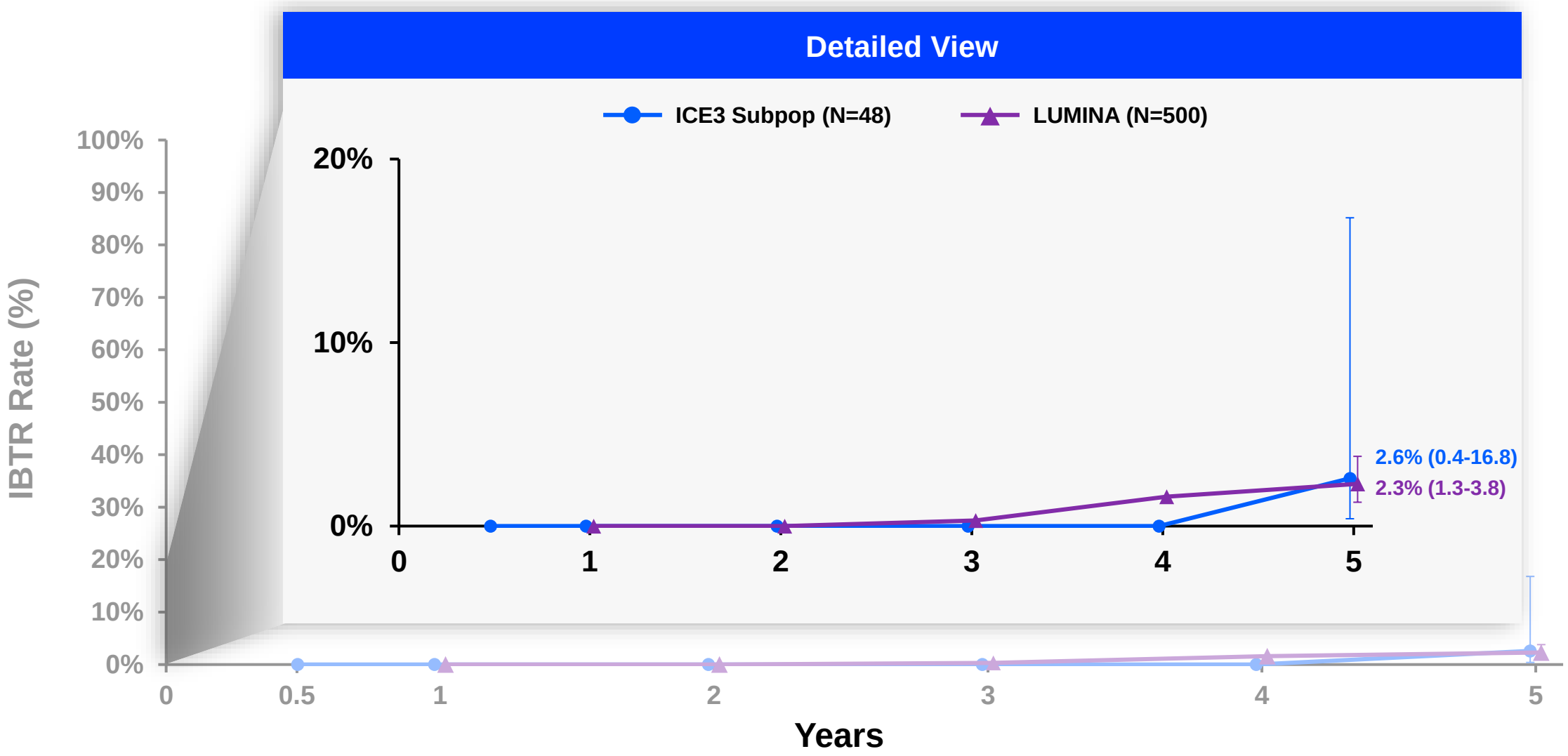
Subpopulation with Adjuvant Endocrine Therapy without Radiation
(N=124)

Subpopulation Based on Biological Characteristics
(N=56)

Subpopulation without Nottingham Component Scores OR with Nuclear Grade of 3
(N=48)

ICE3 Primary Endpoint

+ Endocrine Therapy + Biological Chars. No Nuclear 3/Unknown (N=48) vs. LUMINA (N=500)



Error bars=95% confidence intervals

Proposed Indication – Updated per FDA Recommendation

The ProSense™ is indicated for use in the treatment of patients with early stage, low-risk breast cancer* for the treatment of breast cancer with adjuvant endocrine therapy

*Patients ≥60 years of age with prognostic stage 1A defined as unifocal tumor size ≤1.5 cm, ER+/PR+/-, HER2-, histological grade 1-2 infiltrating ductal carcinoma (excluding lobular carcinoma, extensive intraductal component, or evidence of lymphovascular invasion), and clinically negative lymph node (N0)

FDA-requested Subpopulation Analysis

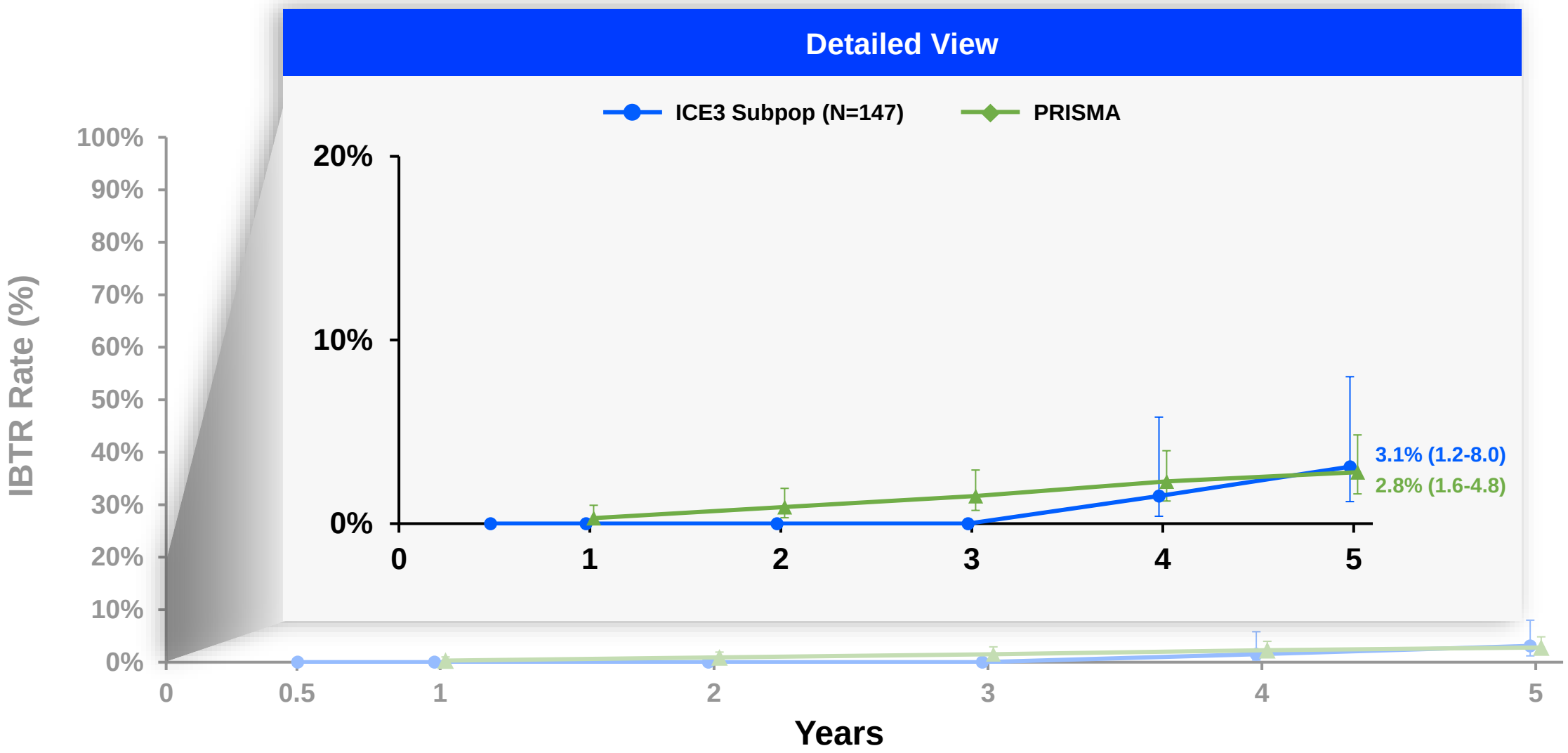
Aligned with Proposed Indications

ICE3 Primary Analysis Population (N=194)

Subpopulation of Patients Aligned with Proposed Indication (N=147)

ICE3 Primary Endpoint

Indicated Subpopulation (N=147) vs. PRISMA with Adjuvant Endocrine Therapy



Error bars=95% confidence intervals

FDA-requested Sub-population Analysis

Aligned with Proposed Indications + Nuclear Grade Restriction

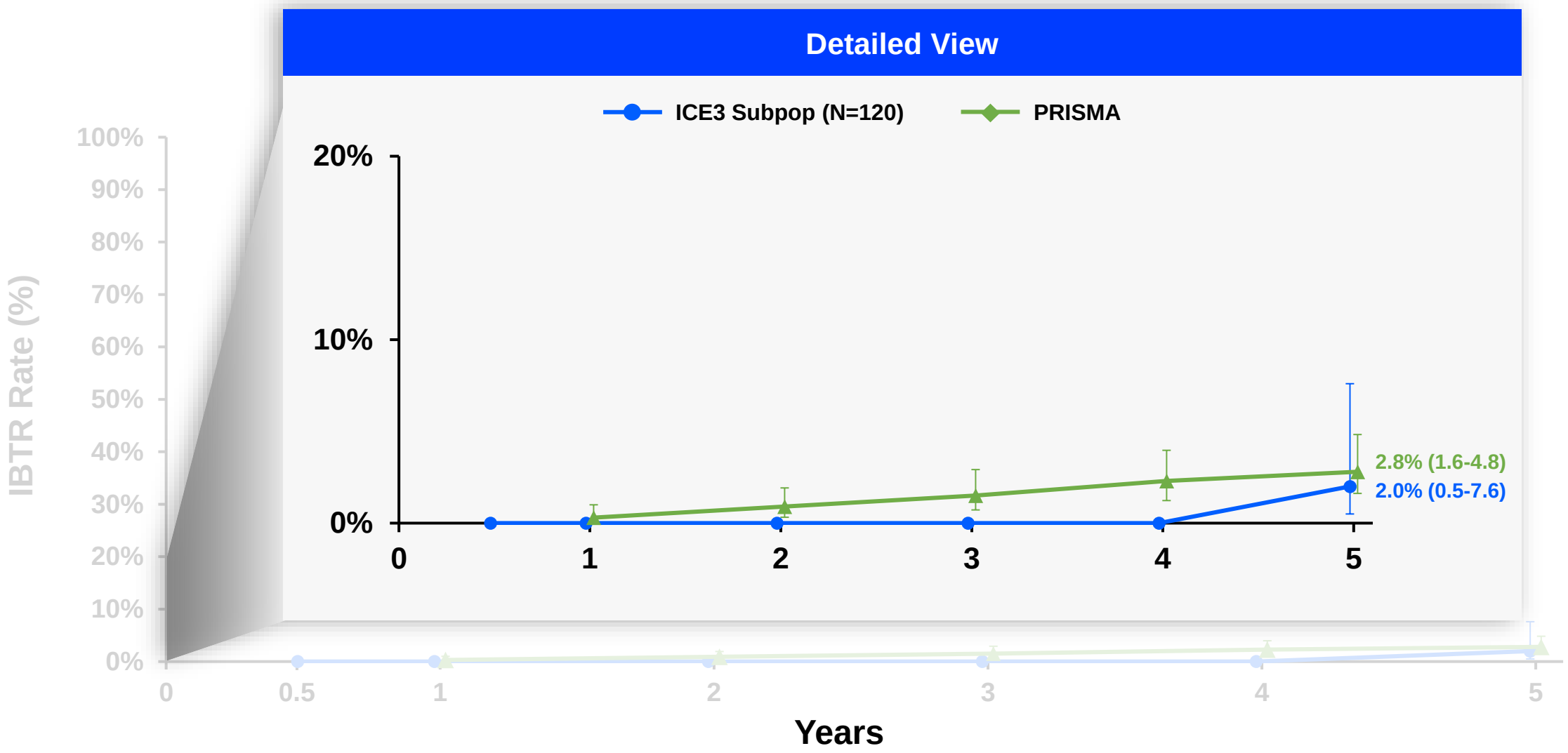
ICE3 Primary Analysis Population
(N=194)

Subpopulation of Patients Aligned with Proposed Indication
(N=147)

Subpopulation without Nottingham Component Scores OR with Nuclear Grade of 3
(N=120)

ICE3 Primary Endpoint

Indicated Subpopulation without Nuclear 3/Unknown (N=120) vs. PRISMA



Error bars=95% confidence intervals

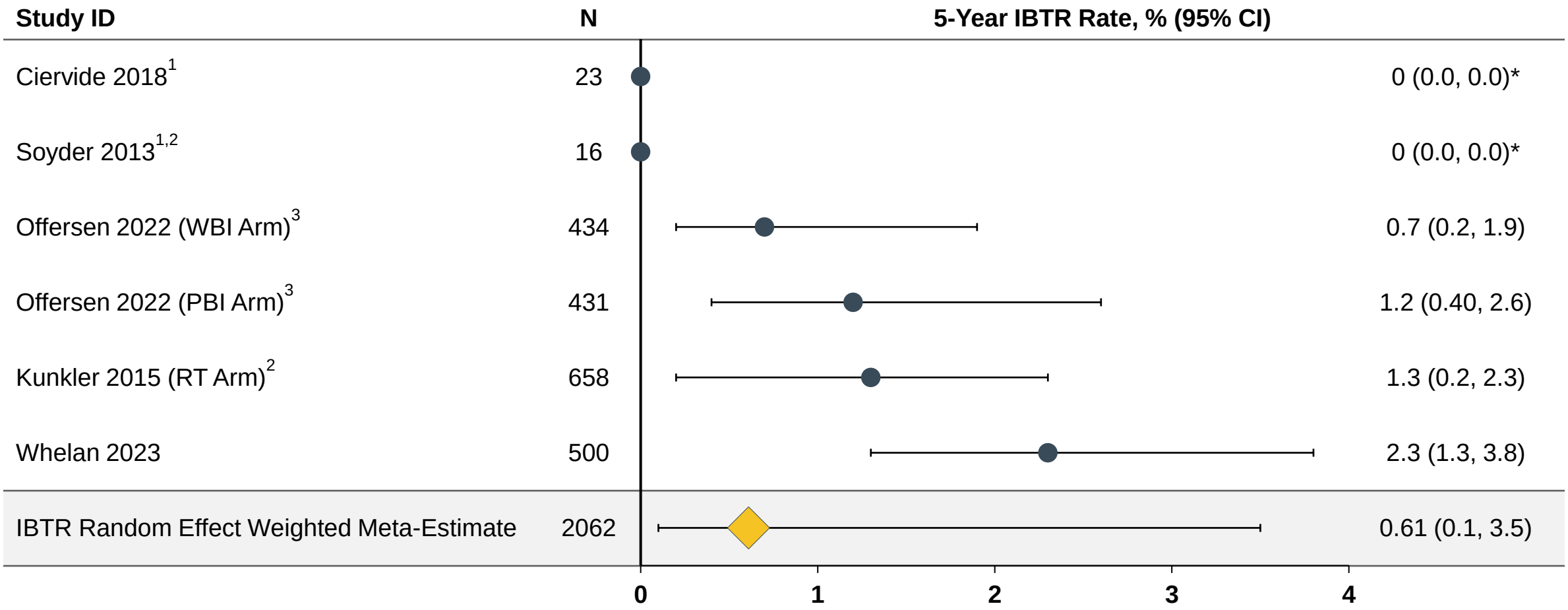
FDA Performed PRISMA Systematic Literature Review and Meta-Analysis

- **25 articles identified with IBTR rates from 0% to 12%**
- **5 articles selected for meta-analysis (IBTR: 0% to 2.3%)**
  - 2 studies included <25 subjects, both with IBTR rates of 0%
- **FDA SLR resulted in overall IBTR rate of 0.61% (CI UB: 3.5%)**
  - IBTR in FDA SLR sub-population with radiation: 0.68% (CI UB: 2.94%)
  - IBTR in FDA SLR population without radiation: 0.47% (CI UB: 35.91%)
- **IceCure concerns:**
  - Unclear if article selection process was applied uniformly
  - IceCure identified articles were excluded, despite relevance
  - Outcome weighting method to derive extremely low IBTR rate

SLR Key Differences – Summary

	IceCure	FDA
Adjuvant Radiotherapy	Excluded	Adjuvant radiotherapy was employed in 21 out of the 25 studies
Sample Size	Excluded samples sizes <100 patients	No exclusion criteria
Adherence to Selection Criteria	Included all included studies in the meta-analysis	Included only 5 of the 25 included studies in the meta-analysis
Weighting Criteria	Weighted based on population alignment – downweighting studies with variability	Used inverse variance weighting – resulted in upweighting of studies with no recurrence reported
Risk of Bias	All studies received “low” risk of bias judgment	Two of the five studies included in the meta-analysis received “serious” risk of bias judgement

FDA Meta-analysis of 5-Year IBTR Rates from Selected Studies



1. Article noted to have moderate or serious risk of bias due to missing data
2. HER2 status was not reported in two studies selected for the quantitative analysis
3. Includes regional recurrences in the reported locoregional recurrence rate

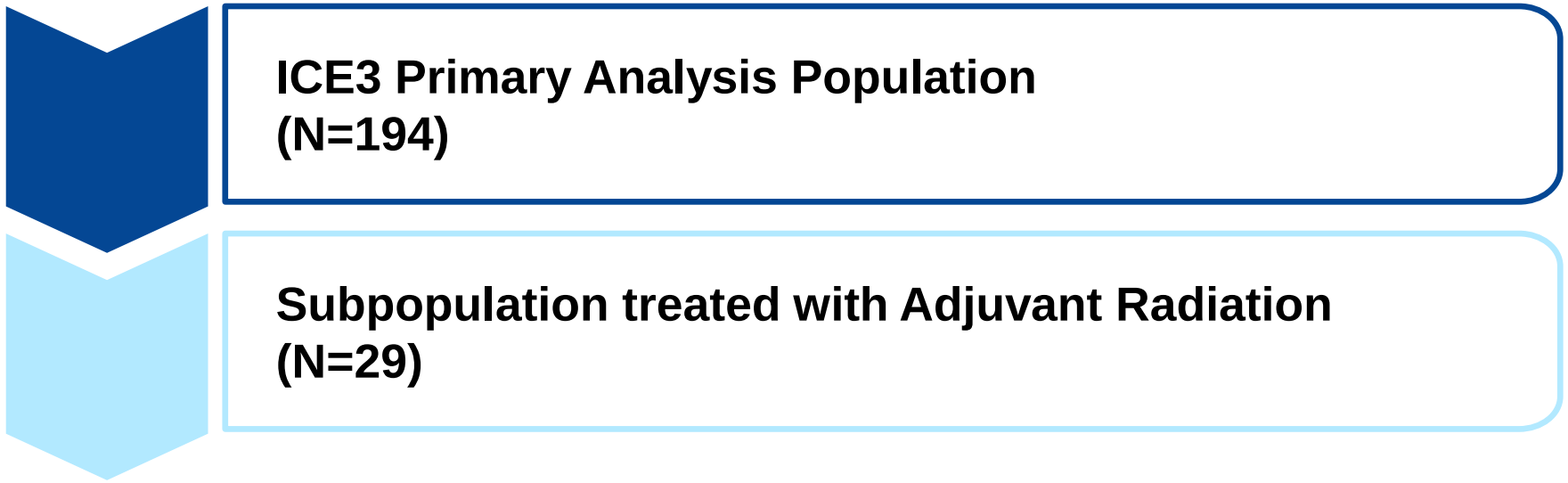
*Indicates corrected values where imputation and zero correction were applied for missing or zero event rates. Corrected values are based on SAS output where missing data for number at risk or events were imputed or corrected as described in methods

FDA Systematic Literature Review (SLR): Weight Compared to Sample Size (ICE3 Study)

Study	Events (Rate)	Number at Risk	Percentage of Total Subjects		Weight	
Ciervide, 2018	0 (0.0%)	16	**2%**	1%	42.1%	**71%**
Soyder, 2013	0 (0.0%)	11		1%	29.3%	
Offersen, 2022 (1)	3 (0.7%)	396		29%	3.8%	
Offersen, 2022 (2)	5 (1.2%)	379		28%	6.3%	
Kunkler, 2015 (2)	5 (1.3%)	324		24%	6.3%	
Whelen, 2023	10 (2.3%)	246		18%	12.3%	
	23 (0.61%)	**1372**		**100%**	**100%**	

FDA's SLR heavily weights the two smallest populations – introduces bias in the resulting meta-analysis rate

Subpopulation Treated with Adjuvant Radiotherapy



- ICE3 subpopulation with radiation 0% IBTR rate
- FDA SLR rate with radiation is 0.68% (95% CI: 0.15-2.94, Range 0-1.3%)

ICE3 subpopulation with radiation has better outcomes than FDA SLR

Comparison of IBTR Results by Censoring Approach

Primary Analysis Population (N=194)

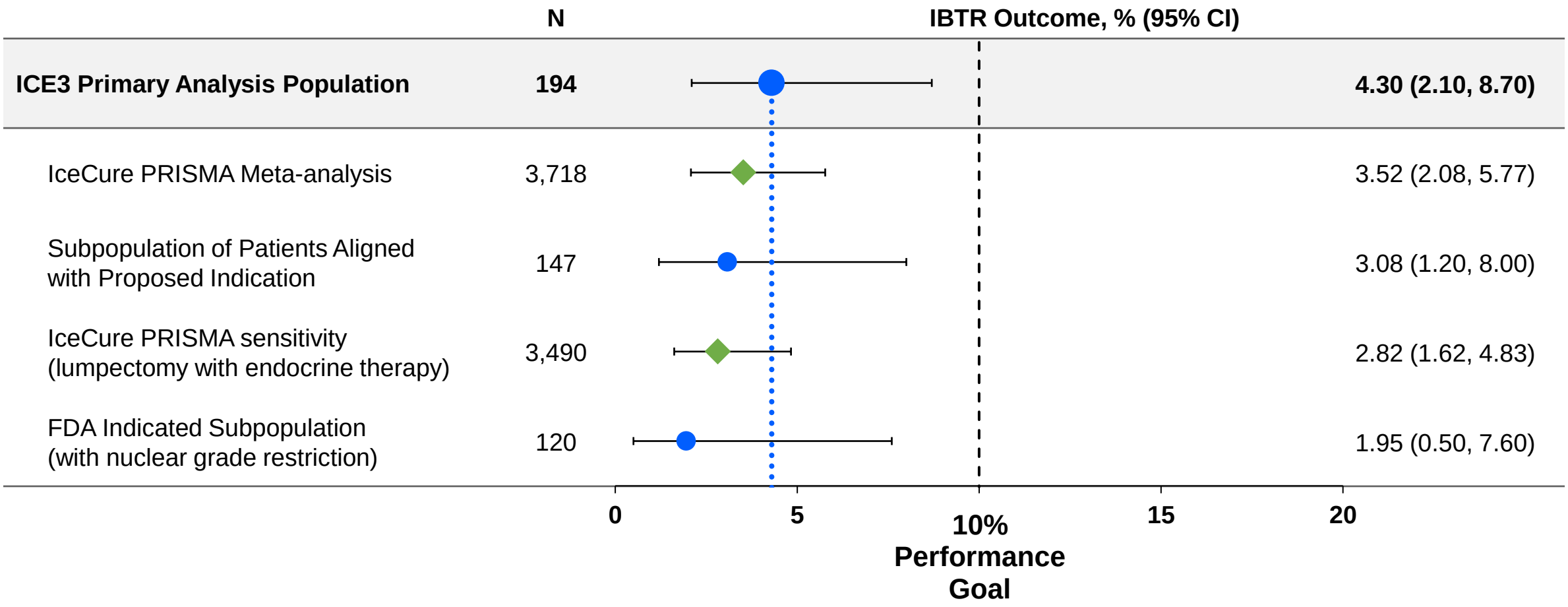
- **FDA recommended censoring method (CIF) and IceCure censoring method agree that the primary endpoint was met**

Number of IBTR events	KM Rate (95% CI) Censoring at IBTR event or study discontinuation (IceCure method)	KM Rate (95% CI) Death censored at time of death, or final follow-up for LTFU	KM Rate (95% CI) Death and LTFU censored at final follow-up (FDA method)	CIF Rate (95% CI) (FDA recommended method)
7 including >Month 60	4.3% (2.1 - 8.7)	4.6% (2.2 - 9.5)	5.0% (2.4 - 10.2)*	4.6% (2.0 - 8.9)
6 through Month 60	3.6% (1.6 - 7.9)	4.0% (1.8 - 8.6)	4.1% (1.9 - 8.9)	4.0% (1.6 - 8.0)

IceCure IBTR rate is conservative given inclusion of >M60 event

*FDA cites 5.2% (2.5-10.7); however, IceCure statisticians are unable to reproduce FDA results
LTFU=lost-to-follow-up or withdrawal from study

Summary of ICE3 Analysis Populations and Respective Literature Comparators



ICE3 IBTR rate similar to lumpectomy in all subpopulation analyses

ICE3 Confirms ProSense™ is Successful in the Treatment of Breast Cancer

Ann Surg Oncol
https://doi.org/10.1245/s10434-024-16181-0

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SURGICAL ONCOLOGY
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ORIGINAL ARTICLE – BREAST ONCOLOGY

Cryoablation Without Excision for Early-Stage Breast Cancer: ICE3 Trial 5-Year Follow-Up on Ipsilateral Breast Tumor Recurrence

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Clinical Perspective

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Patient Experience

Physician/Patient Discussion

Discuss benefits and risks of all options

- Ask the **Choosing Wisely questions**
- **Provide range of options** including de-escalated alternatives

Consider tumor characteristics and patient history to identify best option for the specific patient

Counsel patient that with any treatment for breast cancer there is a risk of:

- Incomplete treatment
- Recurrent tumors

Procedural risks common to all cryoablation systems

- Edema, bruising, hematoma, hypothermic frost injury, and postoperative pain

De-escalated care involves shared decision making

ProSense™: A Needed Minimally Invasive Option

Patients deserve to choose

- Less morbid treatment
- More financially accessible treatment
- Better cosmetic outcome
- Greater quality of life

- **Indicated population with early stage, low-risk breast cancer are ideal candidates for de-escalation**
- **The ICE3 clinical study provides sufficient evidence to conclude that the device benefits outweigh risks for the treatment of early stage, low-risk breast cancer**
- **IceCure is eager to work with FDA to design appropriate special controls, labeling and training to ensure good patient selection and safe & effective use**

Patients should have the choice of all available options

IceCure

IceCure ProSense™ Cryoablation System

General and Plastic Surgery Devices Panel Meeting

November 7, 2024

CC-101

Sponsor Backup Slides Shown

What Data is Available as Real-world Data?

- **The ProSense™ System or an equivalent cryoablation device was used in over 1,600 procedures for the treatment of breast cancer in independent clinical studies**
- **Across the clinical literature, 18 cohort studies conducted in United States, Japan, Spain, Germany, Romania, Italy, and the Netherlands with follow-up to 16 years**
- **10 studies reported 22 recurrences in up to 1,366 patients (1.61%)**
- **No serious device or treatment related adverse events were reported**
- **Post market surveillance (PMS) data was collected in 150 BSC patients**
  - In total, 4/140 (2.9%) of patients reported adverse events (1 hematoma, 2 minor skin burns, and 1 not specified)
  - Physician satisfaction was graded as “Excellent” in 124/141 (88%) cases
  - Physician satisfaction was graded as “Good” in 15/141 (11%) cases and “Medium” in the remaining 2/141 (1%) cases

What Happens to the Destroyed Cells after Cryoablation?

30 minutes: Immediate post-thaw phase

Cells swell & irreversible damage

8 hours to 1 week: Hemorrhagic and inflammatory phase

8-12 hours
Apoptosis progressively increases at the peripheral zone

2 days
Coagulation necrosis, characterized by hemorrhage, edema, and inflammation

7 week
Infiltration of inflammatory cells, fibrin and collagen stranding, and capillary ingrowth sharply demarcate the periphery of the lesion

1 to 3 months: Replacement phase

1 month
Necrotic tissue is largely cleared with new blood vessels at the periphery

3 months
A small fibrotic scar with an intact endothelial layer

In weeks to months, the necrotic tissue is slowly removed by phagocytotic activity of the immune system and replaced by a fibrous collagenous scar

Hai, J. J., & Tse, H. F. (2013). Biophysical principles and properties of cryoablation. *The Practice of Catheter Cryoablation for Cardiac Arrhythmias*, 1-7
Baust, J. G., Gage, A. A., Johansen, T. B., & Baust, J. M. (2014). Mechanisms of cryoablation: clinical consequences on malignant tumors. *Cryobiology*, *68*(1), 1-11

Kameda Medical Center Clinical Trial
465 Patients Over 16 Years - Long Term FU

Prof. Eisuke Fukuma, pioneer in cryotherapy for breast cancer

Group	Year	Tumor Size	# of Patients
IceCure	2014-2022	≤15 mm	560 (465 with long term FU)

Local recurrence (IBTR) - 0.65% (3/465)

Patient selection ⟩ Cryoablation ⟩ Adjuvant Rx ⟩ Follow-up

Age: mean 57 (range 31-83)

ER/PR+, HER2-
Sentinel Node Imaging ± Bx Negative
Whole Breast Radiotherapy
Endocrine/Chemo Rx per Biology

All post-cryo annual follow up

PE, Mammo, US, MRI

IBTR Sensitivity Analysis – Ki67

ICE3 Study: Primary Population N=194

Ki67 Stratification	N	Events	5-Year IBTR	95% LB	95% UB
<14%	93	3	**3.93%**	1.28%	11.76%
≥14%	36	1	**3.33%**	0.48%	21.39%
Unknown	65	3	**5.23%**	1.72%	15.36%

No difference in 5-year IBTR rate by Ki67

IBTR Sensitivity Analysis – Age

ICE3 Study (Primary Analysis Population N=194)

	Primary Population (N=194)		
Age	**Subjects n (%)**	**Recurrence Rate**	**95% CI**
55 to 60 years	4 (2.1)	0%	–
61 to 70 years	47 (24.2)	5.3%	1.4 – 19.8
71 to 80 years	100 (51.5)	4.5%	1.7 – 11.5
81 to 90 years	41 (21.1)	3.0%	0.4 – 19.6
91 to 94 years	2 (1.0)	0%	–

In ICE3 elevated risk not seen in patients under 70

LUMINA Trial Patient Accounting

- **740 registered patients**
  - 224 patients Ki67 ≥13.25%
  - 11 patients had insufficient specimens
  - 4 patients were identified by central monitoring as ineligible
  - 1 patient withdraw
- **500 patients enrolled**
- **246 at risk at 5-years (49.2%)**

DSMB Exclusion – Patient 12

- **Reason for single freeze: machine malfunctioned. Was only able to do 1st freeze, thaw and then only 2 minutes of the 2nd freeze**

Procedure Date	Recurrence Date
18-Jan-2019	No recurrence

DSMB Exclusion – Incomplete Treatment (n=3)

Pt #	Procedure Date	DSMB Meeting Date	Detailed Reason	Outcomes
1	03 Oct 2016	01-03 May 2019	Extremely short treatment that could not cover the lesion. On procedure day, tumor dimensions were 0.7*0.6*0.7 cm, final ice ball dimensions were **1.31***4.52 cm, treatment cycle times were **1:48F1**-8:00T-**1:22F2** (mm:sec)	No Recurrence
2	14 Sep 2016	01-03 May 2019	Extremely short treatment that could not cover the lesion. On procedure day, tumor dimensions were 0.86*0.1*0.84 cm, final ice ball dimensions were **0.4*2.47** cm, treatment cycle times were **1:22F1-1:51T-1:59F2** (mm:sec)	No Recurrence
3	18 Jan 2019	03-05 Sep 2019	Insufficient treatment due to machine malfunction. On procedure day, tumor dimensions were 0.6*0.7*0.3 cm, final ice ball dimensions were **3.33***5.3 cm, treatment cycle times were 9:15F1-8:01T-**2:24F2** (mm:sec)	No Recurrence