Cryotherapy

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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 $-15^\circ$ C
- Metabolic atrophy at $-40^\circ$ C
Historical development of cryotherapy technology

- Cryogens used
  - Liquid $\text{N}_2$ (1960)
  - Joule-Tomson effect (1995)
- Rapid helium thawing
- Progression in probe sizes
  - 5 mm with liquid $\text{N}_2$
  - 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

- High Pressure Argon
- Pressure Valve
- Low Pressure Outlet
- Pressure Valve
- Tubing
- CryoNeedle
- Tip
- High Pressure Helium
Joule-Tompson effect: gas expansion

Heat Exchanger

Helium
+70°C

Argon
-183°C

Temp. Control

Orifice
Typical ice ball shape

17-gauge (1.47 mm) CryoNeedle

18 mm

27 mm

5 mm
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.”
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

<table>
<thead>
<tr>
<th>Risk group</th>
<th>PSA ≤ 0.5 (%)</th>
<th>PSA ≤ 1.0 (%)</th>
<th>ASTRO (%)</th>
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</thead>
<tbody>
<tr>
<td>Low</td>
<td>61</td>
<td>87</td>
<td>92</td>
</tr>
<tr>
<td>Intermediate</td>
<td>68</td>
<td>79</td>
<td>89</td>
</tr>
<tr>
<td>High</td>
<td>61</td>
<td>71</td>
<td>89</td>
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</tbody>
</table>
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?

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
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<tbody>
<tr>
<td></td>
<td>Primary</td>
</tr>
<tr>
<td>Impotence</td>
<td>40-95%</td>
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<tr>
<td>Incontinence</td>
<td>4-27%</td>
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<tr>
<td>Urethral sloughing</td>
<td>4-23%</td>
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<tr>
<td>Pelvic/rectal pain</td>
<td>1-11%</td>
</tr>
<tr>
<td>Penile paresthesias</td>
<td>2-10%</td>
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<tr>
<td>Rectourethral fistula</td>
<td>0-3%</td>
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</tbody>
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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)