

Cryotherapy



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Disclosure

Speaker name:

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I have the following potential conflicts of interest to report:

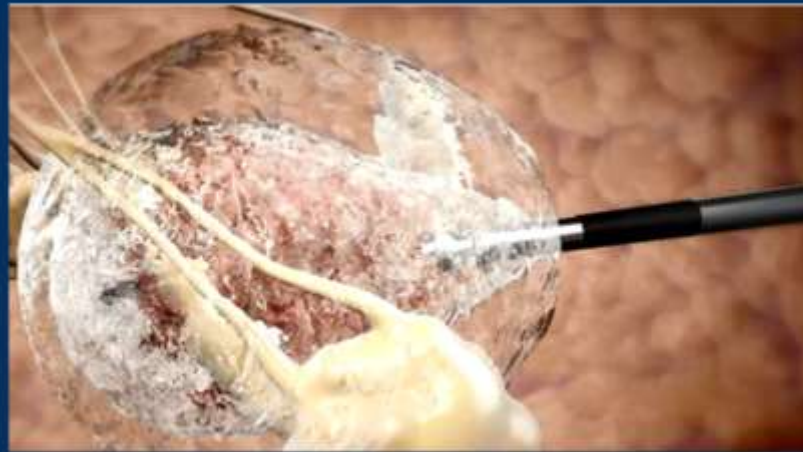
- Consulting
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other: travel grant

- I do not have any potential conflict of interest



What is Cryoablation?

Cryoablation is a minimally invasive image-guided US / CT treatment that uses extreme cold to freeze and accurately destroy diseased tissue within the tumor zone.



What is Cryoablation?



Intracellular ice crystallization:

- Contact with extremely cold cryoprobe
- Intracellular ice crystals form causing cell lysis/death.



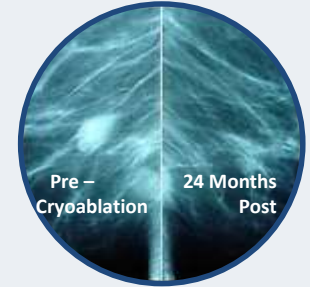
Extracellular ice crystallization:

- Freeze, thaw, freeze cycle
- Repeated, rapid osmotic shifts of fluid into and out of the cell weakens the cell membrane causing membrane rupture and cell death.



Platelet aggregation in capillaries surrounding the tumor:

- Lack of blood supply to tumor starves any remaining cells.
- Prevents regrowth



Post cryoablation & cryoimmunology:

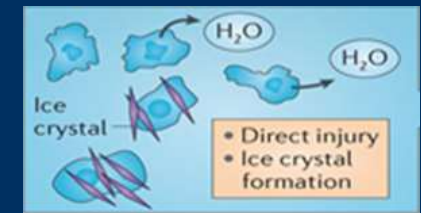
- Area becomes an irregular accumulation of hypoechoic necrotic debris
- Elimination of debris over time
- No artifact that would adversely affect interpretation
- Clinical studies suggest anti-tumoral response are generated through cryoablation.



Mechanism of Action - Direct

1. During the freeze:
Intracellular ice
crystallization

- Contact with extremely cold cryoprobe ($\sim -170^{\circ}\text{C}$ on the probe shaft)
- Intracellular ice crystals form causing cell rupture --> lysis/death



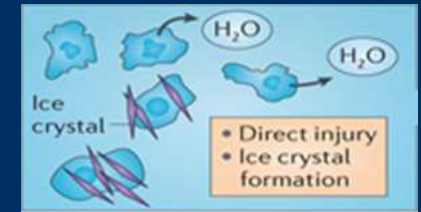
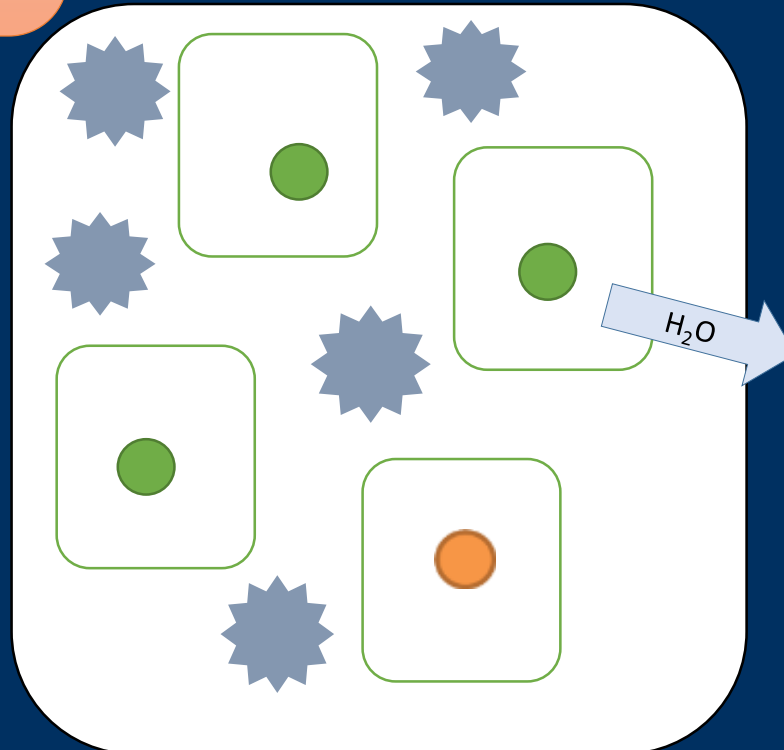
Kaufman, 2004



Mechanism of Action - Direct

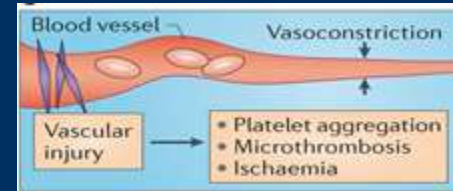
2. During the thaw:
Extracellular ice
crystallization

- Freeze, thaw, freeze cycle
- Repeated, rapid osmotic shifts of fluid into and out of the cell weakens the cell membrane causing membrane rupture and cell death



Mechanism of Action – Indirect/Delayed

3. Delayed Cell Destruction: Vascular stasis



Endothelial damage leads to platelet aggregation, vascular stasis => thrombosis and target-tissue anoxia in capillaries surrounding the tumor

- Lack of blood supply to tissue starves any remaining cells.
- Prevents regrowth

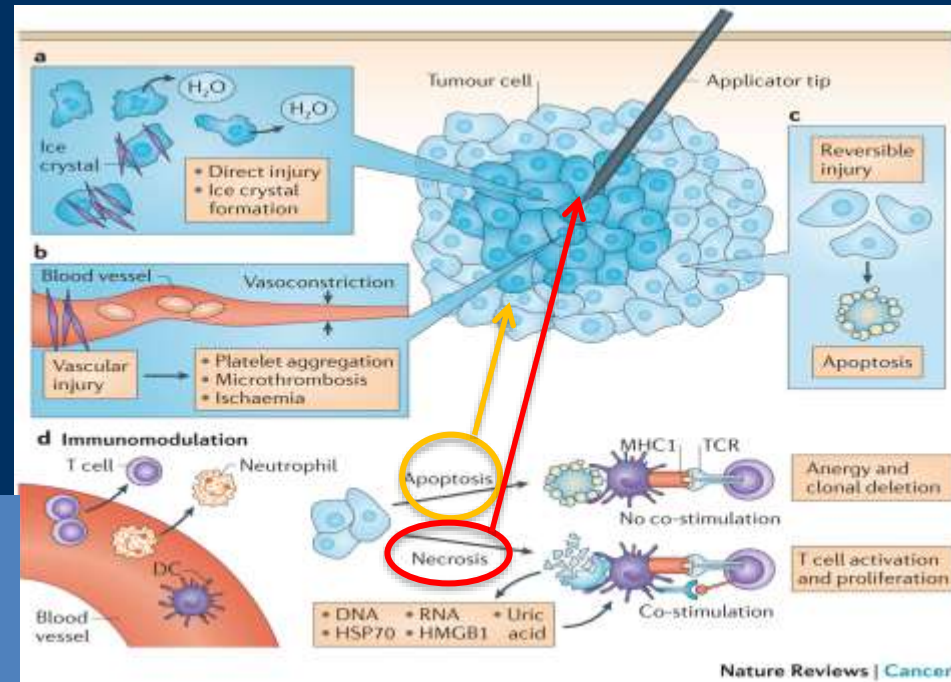
Summary of Killing Mechanisms

Necrosis versus Apoptosis = Stimulation versus Suppression

- **Direct Damage:**
 - intracellular ice formation
 - osmotic dehydration
- **Indirect damage :**
 - ischemia / vascular injury
 - immunologic response

HIGH freeze rate → immune stimulation
/ significant increase in tumor-specific T cells
/ reduction of metastases / improved survival

LOW freeze rate → may alter the immune
response from stimulatory to **suppressive**



Sabel et al., Rate of Freeze Alters the Immunologic Response After Cryoablation of Breast Cancer. *Ann Surg Oncol* (2010) 17:1187–1193



Cryoablation with IceCure



- **System:**
- Optimized for comfortable treatment of various tumors
- Can be done in the physician's office or O.R.
- System utilizes LN2 for cost effective, fast and efficient treatment with stable & low temperature



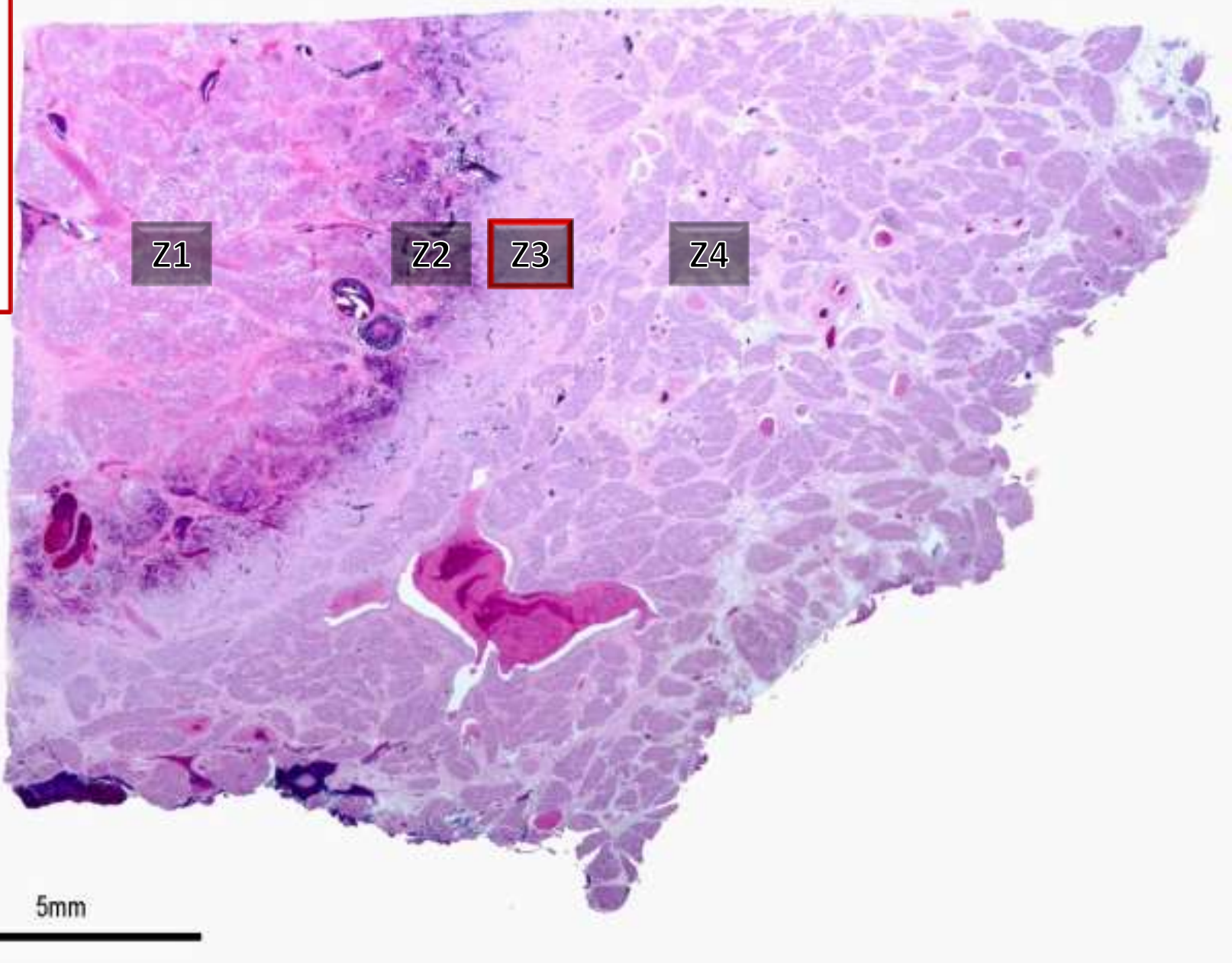
- **Probe:**
- Disposable component
- Various models
- Easy probe placement



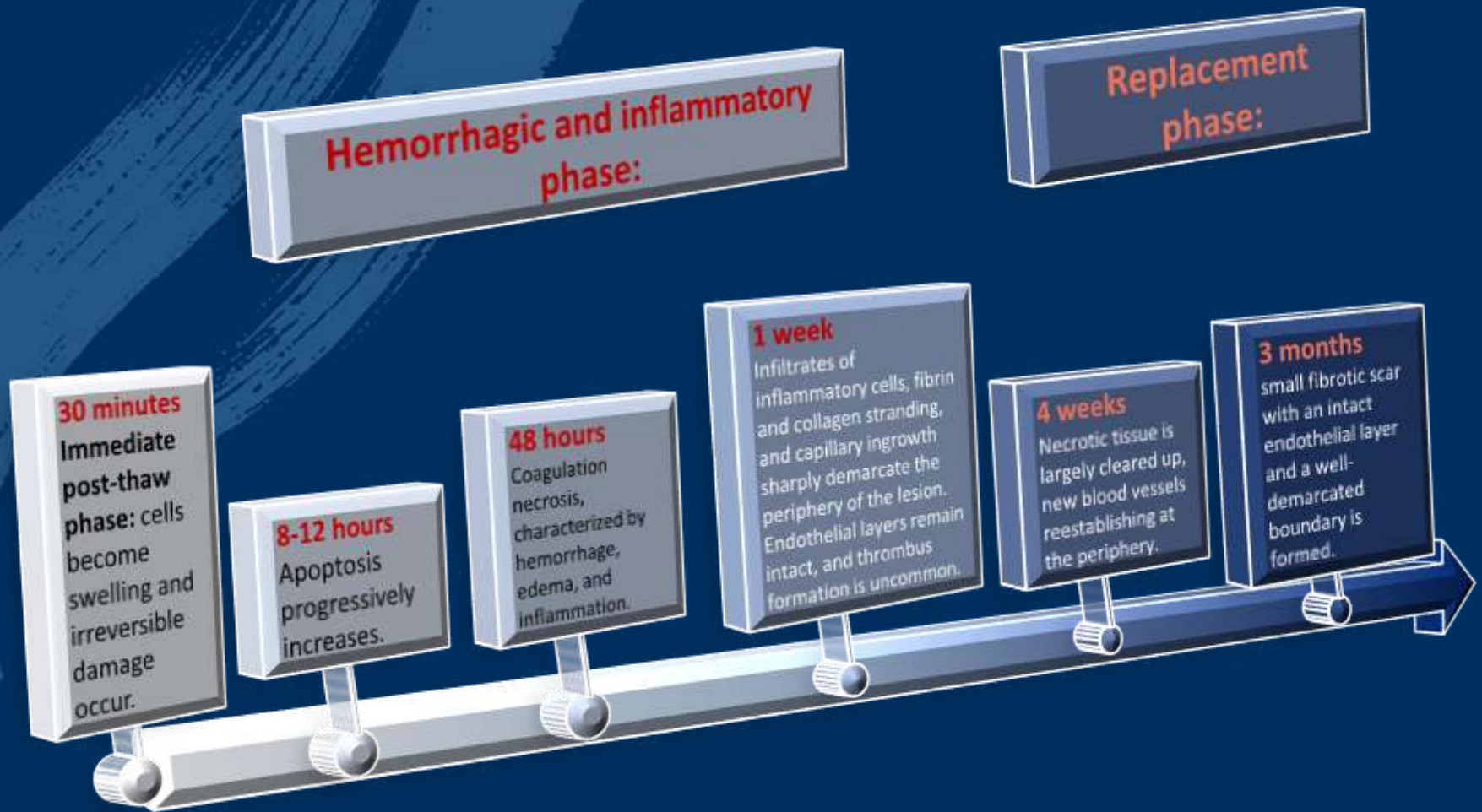
- **Console:**
- Intuitive & flexible touch screen
- Simple operation



An unfrozen hypothermic zone. A transient effect.



Timeline Post-Ablation



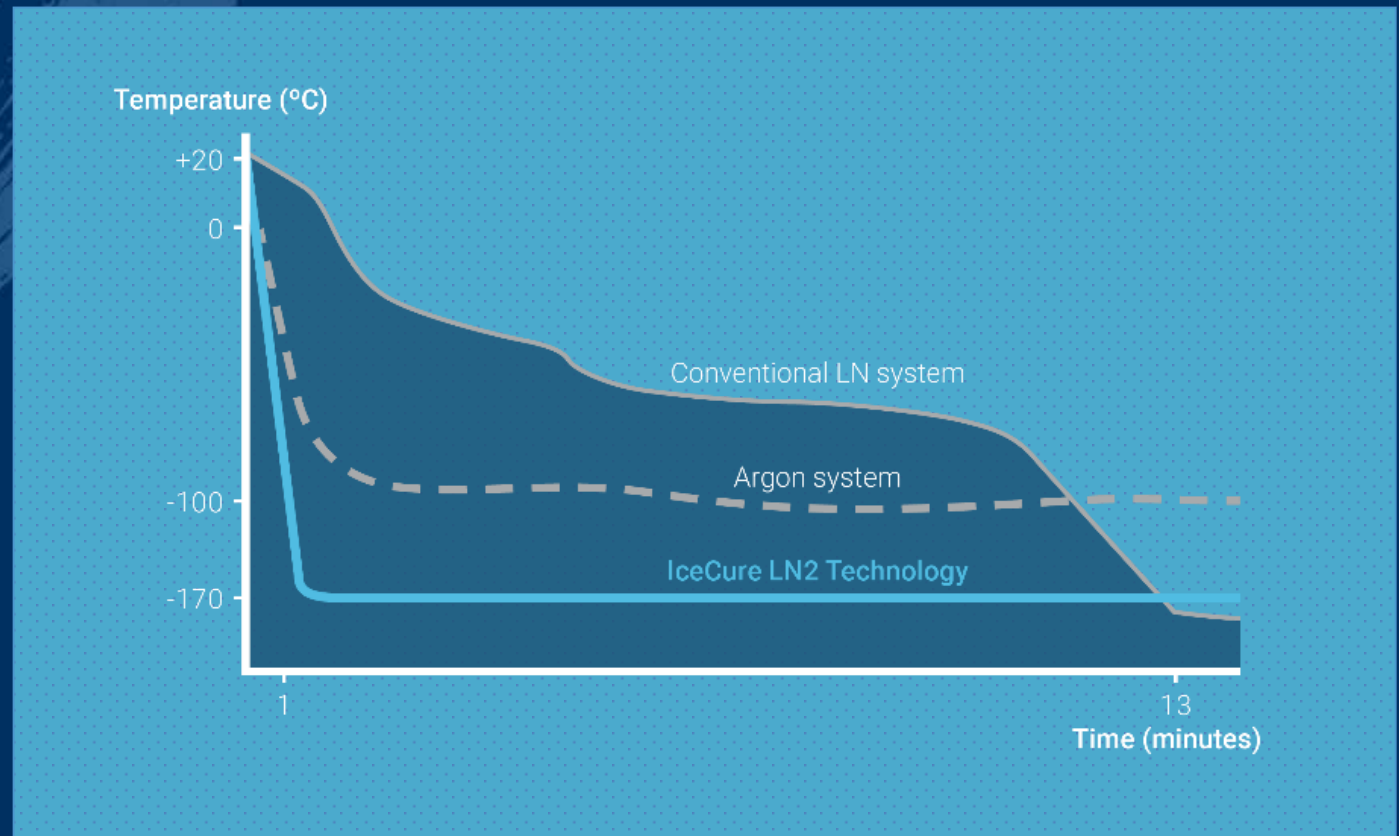
Cryoablation Overview

- The cooling rate and the lowest achieved temperature are the most important factors that affect the effectiveness and efficacy of the cryoablation.
- Two ways to achieve low temperature:
 - ✓ Using expansion of high-pressure gas (“Joule-Thompson” method):
 - Argon can reach -120-150°C. Argon is being used by BTG (Galil Medical) and Healthtronics (Endocare)
 - Nitrogen reaches the “near-critical-point” at -147°C. This system was developed by CryoDynamics, and is being used by Endocare.
 - ✓ Boiling liquefied gas:
 - Nitrous Oxide, boils at -88°C, is used by Medtronic (CryoCath) for Atrial Fibrillation
 - Liquid Nitrogen (LN₂), boils at -196°C, is used by Sanarus and IceCure

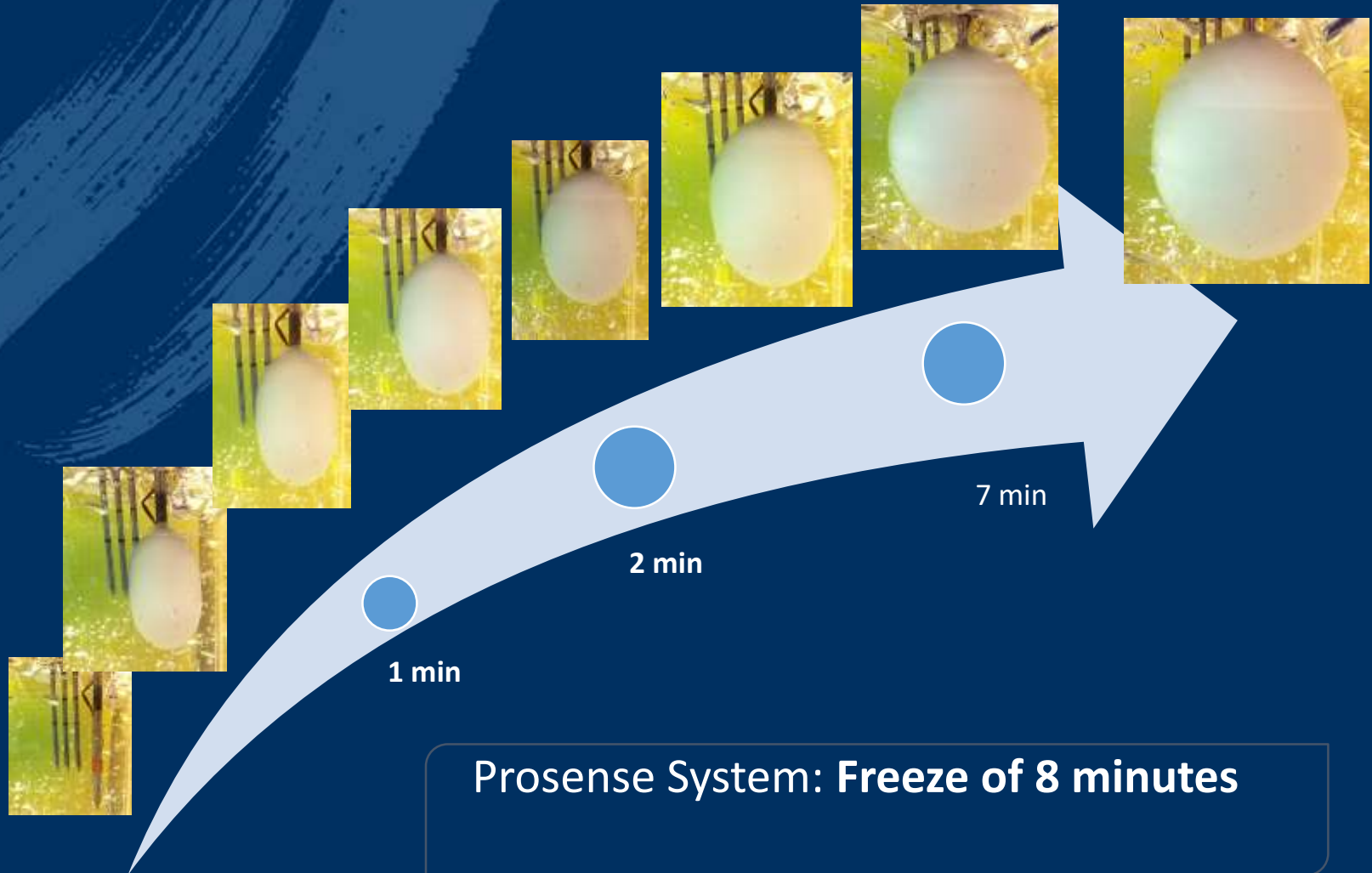


IceCure Superior Liquid Nitrogen (LN2) Technology for Optimum Tumor Destruction

Lower stable temperature and faster cooling rate for larger lethal zone



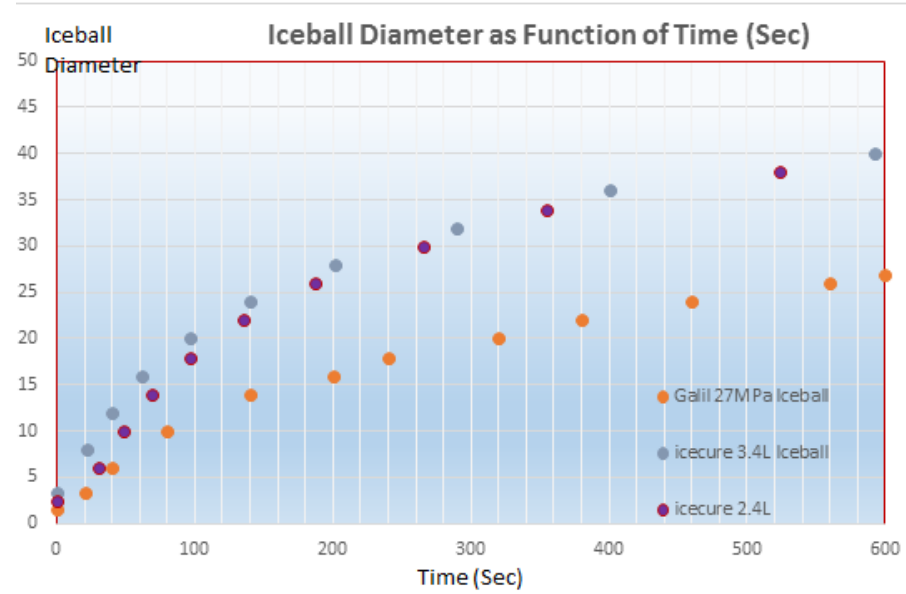
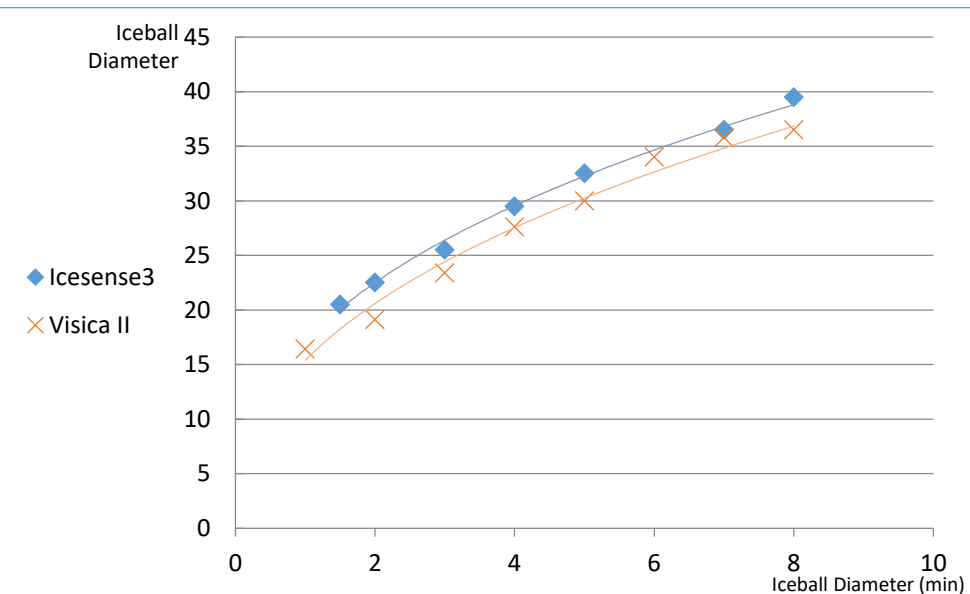
IceCure Iceball Growth During Bench Testing



IceCure ProSense™ Ice Ball Diameter Comparison

ProSense™ versus
Sanarus Visica 2™

ProSense™ versus
Galil Medical



IceCure Competitive Advantage

	3rd Generation IceCure ProSense™	2nd generation Sanarus Visica 2™	1st Generation Galil Medical EndoCare
Tumor destruction method	Liquid nitrogen	Liquid nitrogen	Argon gas
Office setting	✓	✓	
Procedure time	5-40 minutes	10-30 mins	30-60 mins
Cooling rate	Fast	Medium	Slow
Pressure	Low	Low	High
Single operator	✓	2 operators	2 operators
Compact disposable	✓	×	×
Intuitive, flexible user interface	✓	Limited	Limited
Customizable procedure	✓	Limited	Limited
Probe positioning	Focused	Focused	Penetrates beyond the tumor
Procedure release	Heated Nitrogen	Electricity in needle	Electricity in needle
Temperature	Constantly low (-160°C)	Not constant	Constantly medium (-120°C)
Cost of procedure	Low	Low	High



IceCure is Superior to Thermal Ablation Therapies (RF and Microwave)

	Cryoablation IceCure ProSense™	Thermal Ablation (RF & MW)
Pain	Minimal or no pain	Very painful
Anesthesia	Local	High amount to general
Visualization	Ultrasound & CT	MRI only
Accuracy	Very high	Low
Immune response	Positive effect	None
Procedure time	5-40 minutes	30 – 60 minutes
Equipment size	Floor top console	Tabletop



IceCure Indications for Use – in Europe

- **Urology:**

- The system may be used to ablate prostatic tissue.
- The system may be used to ablate kidney tissue including renal cell carcinoma.
- The system may be used for the ablation of prostate tissue in cases of prostate cancer and benign prostatic hyperplasia.

- **Oncology:**

- The system may be used for ablation of cancerous or malignant tissue.
- The system may be used for ablation of benign and malignant breast tumors .
- The system may be used for ablation of benign and malignant lung tumors.
- The system may be used for ablation of benign and malignant bone tumors.
- The system may be used for ablation of benign and malignant liver tumors.
- The system may be used for ablation of benign tumors.
- The system may be used for palliative intervention.



IceCure Breast Application



12 month follow up



IceCure Indications for Use – in Europe

- **Dermatology:**

- The system may be used for the ablation or freezing of skin cancers and other cutaneous disorders.

- **Gynecology:**

- The system may be used for the ablation of malignant neoplasia or benign dysplasia of the female genitalia.

- **General surgery:**

- The system may be used for the ablation of leukoplakia of mouth, angiomas, sebaceous hyperplasia, basal cell tumors of the eyelid or canthus area, ulcerated basal cell tumors, dermatofibromas, small hemangiomas, mucocele cysts, multiple warts, plantar warts, hemorrhoids, anal fissures, perianal condylomata, pilonidal cysts actinic and seborrheic keratoses, cavernous hemangiomas, recurrent cancerous lesions. The system may be used for the destruction of warts or lesions. The system may be used for the palliation of tumors of the oral cavity, rectum, and skin. The system may be used for ablation of breast fibroadenomas and breast tumors.



IceCure Indications for Use – in Europe

Thoracic surgery:

- The system may be used for the ablation of arrhythmic cardiac tissue.
- The system may be used for the ablation of cancerous lesions, including lung tissue.

Proctology:

- The system may be used for the ablation of benign or malignant growths of the anus and rectum.
- The system may be used for the ablation of hemorrhoids.



IceCure Indications for Use – in the U.S.A.

ProSense™ cryoablation system is indicated for use as a cryosurgical tool in the fields of general surgery, dermatology, thoracic surgery, gynecology, oncology, proctology, and urology as detailed below. The ProSense™ cryoablation system may be used with an ultrasound device to provide real-time visualization of the cryosurgical procedure.

Urology:

- The system may be used to ablate prostatic tissue.
- The system may be used for the ablation of prostate tissue in cases of prostate cancer and benign prostatic hyperplasia.

Oncology:

- The system may be used for ablation of cancerous or malignant tissue.
- The system may be used for ablation of benign tumors.
- The system may be used for palliative intervention.

Dermatology:

The system may be used for the ablation or freezing of skin cancers and other cutaneous disorders.



IceCure Indications for Use – in the U.S.A.

Gynecology:

The system may be used for the ablation of malignant neoplasia or benign dysplasia of the female genitalia.

General surgery:

- The system may be used for the ablation of leukoplakia of mouth, angiomas, sebaceous hyperplasia, basal cell tumors of the eyelid or canthus area, ulcerated basal cell tumors, dermatofibromas, small hemangiomas, mucocele cysts, multiple warts, plantar warts, hemorrhoids, anal fissures, perianal condylomata, pilonidal cysts actinic and seborrheic keratoses, cavernous hemangiomas, recurrent cancerous lesions.
- The system may be used for the destruction of warts or lesions.
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- The system may be used for ablation of breast fibroadenomas.



IceCure Indications for Use – in the U.S.A.

Thoracic surgery:

- The system may be used for the ablation of arrhythmic cardiac tissue.
- The system may be used for the ablation of cancerous lesions.

• Proctology:

- The system may be used for the ablation of benign or malignant growths of the anus and rectum.
- The system may be used for the ablation of hemorrhoids.
- The ProSense™ cryoablation system is indicated for patients whom the surgeon has designated as eligible for cryotherapy.



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