Cryotherapy

Wayne Butler, PhD

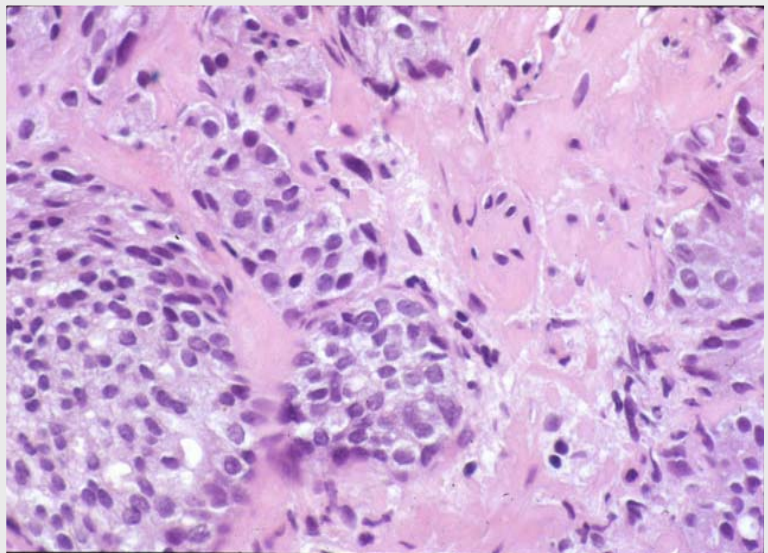
Schiffler Cancer Center

Wheeling Hospital

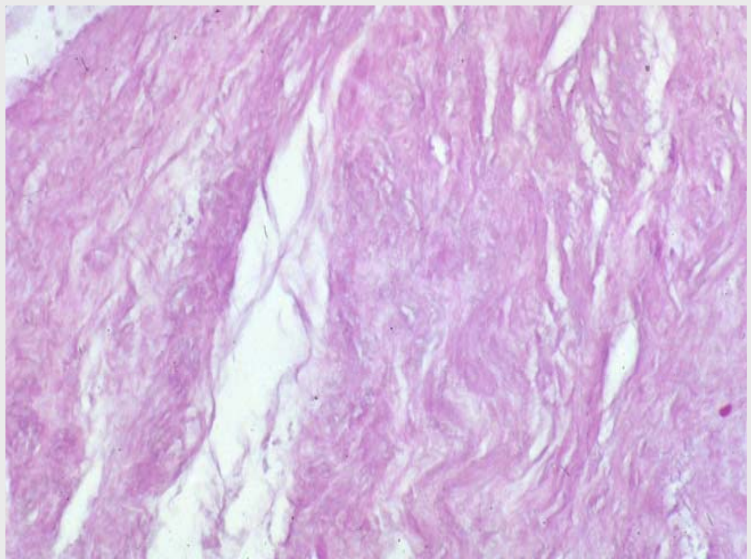
Goal of cryotherapy

- Freeze tissue sufficiently to produce a zone of necrosis
- Freezing will destroy the target lesion and a margin of surrounding tissue

pretreatment



post treatment

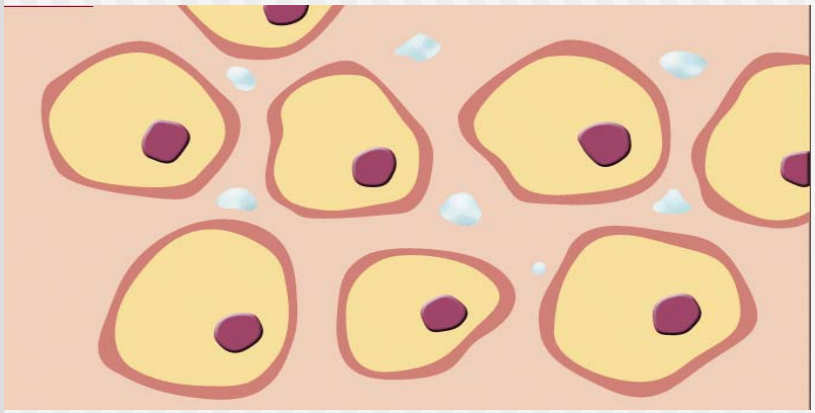


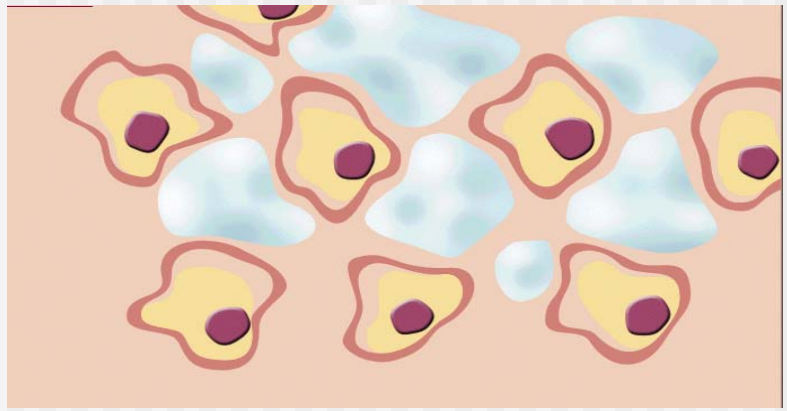
Sites commonly treated with cryotherapy

- Kidney
  - Laparoscopic or open placement of cryoneedles
  - Ultrasound guided (CT or MRI rarely)
- Prostate
  - All localized stages and local failures
  - Transperineal, US guided template approach

Principles of cryobiology

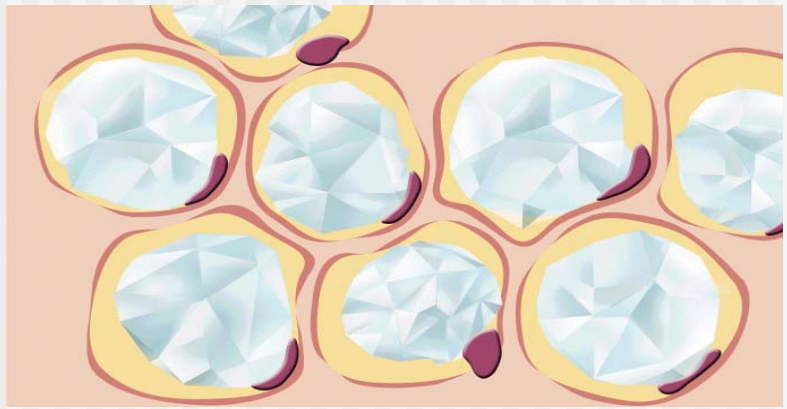
- Pure water freezes at 0° C
- Extracellular ice forms at –8° C





Principles of cryobiology (2)

- Intracellular ice forms at –15° C
- Metabolic atrophy at –40° C



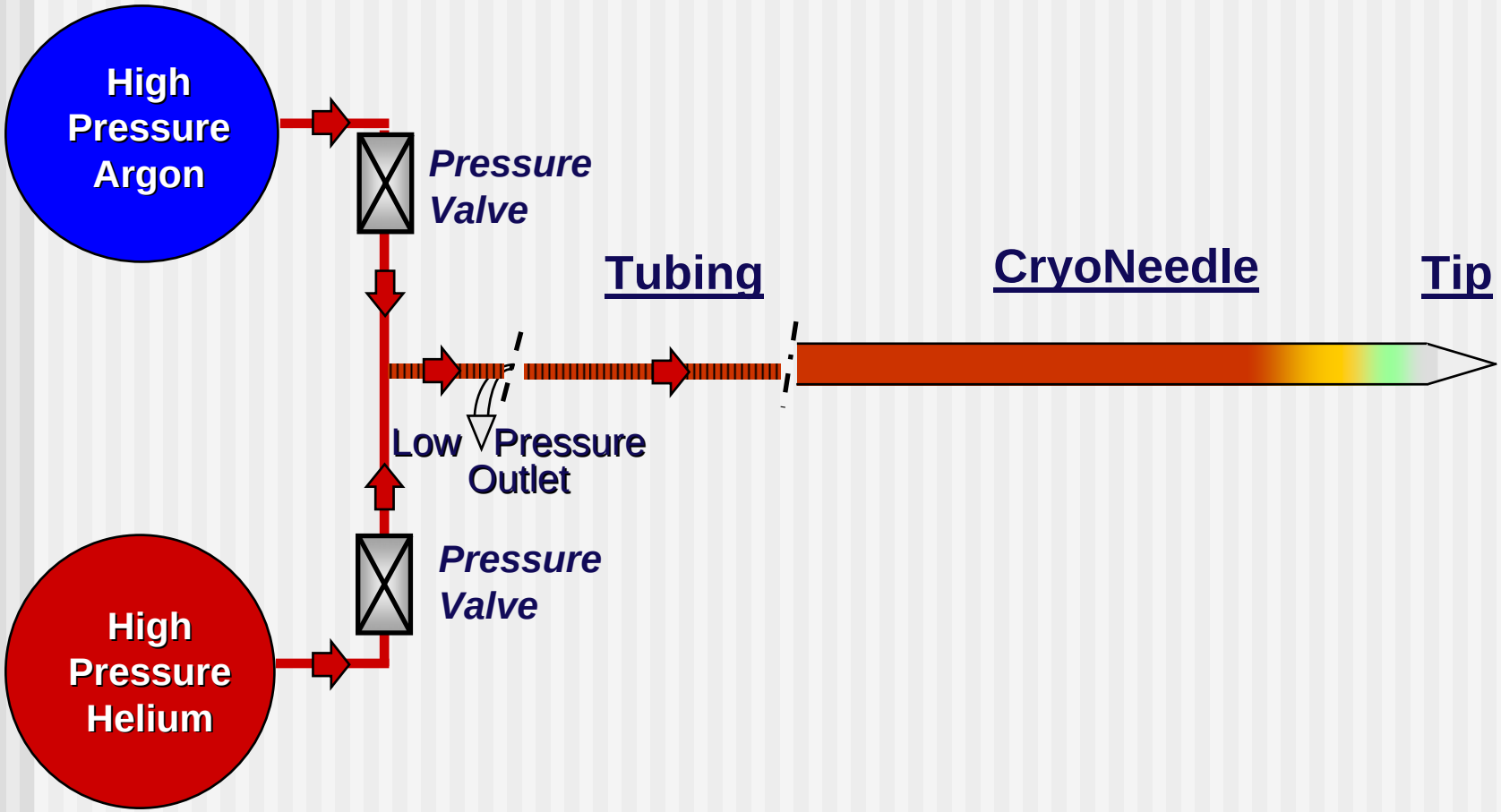
Historical development of cryotherapy technology

- Cryogens used
  - Liquid N_2 (1960)
  - Joule-Tomson effect (1995)
- Rapid helium thawing
- Progression in probe sizes
  - 5 mm with liquid N_2
  - 17 gauge template now

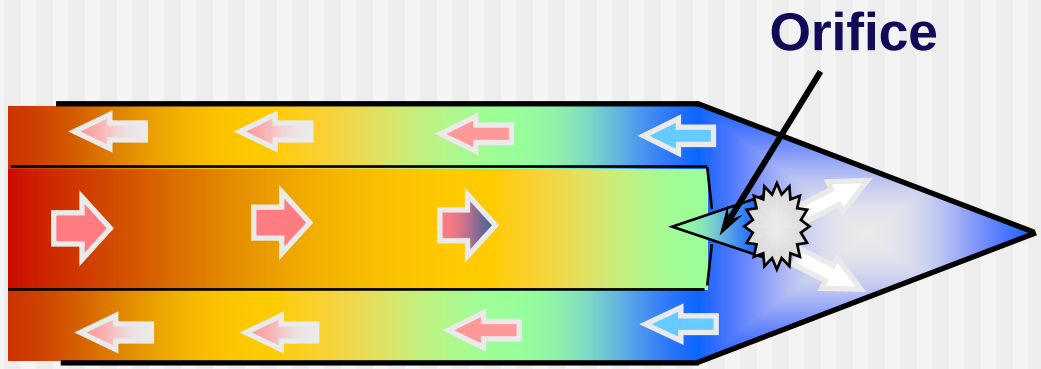
Thermal details

- Low cooling rate is not always lethal to cells
- High cooling rate is more likely to damage cell membrane and cause cell death
- Procedure requires 2 freeze/thaw cycles to –40° C for > 3 minutes to maximize cell kill
- Urethra and rectum must be kept warm

Treatment equipment schematic



Joule-Tompson effect: gas expansion



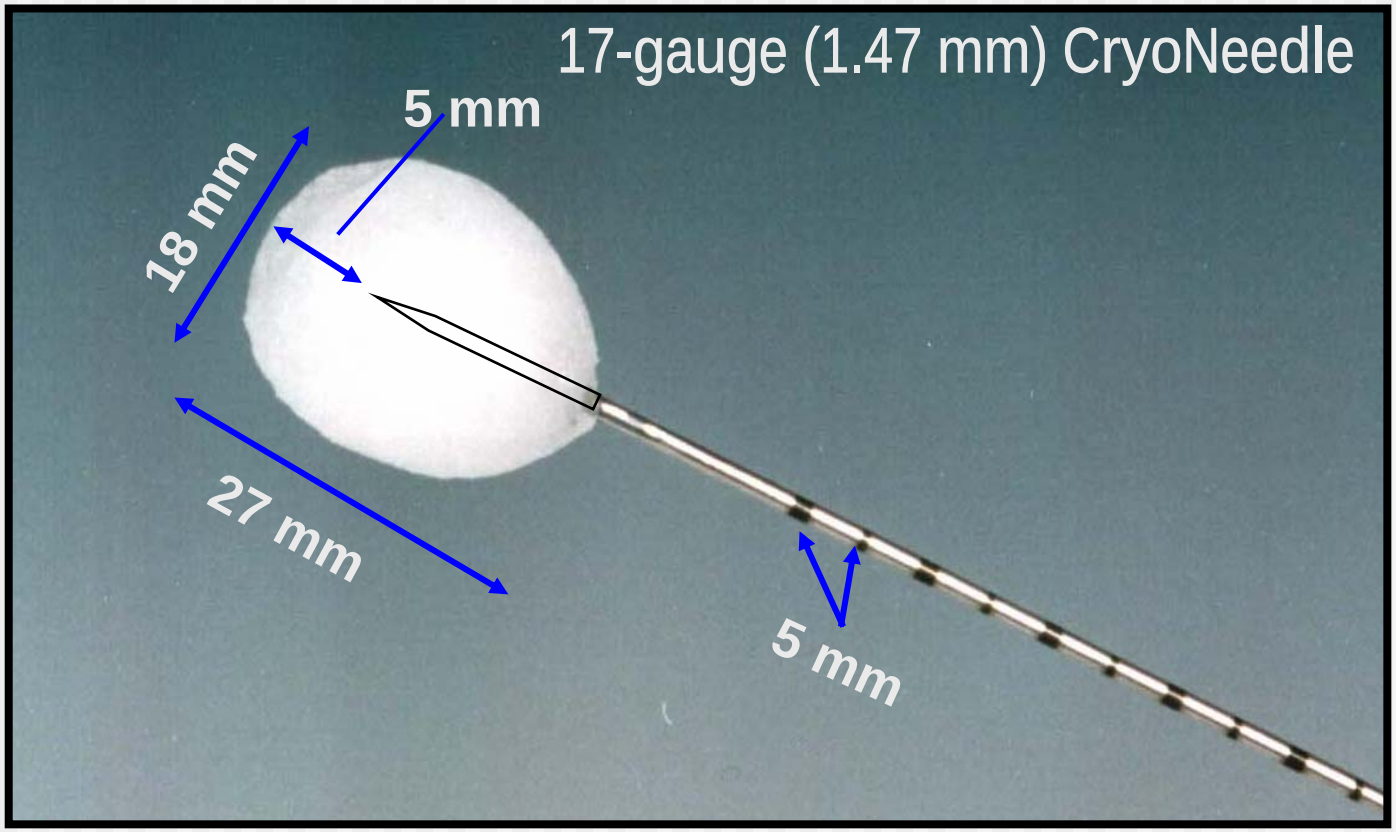
Heat Exchanger

Helium
+70°C

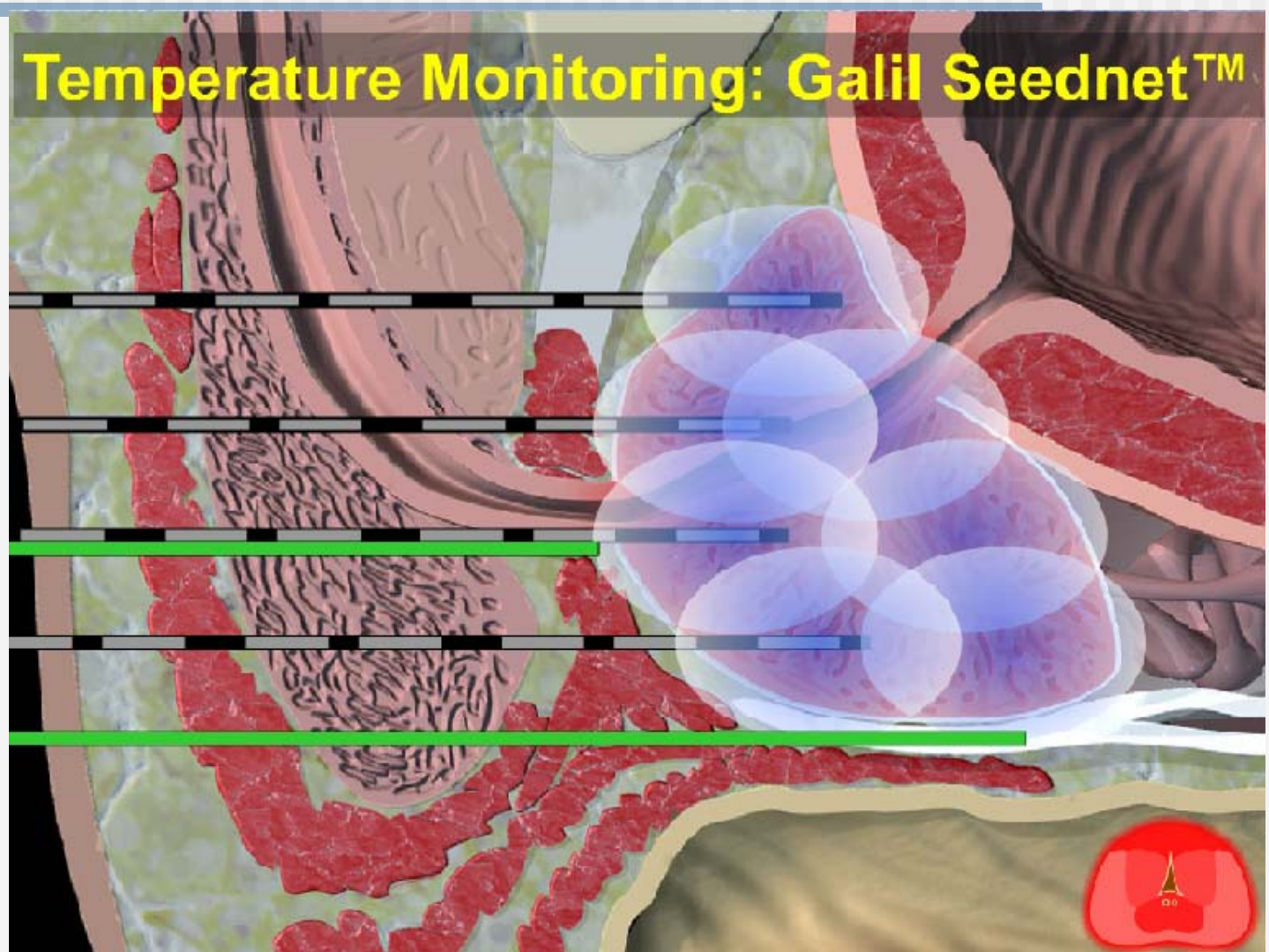
Argon
-183°C

Temp. Control

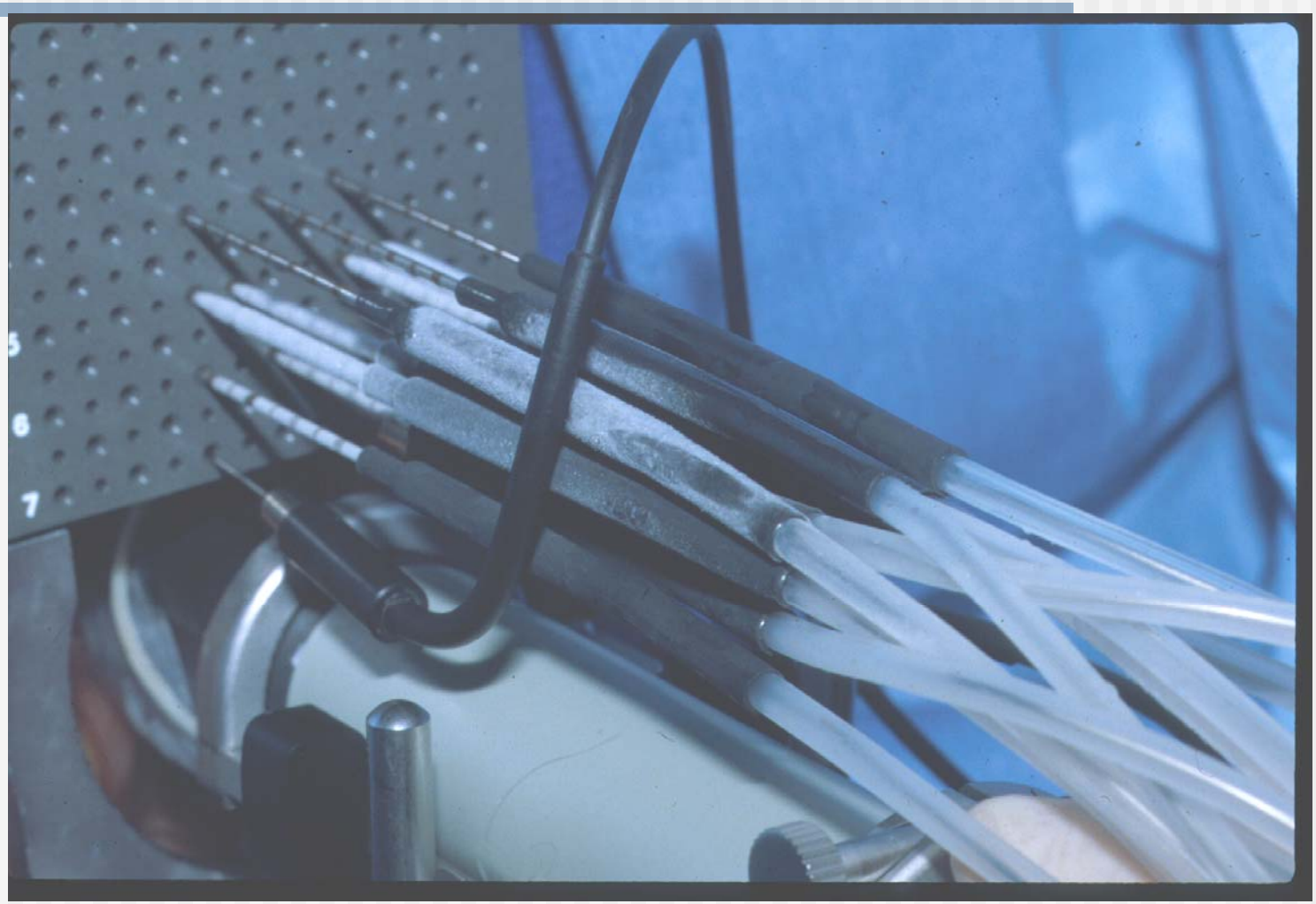
Typical ice ball shape



Temperature monitoring



Cryoneedles and temperature probes in a prostate ultrasound template



Six questions regarding prostate applications

- Does cryotherapy result in cancercidal thermal dosimetry?
- Does cryotherapy routinely ablate the entire gland?
- Are all locations within the prostate treated equally well?
- Does cryotherapy treat the periprostatic region?
- How is freedom from biochemical progression defined?
- Does modern cryotherapy have a favorable morbidity profile?

Does cryotherapy result in cancercidal thermal dosimetry?

- Mean distance from the urethra to the nearest cancer foci is 3 mm (range 0 – 18 mm)
  - 66% of specimens have CaP within 5 mm of urethra
  - 45% have CaP within 1 mm of urethra
  - 17% of prostate cancer abuts the urethra
- Decreasing urethral-cancer distance is correlated with increasing PSA and Gleason score

Does cryotherapy routinely ablate the entire gland?

- Because of the shape of the ice ball, freeze coverage of the apex is incomplete
  - Prostate cancer is present in 74% of apical sections
- Rectal warming to protect the rectal wall creates a cancer sparing zone similar to that around the urethra
- “The goal of cryosurgery for prostate cancer is to ablate the entire gland.” Katz and Rukstalis, Urol 2002

Are all locations within the prostate treated equally well?

- 106 patients with 4-core biopsy after cryotherapy (Chin *et al*, J Urol 2003)
  - Residual prostate cancer in 14.2% of cores
  - Viable prostate glands: 42.4%
  - Viable stroma: 27.4%
- 58/106 treated with hormones
- Maximum follow-up 43 months

Does cryotherapy treat the periprostatic region?

- Patterns of prostate cancer recurrence
  - Apex: 10%
  - Seminal vesicles: 44%
- Thermal profile: Temperature
  - At edge of ice ball = 0° C
  - 3.1 mm inside ice ball = -20° C
- Extracapsular treatment margins are not easily determined

How is freedom from biochemical progression defined?

- ASTRO definition of 3 consecutive rises separated by several months each
- Surgical definition of a PSA cut point
- “PSA nadir ≤ 0.4 ng/mL is necessary to define a high likelihood of a good biochemical or biopsy outcome.”
  Shinohara, *et al* J Urol 1997

Primary cryotherapy
Bahn *et al*, Urology 2002

- 590 consecutive patients
- Mean follow-up 5.43 years
  - Minimum follow-up ~ 3 months
- 540 (92%) had androgen deprivation therapy
  - Duration: 3 – 12 months
- Positive biopsy rate: 13%

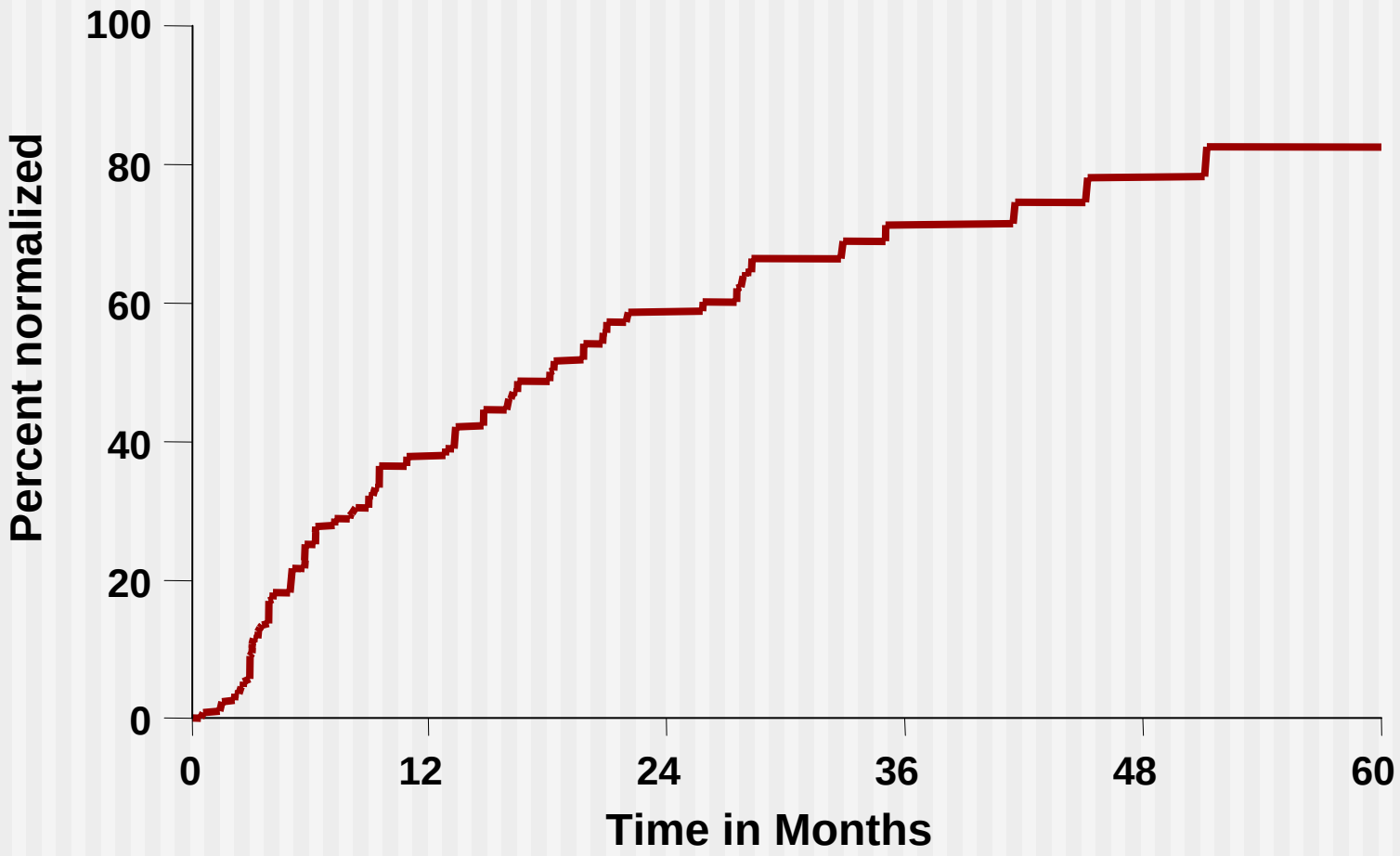
Primary cryotherapy survival

Bahn *et al*, Urology 2002

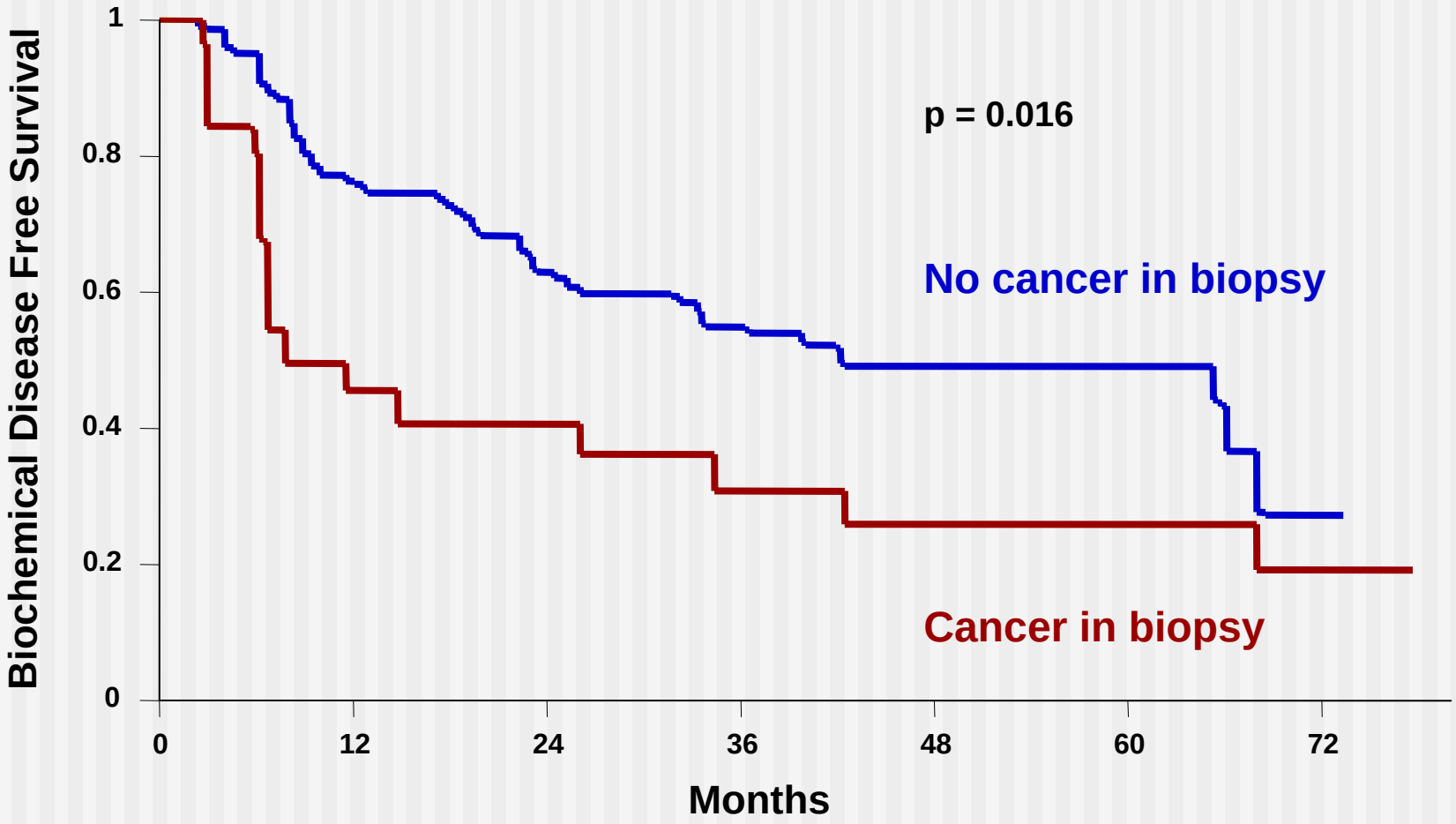
7-year freedom from biochemical progression

Risk group	PSA ≤ 0.5(%)	PSA ≤ 1.0 (%)	ASTRO (%)
Low	61	87	92
Intermediate	68	79	89
High	61	71	89

Testosterone normalization following 6 months ADT



Salvage cryotherapy:
PFS stratified by post-cryo biopsy status



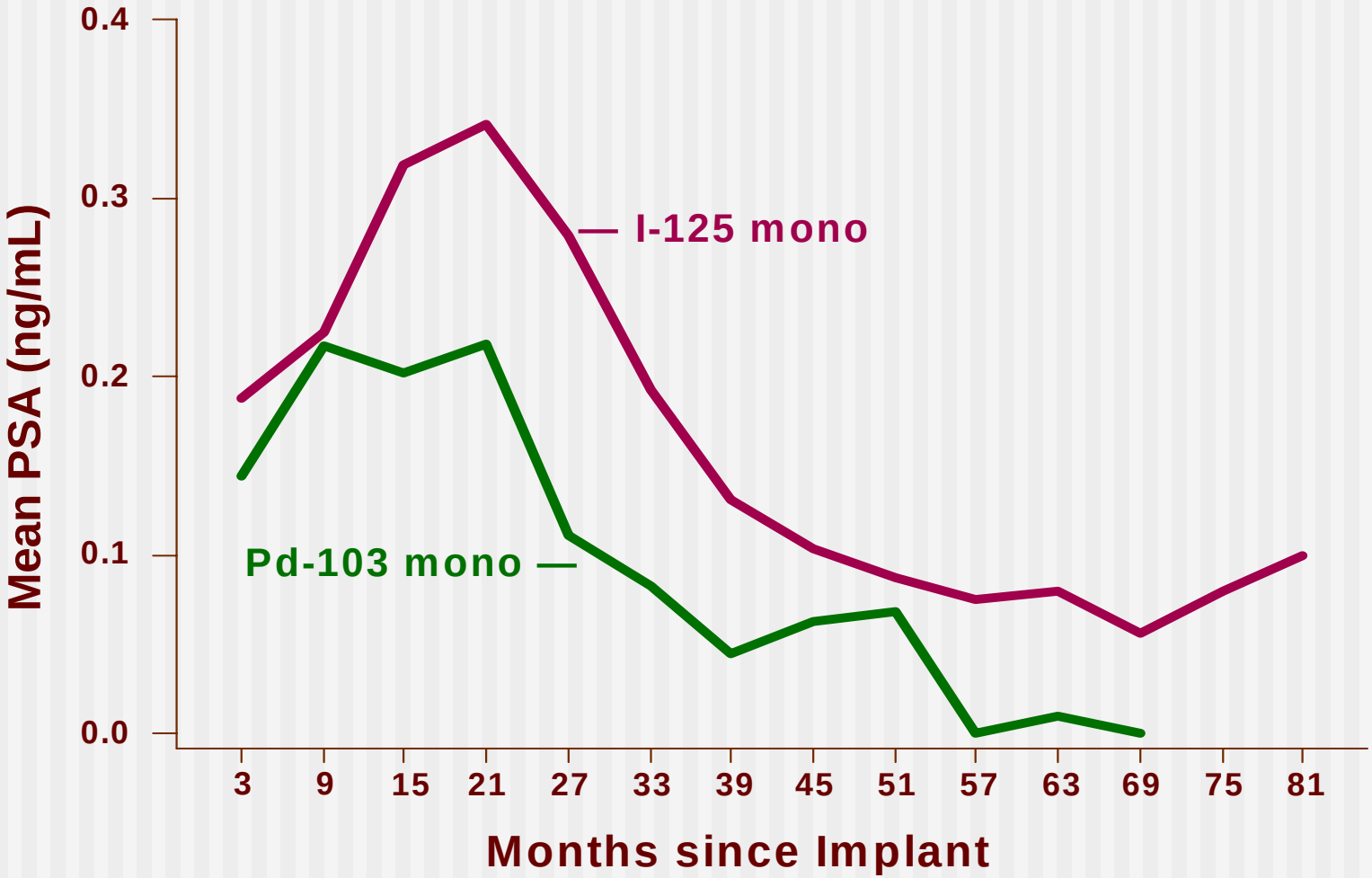
Izawa *et al* (IJROBP 2003)

Are cured patients “successfully” salvaged if they hadn’t failed originally?

- Positive biopsy in XRT and brachytherapy patients is meaningless for 1st few years
- Both radiation modalities have an extensive literature on PSA “spikes” or “bounces” in 1st few years post treatment
- False PSA progression is most common and pronounced in patients receiving ADT

PSA kinetics in patients with preimplant ADT

Merrick et al. Brachytherapy 2004



Does modern cryotherapy have a favorable morbidity profile?

	Incidence	
Complication	**Primary**	**Salvage**
Impotence	**40-95%**	**~100%**
Incontinence	**4-27%**	**20-73%**
Urethral sloughing	**4-23%**	**5-44%**
Pelvic/rectal pain	**1-11%**	**21-77%**
Penile paresthesias	**2-10%**	**6-10%**
Rectourethral fistula	**0-3%**	**0-11%**

Shinohara, *et al.,* Urol Clin N Am 2003

Cryotherapy conclusions

- Inadequate cancercidal thermographic distribution
- 3rd generation cryotherapy has short follow-up
- Relatively poor biochemical survival
  - Distortion of biochemical outcome by ADT
  - Excessive rate of residual CaP and benign elements
  - Excessive apical and SV recurrences
- Substantial morbidity (even with 3rd generation cryo)