Prostate Cancer
Innovations in Surgical Strategies
Update 2007!

Curtis A. Pettaway, M.D.
Professor

Department of Urology
The University of Texas
M. D. Anderson Cancer Center

Radical Prostatectomy Pathologic Features PSA Era

- Detecting Curable Cancers
  - ⇓ Distant Metastasis
  - ⇓ Lymph Node Metastasis
  - ⇓ Seminal Vesicle Involvement
  - ⇑ Organ Confined Cancer
- Majority (> 75%) Clinically Significant

Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

Anna Bill-Axelson, M.D., Lars Holmberg, M.D., Ph.D., Mirja Ruutu, M.D., Ph.D., Michael Häggman, M.D., Ph.D., Swen-Olof Andersson, M.D., Ph.D., Stefan Bratell, M.D., Ph.D., Anders Spångberg, M.D., Ph.D., Christer Busch, M.D., Ph.D., Stig Nordling, M.D., Ph.D., Hans Garmo, Ph.D., Juni Palmgren, Ph.D., Hans-Olov Adami, M.D., Ph.D., Bo Johan Norlén, M.D., Ph.D., Jan-Erik Johansson, M.D., Ph.D., for the Scandinavian Prostate Cancer Group Study No. 4

- **Patients**
  - 695, <75 years, 10 year life expectancy
  - >50% symptoms
- **Clinical Stage**
  - T_1-T_2
  - Negative Bone Scan
- **Serum Prostate Specific Antigen**
  - <50 ng/ml
  - Median, 12.3 – 13.5 ng/ml
- **Endpoints Estimate @ 10 Years**
  - Disease specific and overall mortality
  - Metastases, local progression
- **Mean Follow-Up**
  - Prostatectomy, 85. years
  - Watchful waiting, 8.8 years

N Engl J Med 352:1977, 2005

Radical Prostatectomy versus Watchful Waiting Results @ 10 Years

	Radical Prostatectomy (%)	Watchful Waiting (%)	Percent Relative Reduction	p Value
Disease Specific Mortality	9.6	14.9	44	0.01
Distant Metastasis	15.2	25.4	40	0.004
Local Progression	19.2	44.2	67	<0.001
Overall Mortality	27	32	26	0.04

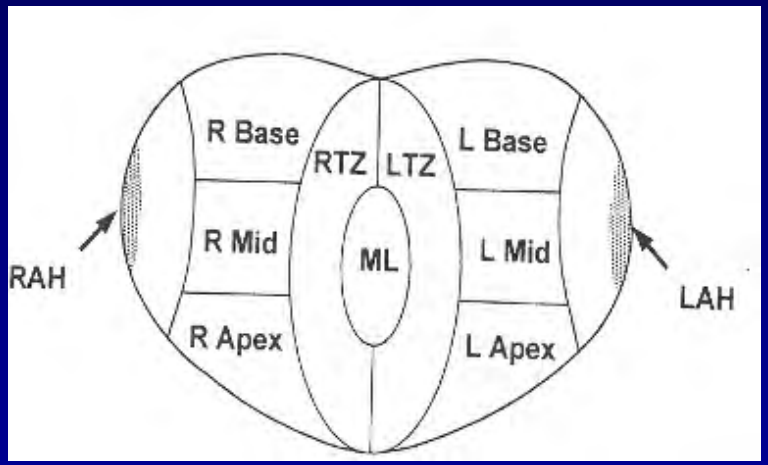
Bill-Axelson et al. N Engl J Med 352:1977, 2005

Prostate Cancer 2007

Increasing Favorable Tumor Detection!

- **New Biopsy Strategies**
- **Lower Prostate Specific Antigen Cut-Offs**

Prostate Biopsy
TRUS Guided
Multisite Biopsy Strategy[1-3]



Sextant pattern - high false negative rate

- 11 core multisite BX increases cancer detection 33% by adding
  - Anterior horns
  - Transition zone
  - Midline
- 10-12 core sextant & laterally directed BX most common currently

[1] Babaian et al., J Urol 163: 152, 2000
[2] Chen et al., Urology 53: 951, 1999
[3] Singh et al., J Urol 171: 1089, 2004

Prostate Cancer Incidence
Serum PSA Levels ≤ 4ng/mL

Study	# Men	% Biopsied	Serum PSA Interval ng/ml	Cancer Incidence %	Organ Confined (%)	Clinically Significant Cancer (%)
Catalona[1]	914	36	2.6-4.0	22	81	83
Babaian [2]	268	56	2.5-4.0	24	86	71
Thompson [3]	193		3.1-4.0	27	---	---
	482		2.1-3.0	24	---	---
	998	83	1.1-2.0	17	---	---
	791		0.6-1.0	10	---	---
	486		≤ 0.5	6.6	---	---

[1] JAMA 277: 1452, 1997 – biopsy technique not specified [2] J Urol 165: 2001
[3] N Engl J Med, 350: 2239, 2004 – PCPT 1 control arm, incidence of high grade cancer 12.5 – 25%

Prostate Cancer Dilemmas: 2007

- **Do all "favorable risk" tumors need immediate treatment?**
  - **Active surveillance ± delayed intervention**

- **Are "minimally invasive" surgical alternatives to open retropubic prostatectomy effective?**
  - **Cryosurgical ablation of prostate**
  - **High intensity focused ultrasound (HIFU)**
  - **Robotic assisted laparoscopic prostatectomy (RALP)**

(1) T1c-T2a and Gleason Score ≤ 6, and serum PSA level < 10 ng/ml

Active Surveillance Favorable Risk Prostate Cancer [1] Rationale

- **Lead Time [2]**
  - **"PSA screening" results in detection of cancer 10 years prior to "clinical detection"**
  - **Over-diagnosis → over-treatment**
- **Favorable Natural History [3]**
  - **Gleason ≤ 6 prostate cancer managed by watchful waiting**
    - **80-90% cancer specific survival**

(1)T1c – T2a & Gleason ≤ 6 & Serum PSA < 10 ng/ml
(2) Draisma et al: J Natl Cancer Instit 95:868, 2003
(3) Albertsen et al. JAMA 293:2095, 2005

Active Surveillance Favorable Risk Prostate Cancer "Fears"

- **Undersampling**
  - **Presence of "high grade" cancer not always predicted**
- **Imprecise Prediction of Disease Biology [(1)]**
  - **Gleason score 6 cancers exhibit > 2 ng/ml/yr increase in 25%**
- **Inability to Rescue**
  - **Surveillance compromises ability for later cure if required**

(1) D'Amico et al.: N Eng J Med 351:125, 2004

Active Surveillance Favorable Risk Prostate Cancer Toronto Experience [1]

- Patients
  - N = 299
- Characteristics
  - PSA < 10 ng/ml, T1c – T2a
  - Gleason score ≤ 6
  - 20% cohort – intermediate risk features [2]
- Intervention
  - PSA DT < 2 years [3]
  - Gleason score ≥ 8 on rebiopsy [3]
- Follow-up
  - 64 months
    - 66% remain on surveillance
    - 34% OFF
      - 15% biochemical progression
      - 3% clinical progression
      - 4% histologic progression
      - 12% patient preference

(1) Klotz: J Clin Oncol 23:8165, 2005
(2) PSA < 15, Gleason score, 3+4=7
(3) Later changed to PSA DT < 3 years and Gleason 4+3=7

Active Surveillance Favorable Risk Prostate Cancer Toronto Experience: Results

- Prostate Cancer Death
  - 2/299
- Median PSA DT
  - 7 years
- Radical Prostatectomy Data
  - 24 men PSA DT < 2 years
    - 10/24 (42%) = pT2
    - 14/24 (58%) ≥ pT3

(1) Klotz: J Clin Oncol 23:8165, 2005

Active Surveillance Favorable Risk Prostate Cancer Hopkins Experience

- Selection Criteria
  - T1C, PSA density $\leq$ 0.15 ng/ml/cm^3
  - Biopsy Gleason score $\leq$ 6, $\leq$ 2 positive cores, $\leq$ 50% core involved
- Patients
  - N = 320 men from 1995-2005
  - 1% of newly diagnosed prostate cancer enrolled
- Intervention
  - 98 total (31%)
  - 38 radical prostatectomy (RP)
- Comparison Study – Pathologic Features
  - Delayed RP, N = 38
    - Median 26.5 months (12-73)
  - Immediate RP, N = 150
    - Median 3 months (1-9)

Warlick et al: J Natl Cancer Instit 98:355, 2006

Active Surveillance Favorable Risk Prostate Cancer Hopkins Experience: Immediate versus Delayed Prostatectomy [1]

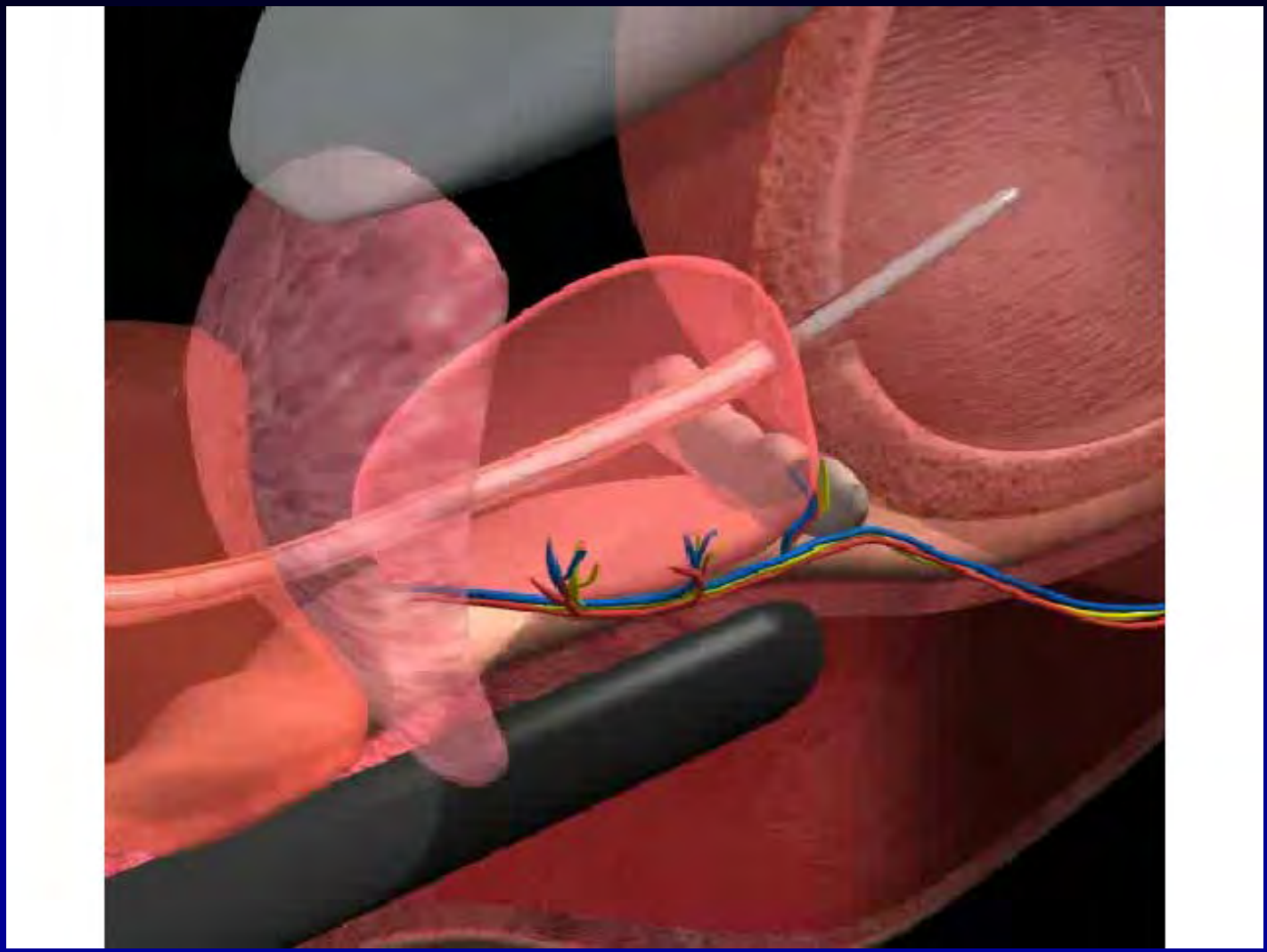
- **Incidence Noncurable Prostate Cancer [2]**
  - **Delayed RP**
    - **9/38 (23%)**
  - **Immediate RP**
    - **24/150 (16%)**
  - **Relative Risk**
    - **Unadjusted = 1.48 (0.75 – 2.92) p = 0.266**
    - **Adjusted [3] = 1.08 (0.55 – 2.12) p = 0.819**

(1) Warlick et al: J Natl Cancer Instit 98:355, 2006
(2) < 75% chance BDF @ 10 years (pT_2 + Gleason > 4+3=7 or positive margin, pT_{3A} & Gleason = 7 or positive margin, or > pT_{3A} or positive lymph nodes
(3) Age, PSA density

Active Surveillance Favorable Risk Prostate Cancer

- Rational, Increased Acceptance
- Optimal Strategy
  - In evolution
    - Biomarkers urgently needed!
    - Clinical trial should be supported

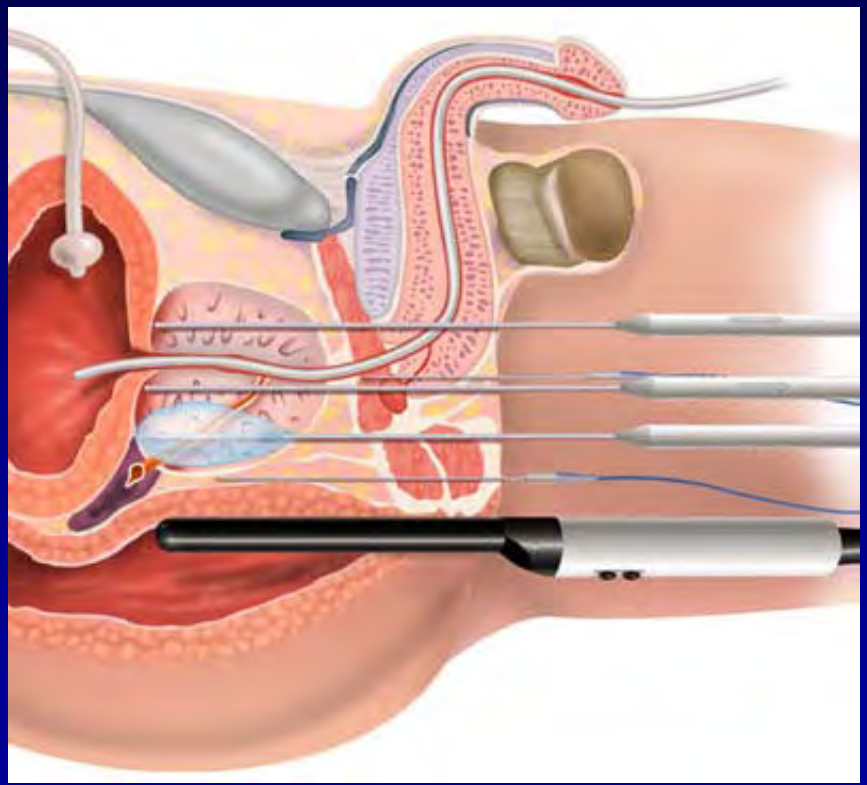

COLD KILLS



Treatment Planning

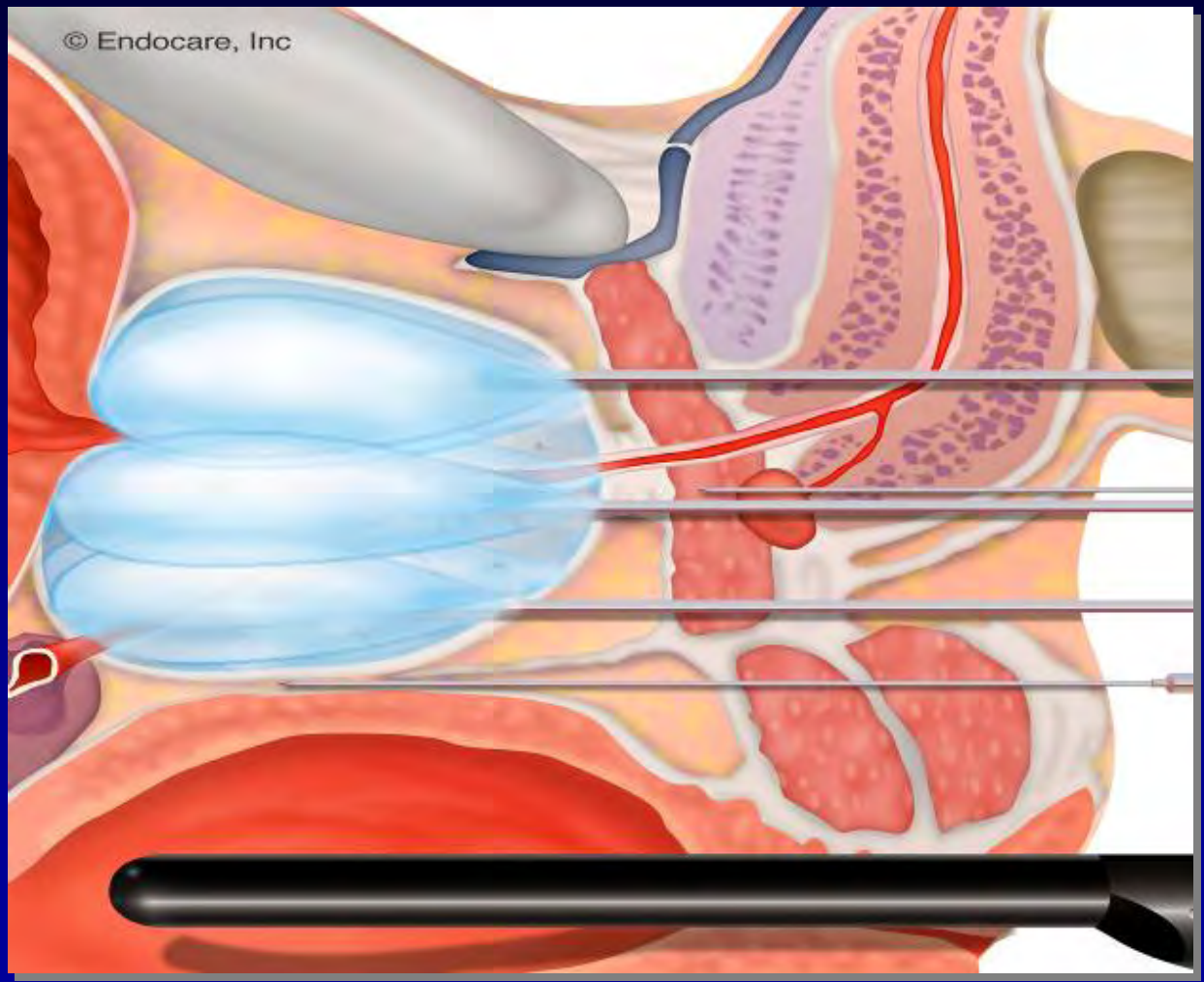
- **Individual patient anatomy can be entered into a computer-based treatment planning system.**
- **This computer system helps optimize positioning of the cryotherapy probes and thermocouple positions.**

Placement of Cryoprobes and Thermocouples



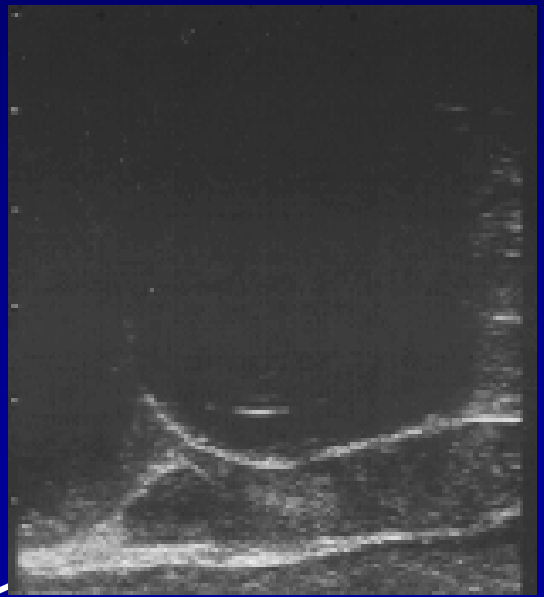
- Cryoprobes and thermocouples are placed transperineally through a grid or by manual guidance.
- They are guided into place with ultrasound.

Ice Formation and Monitoring



Probes Placed before Freezing

Freeze Started in the Anterior



Sagital Image of Posterior Ice Start

Ice Stopped at Denonvillier’s Fascia

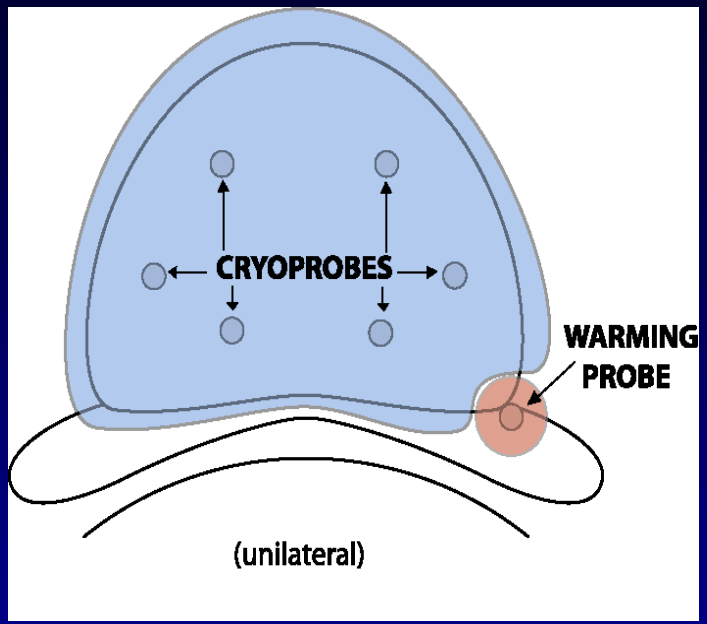
Efficacy of Primary Cryotherapy

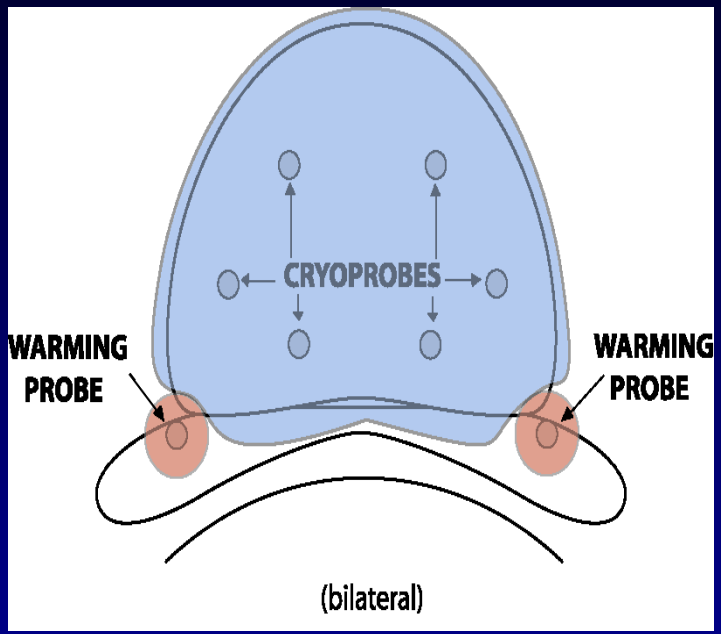
					PSA – Recurrence Free Survival						
Ref.	N	Crygen	Median F/U (Mos.)	Nadir PSA undetectable (%)	Low	Medium	High	When	Definition	Neg Biopsies (%)	ADT (%)
Prepelica, 2005	65	A	35				83%	3 Yrs	ASTRO	7/8 (88)	68
Han, 2003	122	A	12		75%			1 Yr	PSA >0.5 ng/ml		37
Donnelly, 2002	76	N	50		75%			50 Mos	PSA >1.0 ng/ml	63/73 (86)	34
Bahn, 2002	590	A/N	68		92%	89%	89%	7 Yrs	ASTRO	514/590 (87)	91
Long, 2001	975	A/N	24		76%	71%	61%	5 Yrs	PSA >1.0	(82)	33
De La Taille, 2000	35	A	8.3	22 (63)	70%			9 Mos	PSA increase 0.2 above nadir		100
Koppie, 1999	176	N	31	88 (49)	56%			3 Yrs	Nadir >0.5 or PSA increase of 0.2	103/167 (61)	28

Primary Cryotherapy Complications (%)

	N	Erectile Dysfunction	Fistula	Incontinence	Sloughing / TURP
Han, 2003	122	87	0	4.3	5.8
Ellis, 2006	75	82	0	5.5	6.7
Long, 2001	975	93	0.5	7.5	13
Bahn, 2001	590	95	0.1	4.3	5.5

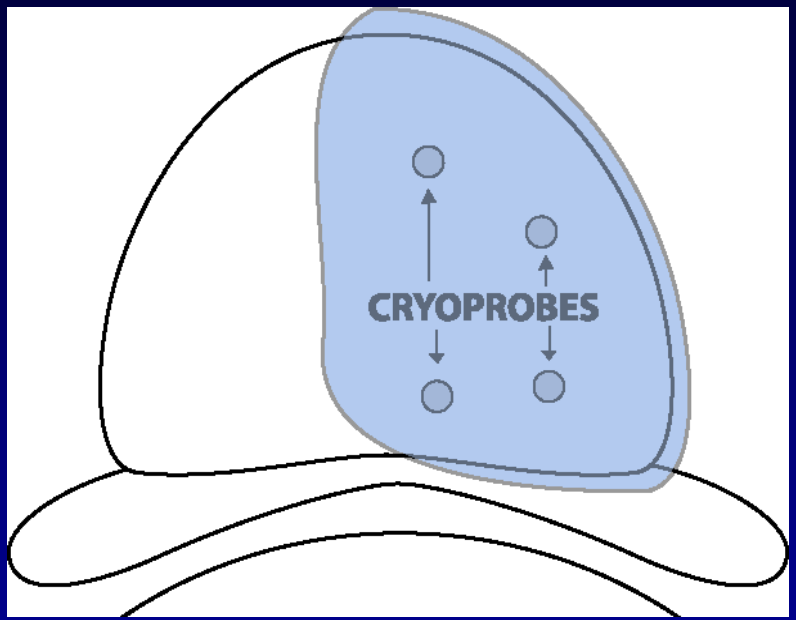
Nerve-Sparing Prostate Cryoablation





Goal: Treat prostate tissue while warming one or both neurovascular bundles to improve erectile function.

Focal Prostate Cryoablation



Goal: Completely treat the side of the prostate with the cancer, avoiding any ice ball formation on the contralateral side in order to improve erectile function.

Focal Cryotherapy – Early Results

Study	N	Follow-up (months)	PSA Results	Positive Post-Treatment Biopsy (%)	Potency (%)
Onik, 2002	9	36	Stable	0/6 (0%)	7/9 (77%)
Bahn, 2006	31	70	26/28 (93%) (by Astro)	1/25 (4%)	24/27 (89%) With or without drugs
Lambert, 2007	25	28	21/25 (84%) (>50% nadir Reduction)	3/7 (43%) 1/7 (14% Ipsilateral)	17/24 (71%) With or without drugs

Prostate Cryoablation Versus External Beam Radiotherapy A Randomized Controlled Trial [1]

- Patients
  - N = 244
  - T1-3, Nx M0
  - PSA < 20 ng/ml
- Treatment
  - Neoadjuvant Androgen Deprivation
    - Cryoablation
    - External beam radiotherapy (68-73 GY)
- Results @ 3 years
  - Biochemical Failure [2]
    - Cryoablation = 25 (20%)
    - External Beam = 35 (26%)
  - Positive Prostate Biopsy
    - Cryoablation = 6.6%
    - External Beam = 26.3%

(1) Donnelly et al: J Urol 177(4):1141A, 2007
(2) Astro definition: Nadir + 2 ng/ml PSA

Cryotherapy - Conclusions

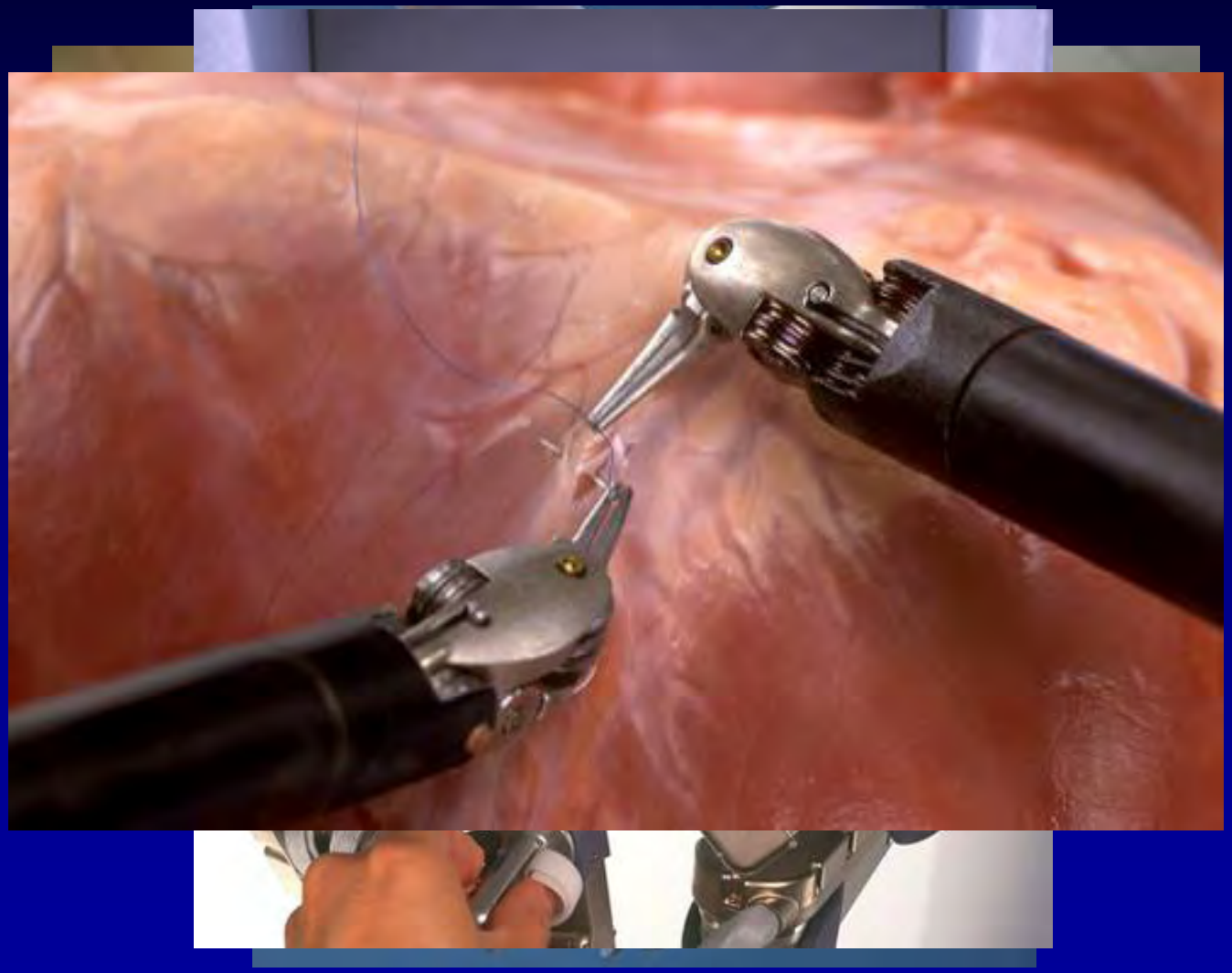
- **Minimally invasive**
  - **Outpatient**
  - **Rapid recovery**
- **Cryotherapy is an acceptable alternative to EBRT**
  - **Equivalent PSA outcomes**
  - **Fewer positive biopsies (based on a randomized trial)**
- **High potency rates with focal cryo (approximately 70-90%)**
  - ***Longer follow-up needed!***
- **Most appropriate in older patients as an alternative to radiation therapy**

Laparoscopic Prostatectomy

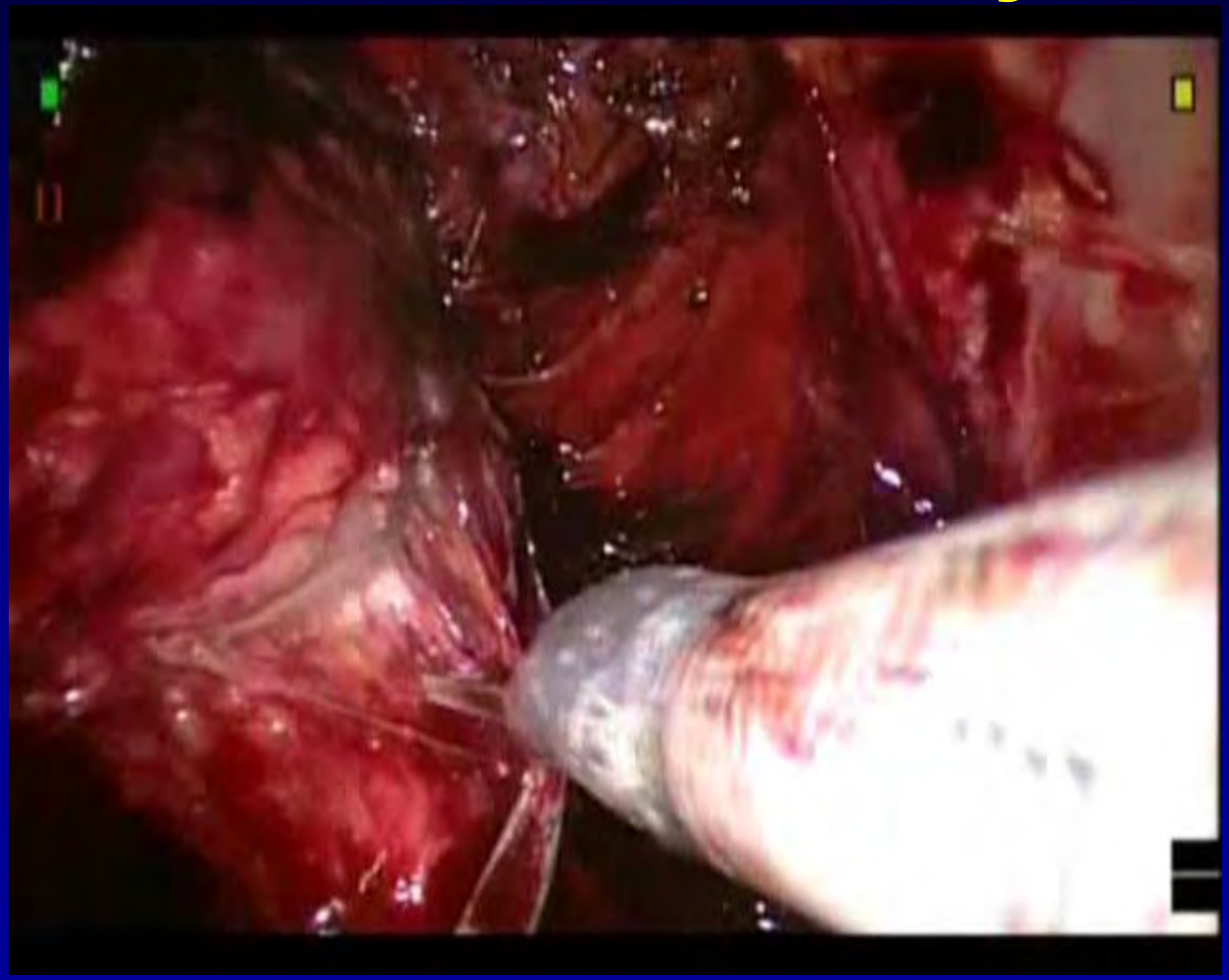
- ⇓ Blood Loss
- ⇓ Transfusion
- ⇓ Bladder Neck Contractures
- ⇓ Pain Medication Requirement
- ⇓ Time to Return to Normal Activity

Guillonneaut et al. Crit Rev Oncol Hematol 43:123, 2002
Rass Weirer et al. J Urol 169:1689, 2003
Bhayani et al. Urology 61:612, 2003
Hara et al. J Urol 169:2045, 2003

Robotic Assisted Laparoscopic Prostatectomy



Robotic Assisted Laparoscopic Prostatectomy



Robotic, Laparoscopic, Open Radical Prostatectomy: Perioperative Comparisons (1)

Method	No. Patients	No. Series	Years	OR Time	Mean EBL (ml)	Blood Transfusion (%)	Conversion Rate (%)	Catheter Time (Days)
Robotic	373	10	2001-2004	254	231	3.9	1.1	8.1
Laparoscopic	1106	5	2001-2002	225	505	8.4	1.4	6.1
Open	3200	3	1994-2001	182	727	24	—	7-21

(1) El-Hakim et al. Expert Rev. Anticancer Ther. 6(1):11, 2006

Robotic, Laparoscopic, Open Radical Prostatectomy: Complications/Mortality (1)

Method	No. Patients	No. Series	Overall Complications	Minor Complications	Major Complications	Mortality
Robotic	373	11	8.3	4.6	3.8	0
Laparoscopic	1006	4	16.8	13.0	4.9	0
Open	6677	4	10.3	6.3	4.0	0.04

(1) El-Hakim et al. Expert Rev. Anticancer Ther. 6(1):11, 2006

Robotic, Laparoscopic, Open Radical Prostatectomy: Pathological Comparisons [1]

Method	No. Patients	No. Series	Years	pT_2	pT_3	Margin+	pT_2+	pT_3+
Robotic	373	11	2001-2005	77.5	21.6	15	8.5	57.3
Laparoscopic	1439	4	2001-2002	72.4	26.5	19.9	13.8	31.3
Open	22,164	5	2000-2004	64	32.2	24.1	17.5	42.7

(1) El-Hakim et al. Expert Rev. Anticancer Ther. 6(1):11, 2006

Robotic, Laparoscopic, Open Radical Prostatectomy: Continence Rates

Method	No. Patients	Age	Follow-Up (Months) 1	3	6	12	Eval Method	Definition
Robotic								
Bentas	38	61.3		84	—	—	Questionnaire	0-1 pad/24 hr
Ahlering	45	61.4	63	81	—	—	Questionnaire	0 pads
Ahlering	60	62.9		76	—	—	Questionnaire	0 pads
Menon	200	59.9		—	96	—	Questionnaire	0-1 pad/24 hr
Tewari	100		65	—	—	—		
Laparoscopic								
Guillonneau	60	64			73		Questionnaire	0 pads
Rassweiler	179	64	36	54	74	97	Questionnaire	0 pads
Turk	125	59.9		75	86	92	Telephone Patient Interview	0-1 pad
Open								
Kundu/Catalona	2737	61±7.4				93 (2)	Questionnaire	0 Pads
Walsh	64	57		54	80	93	Questionnaire	0 Pads
PCOS	1291	62.9			38.6	60.5	Questionnaire	0 Pads

(1) El-Hakim et al. Expert Rev. Anticancer Ther. 6(1):11, 2006

(2) Data at ≥ 18 mos.

Robotic, Laparoscopic, Open Radical Prostatectomy: Postoperative Potency

Method	No. Evaluated	Age	Follow-up (months)	Spontaneous Erections	Intercourse	Evaluation Method
Robotic						
Bentos	37	61.3	15	22	—	Questionnaire
Menon	200	<60	6	82	64	Questionnaire
Laparoscopic						
Guillonneau	20	64	1-12	45	5	Patient Interview
Turk	44	59.9	1-15	59	—	Patient Interview
Eden	79	62.2	12	62	—	Patient Interview
Osnek/Abbou	25	64.8	12	56	—	Questionnaire
Open						
Kundu/Catalona	1834	61±7	≥18	75		Questionnaire
Walsh	64	57	6	54		Questionnaire
			12	73		
			18	86		
PCOS	1291	62.9	≥18	44		Questionnaire

(1) El-Hakim et al. Expert Rev. Anticancer Ther. 6(1):11, 2006

Robotic Prostatectomy Conclusions

- Safe, Effective Form of Prostate Removal
  - Similar perioperative complications
  - ⇓ blood loss
  - Comparable rates negative surgical margins among low-intermediate risk patients
    - Role in high risk/locally advanced remains to be defined
  - Postoperative urinary/sexual function
    - Results encouraging
      - May lead to earlier return of urinary/sexual function
- Future Role
  - Here to stay!
    - Prospective comparison studies
    - Cost must decrease
    - Facilitate training future surgeons