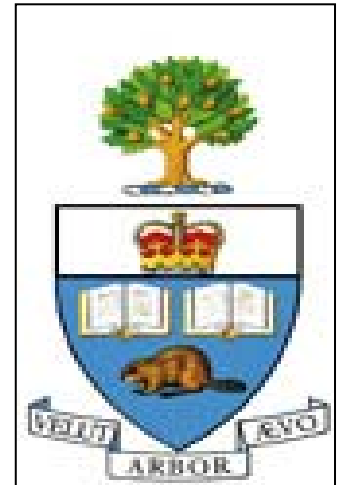


Prostate Cancer and Oxygen: New Concepts and Therapies

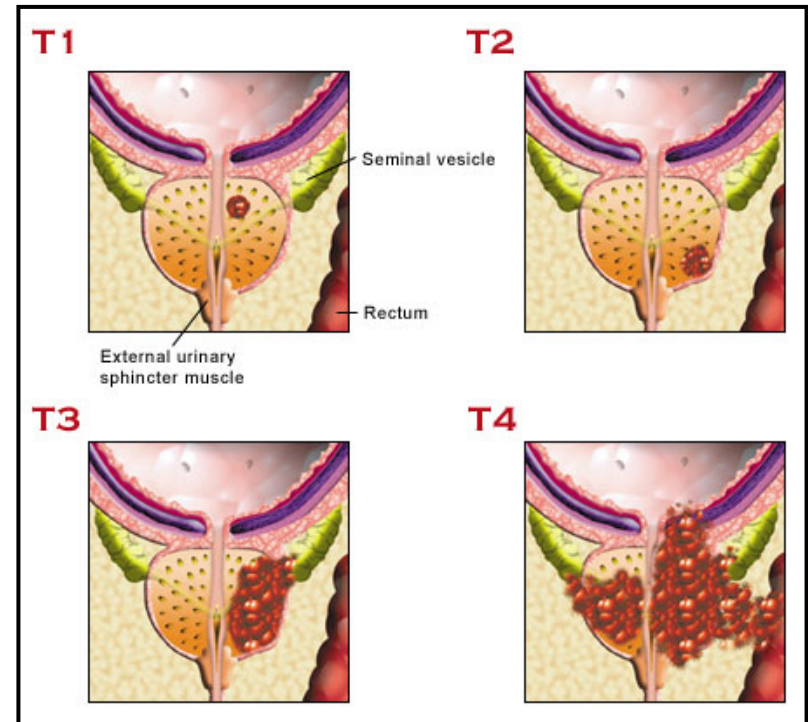
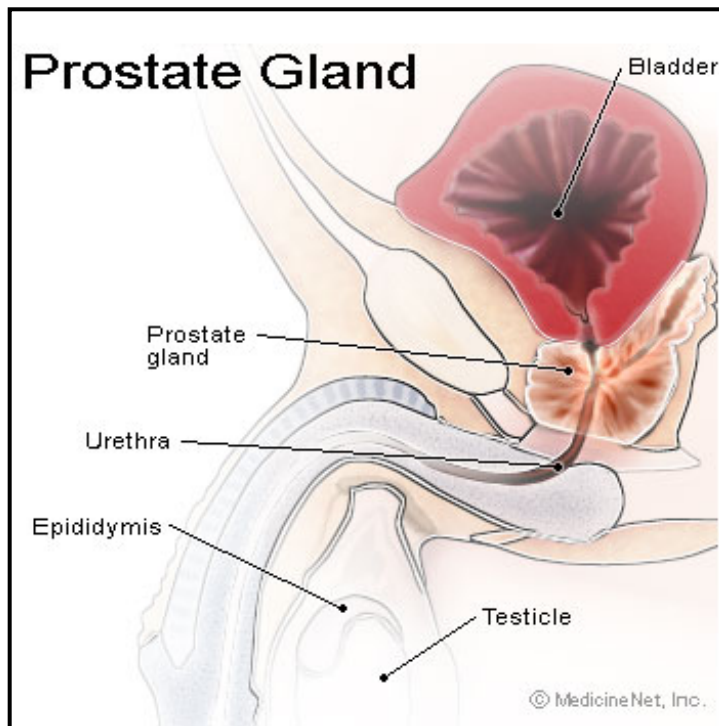


Robert Bristow MD PhD FRCPC
Departments of Radiation Oncology and
Medical Biophysics,
University of Toronto and
Ontario Cancer Institute/Princess Margaret Hospital
(University Health Network)



Bristow-Brampton-2009

Prostate Cancer: Some Basics



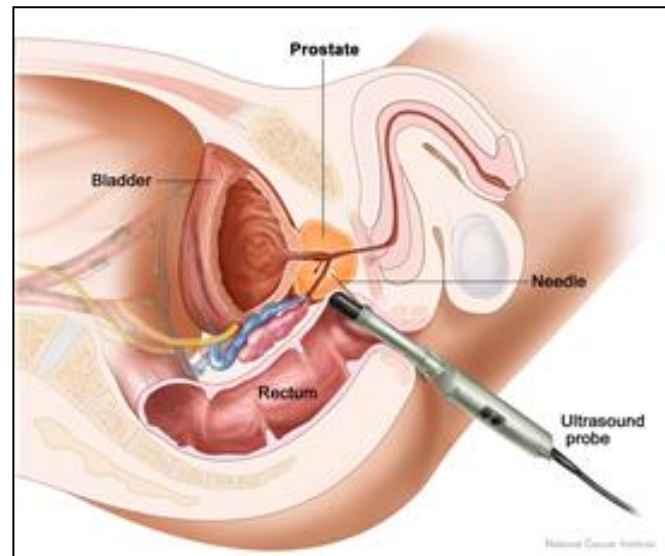
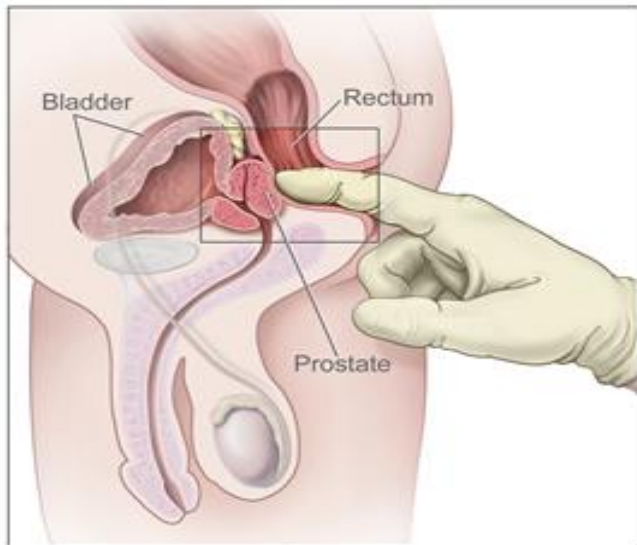
Risk factors: age, family history, high-fat diet, African ancestry

Currently, the **extent and prognosis** of prostate depends on:

- (1) a digital rectal exam (DRE) and spread of disease (TNM)
- (2) the prostate specific antigen (PSA) blood test
- (3) the pathologic grade (Gleason score)



Prostate Cancer: Some Basics



Age and race-adjusted cut-off values for PSA

Age	Caucasians	Blacks	Asians
40-49	2.5	2.0	2.0
50-59	3.5	4.0	3.0
60-69	4.5	4.5	4.0
70-80	6.5	5.5	5.0

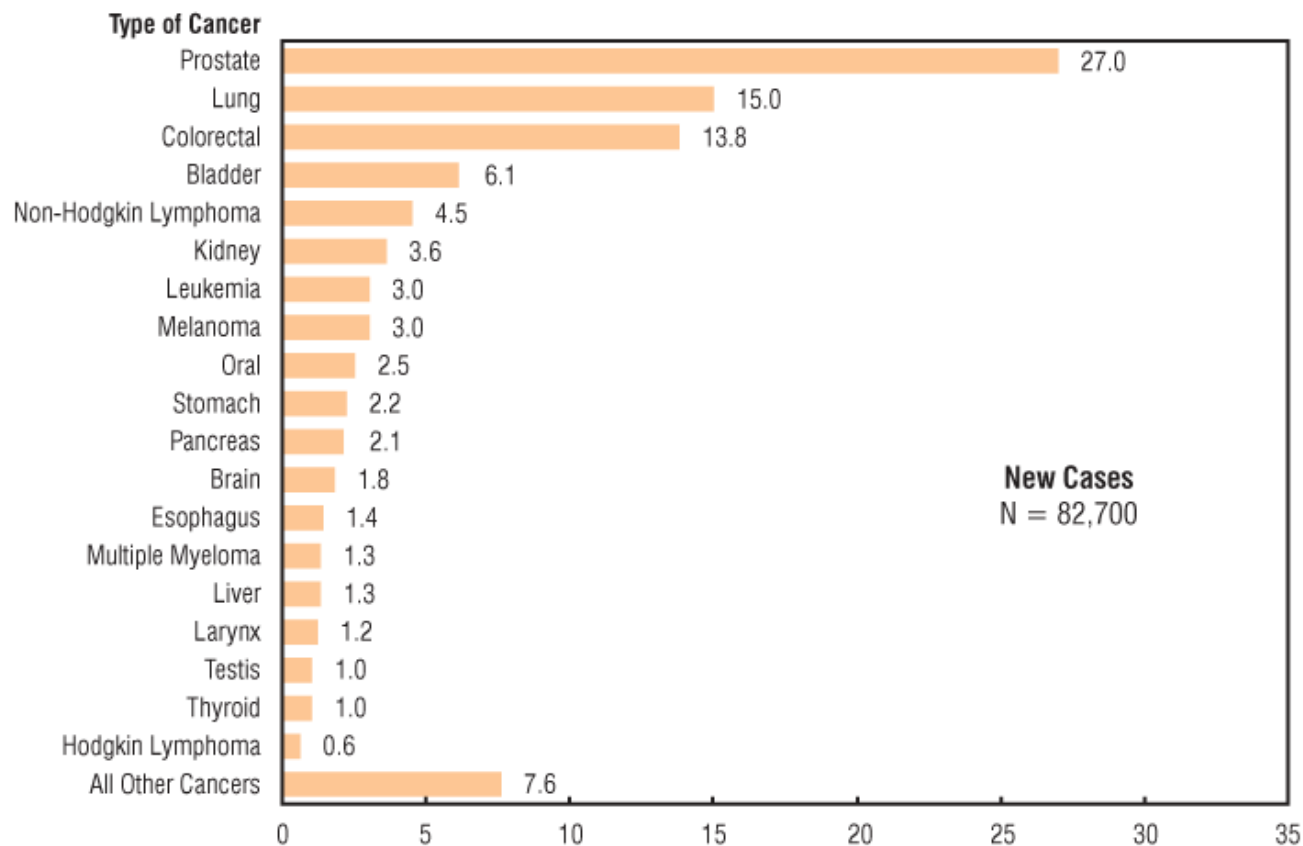
Source: Prostate Cancer A Guide for Patients, by Dr. Laurence Klotz

Canadian Prostate Cancer Statistics

- In 2007: 22,300 men diagnosed with prostate cancer and 4,300 will die from it
- On average, 439 men are diagnosed each week
- One in 6 men will be diagnosed with prostate cancer, mostly after the age of 60
- One in 27 will die from it
- Test at age 40-50 depending on risk factors



New Cases of Cancer in Men: 2007



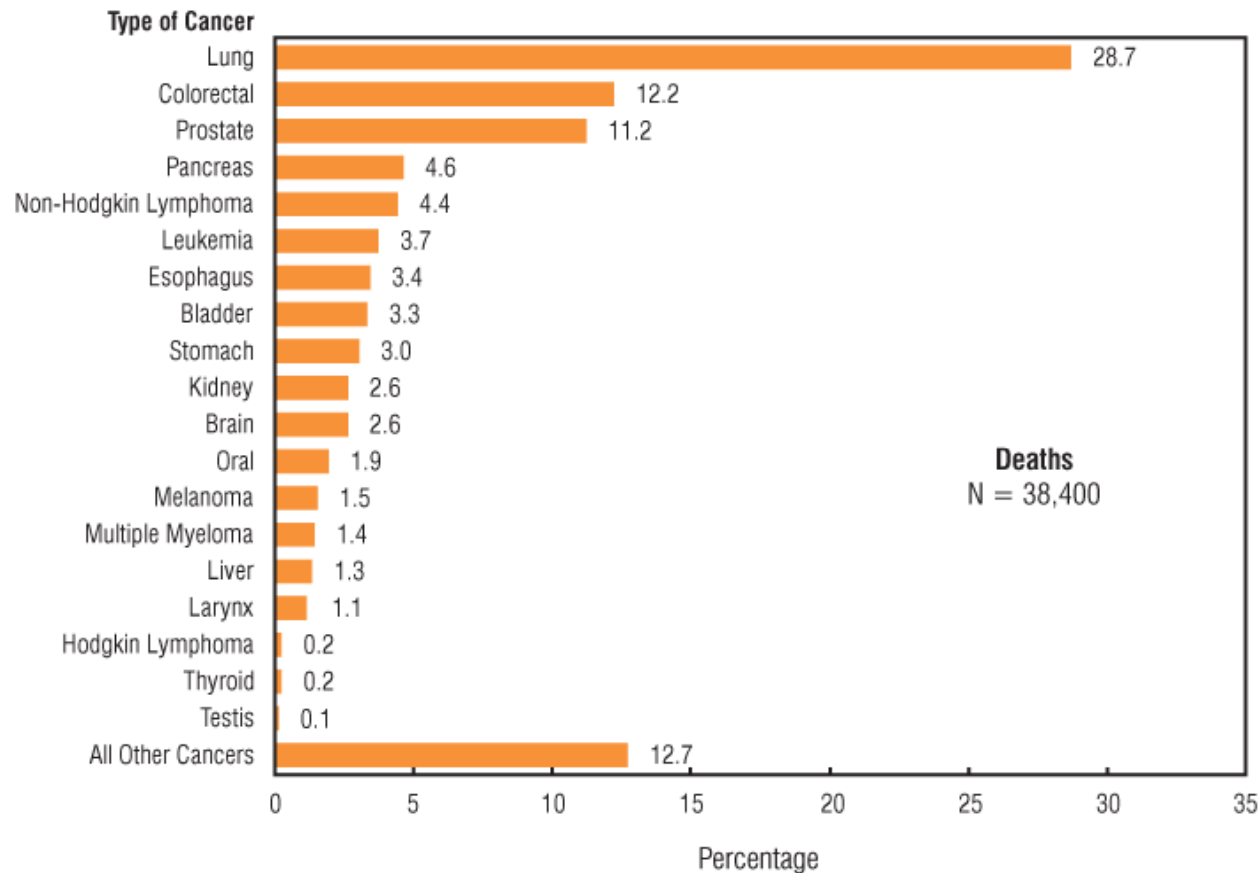
Note: Incidence figures exclude an estimated 69,000 new cases of non-melanoma (basal cell and squamous cell) skin cancer among both sexes combined. Mortality figures for 'all other cancers' include about 220 deaths with underlying cause 'other malignant neoplasms' of skin among both sexes combined.

Source: Surveillance Division, CCDPC, Public Health Agency of Canada

Canadian Cancer Society/National Cancer Institute of Canada: *Canadian Cancer Statistics 2007*



Deaths From Cancer in Men: 2007



Note: Incidence figures exclude an estimated 69,000 new cases of non-melanoma (basal cell and squamous cell) skin cancer among both sexes combined. Mortality figures for 'all other cancers' include about 220 deaths with underlying cause 'other malignant neoplasms' of skin among both sexes combined.

Source: Surveillance Division, CCDPC, Public Health Agency of Canada

Canadian Cancer Society/National Cancer Institute of Canada: *Canadian Cancer Statistics 2007*



Treatment Options & Side Effects

Indolent Disease

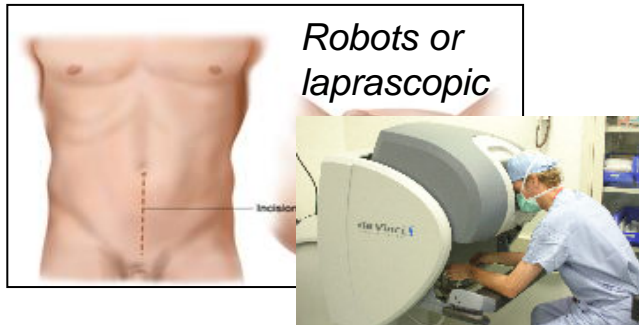
Active Disease

Aggressive Disease

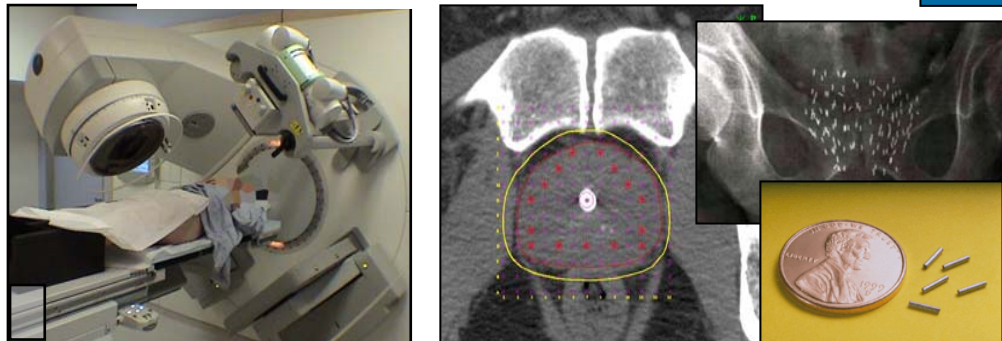
**WATCH
THE PSA
CAREFULLY**

“Active Surveillance”

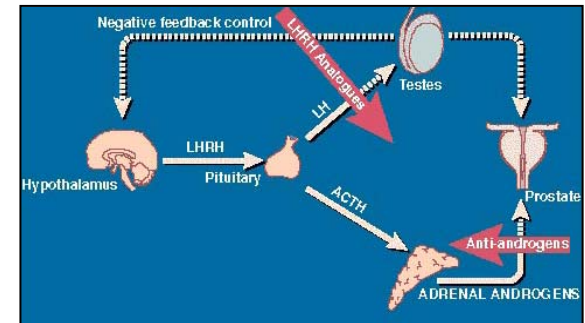
Surgery = Radical Prostatectomy



Radiotherapy or brachytherapy (seeds)



Hormone Therapy
(injections/tablets)



Chemotherapy

Combinations



Increasing Stage and Aggression

Risk Groupings and Treatment:

(Active Surveillance, Surgery, Radiotherapy, Hormone Therapy and Chemotherapy)

PROGNOSTIC FACTORS

- Traditional: T-stage, PSA, Gleason Score
- Newer: Percent Positive Biopsies, Ki-67, PSA DT < 10 months
- Promising: p53, BAX-BCL2, EGFR, MDM2, SURVIVIN, p16^{INK4a}, **Hypoxia, Repair**
- Future: **New targets and stem cells**

RISK GROUPS

- LOW: T1/T2; PSA <10; GS 4-6
(Brachy, HIFU, Cryo, EBRT; Surgery, AS)
- INTERMEDIATE: T1/T2; GS 7; PSA 10-20
(Brachy/EBRT +/- Hormones; Surgery, Other)
- HIGH: PSA > 20; GS 8-10; T3-T4
(EBRT + Hormones +/- Chemo; New Agents, Surgery)

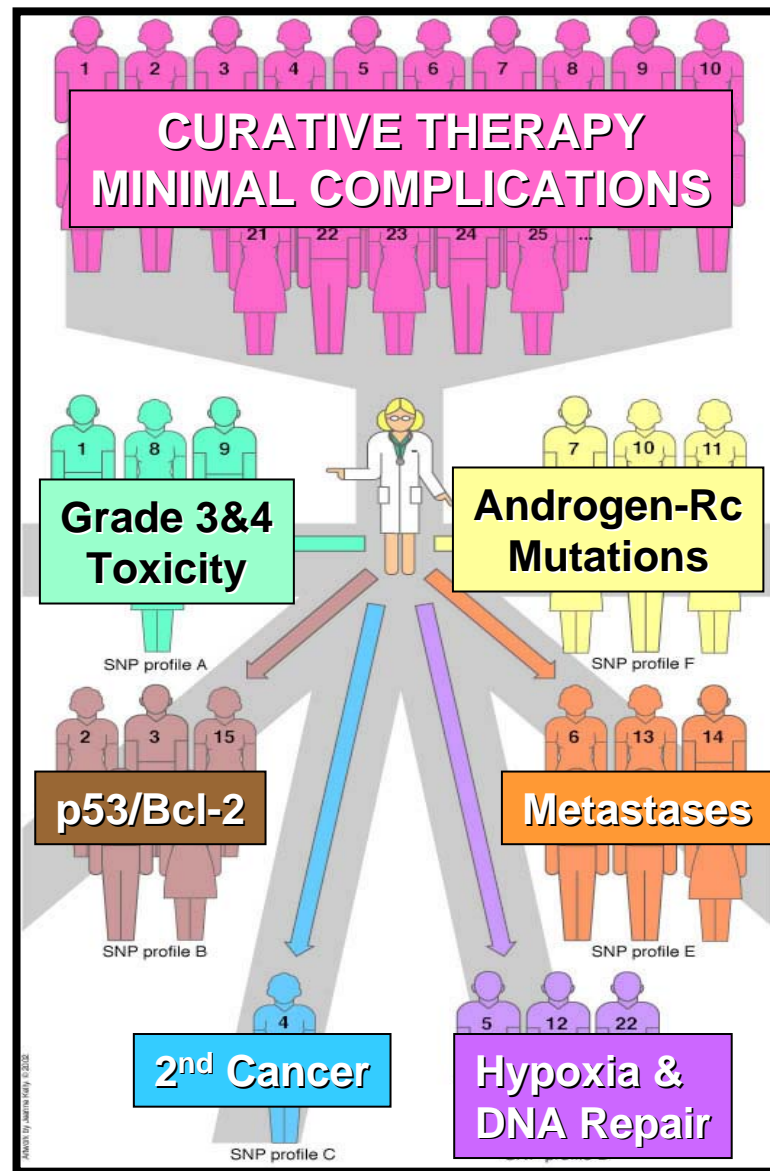
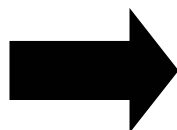
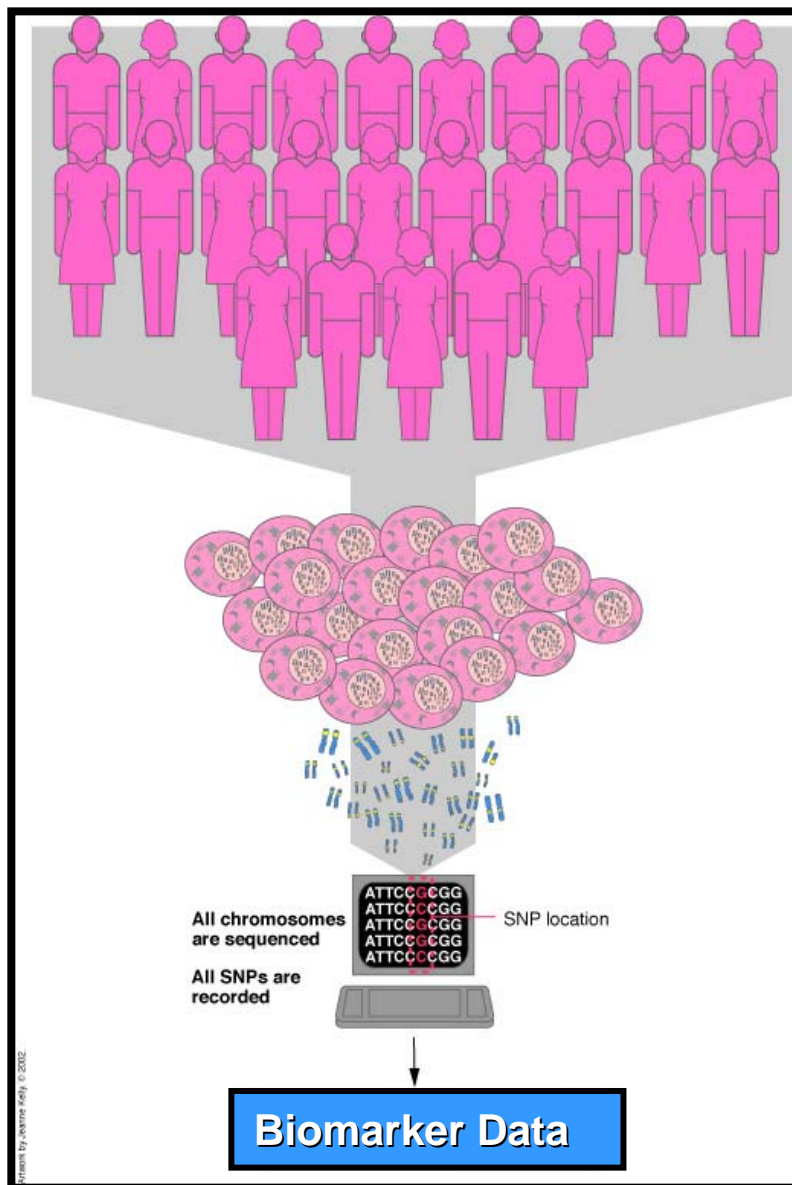


The New Era of Prostate Cancer Research

- The 20th century approach to cancer: Seek and destroy
- The 21st century approach: target and control
- **Personalized genetic medicine**
- **To treat patients with fewer side effects.**
- To prevent deaths in patients who are currently incurable.

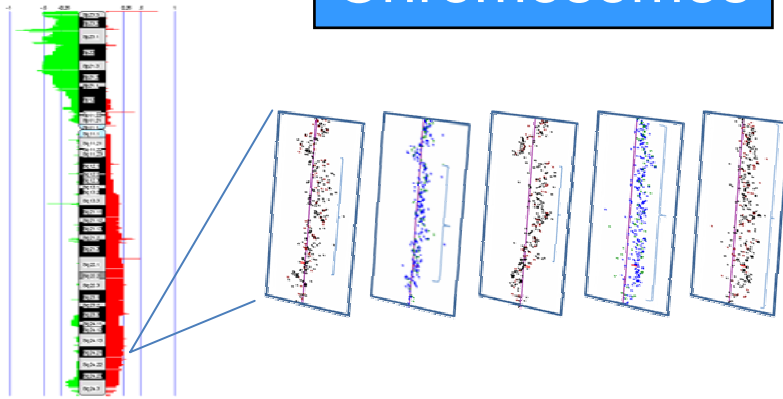


Individual Oncology: Predict-Change Treatment



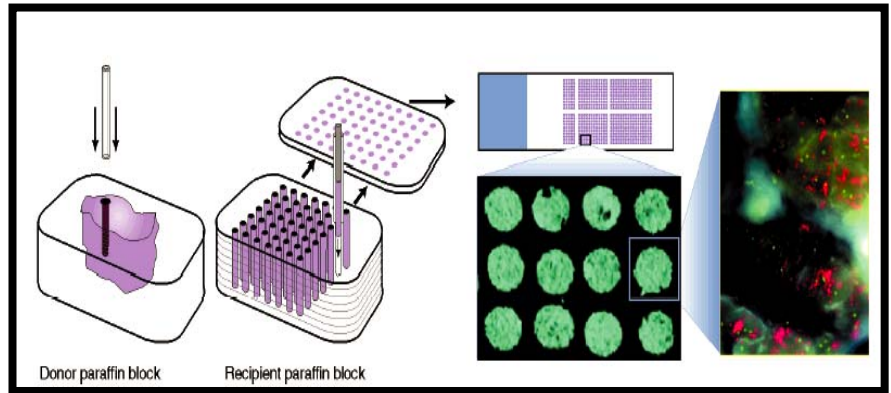
Predict Sensitive and Resistant Patients

Chromosomes



Prostate Ca Example:
Frozen biopsies from ~250 men
Oxygen measurements
DNA repair pathways
Clinical results

RNA ARRAYS



TISSUE ARRAYS

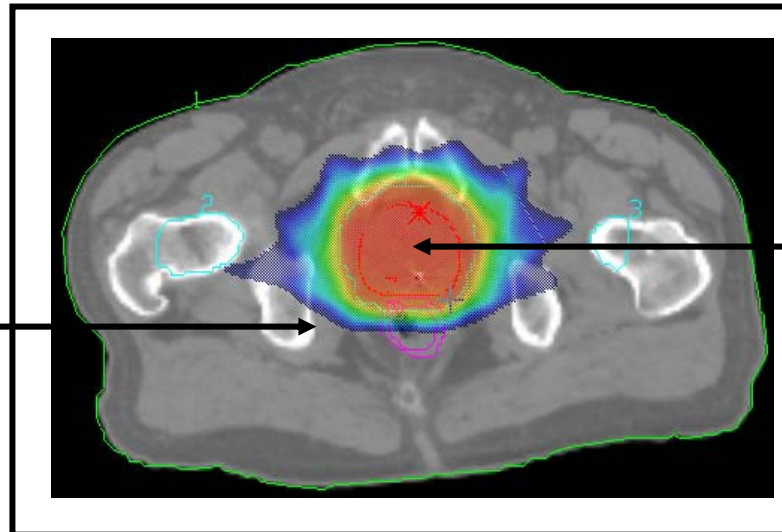
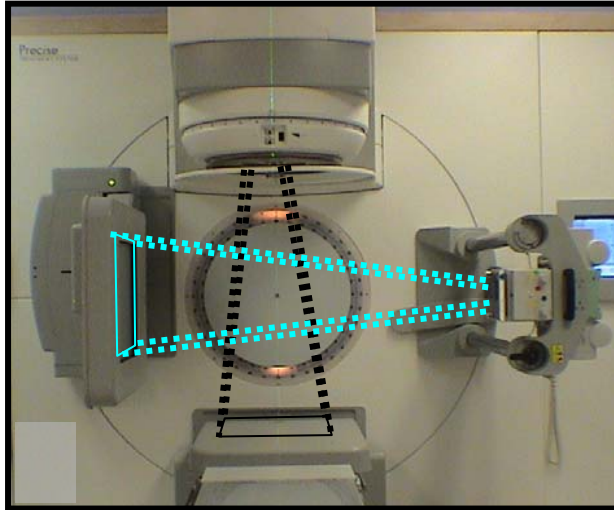
The Last 10 Years

“Decreased mortality for men with prostate cancer”

- **New technologies in biology and imaging**
 - Fluorescence In Situ Hybridization (FISH) and DNA/RNA/Protein CHIPs to diagnose mutations (FISH and CHIPs !)
 - Use of MR techniques to predict tumour spread and response pre- and post-therapy
- **New biologic targets and new drugs**
 - Challenge is to have individual biomarkers of response
- **Better use of PSA-DT and kinetic analyses** to predict local resistance and systemic spread
 - Choose those patients who require local and systemic therapy
 - Select best patients for best salvage therapies
- **10 years of improved technology:**
 - Hypofractionation, precision targeting, IMRT, robotics, HIFU, cryotherapy, sub-prostate targeting, less side-effects



Precision-Guided Radiotherapy to Kill Cancer Cells and Protect Normal Cells



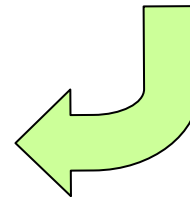
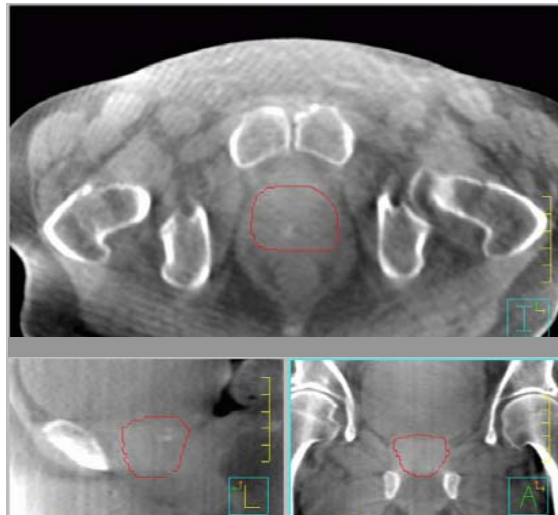
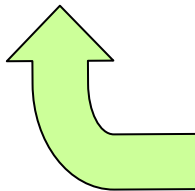
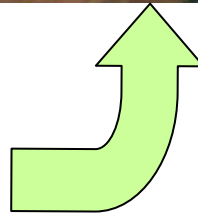
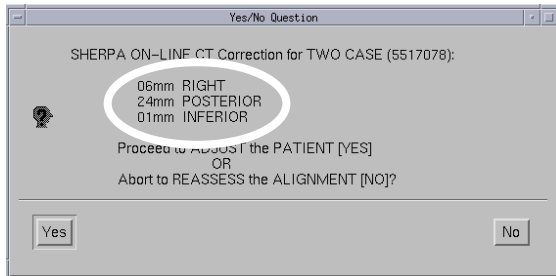
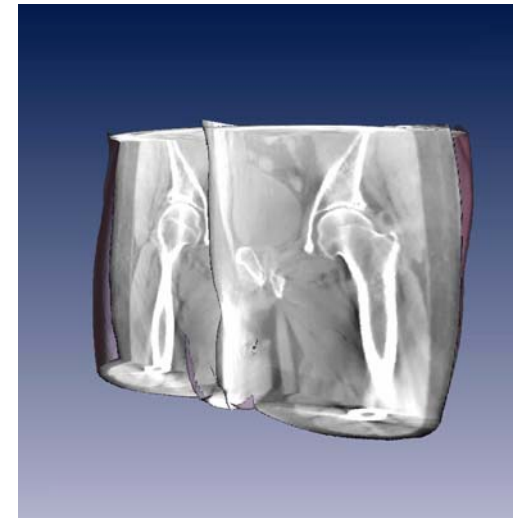
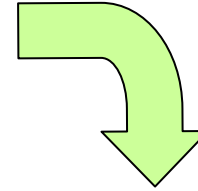
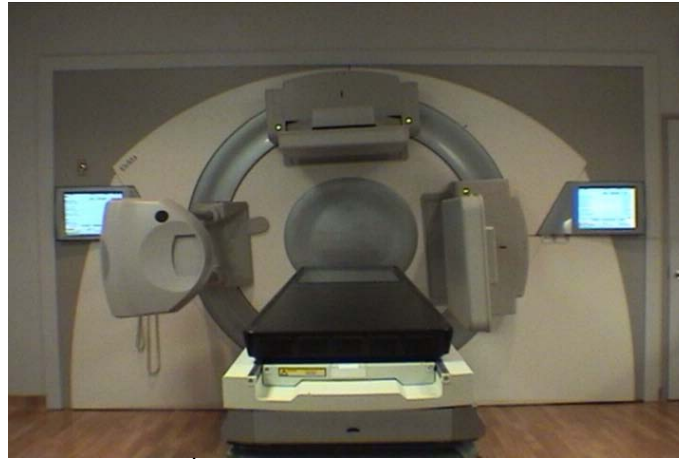
Low Dose
To Normal
Cells

High Dose
To Cancer



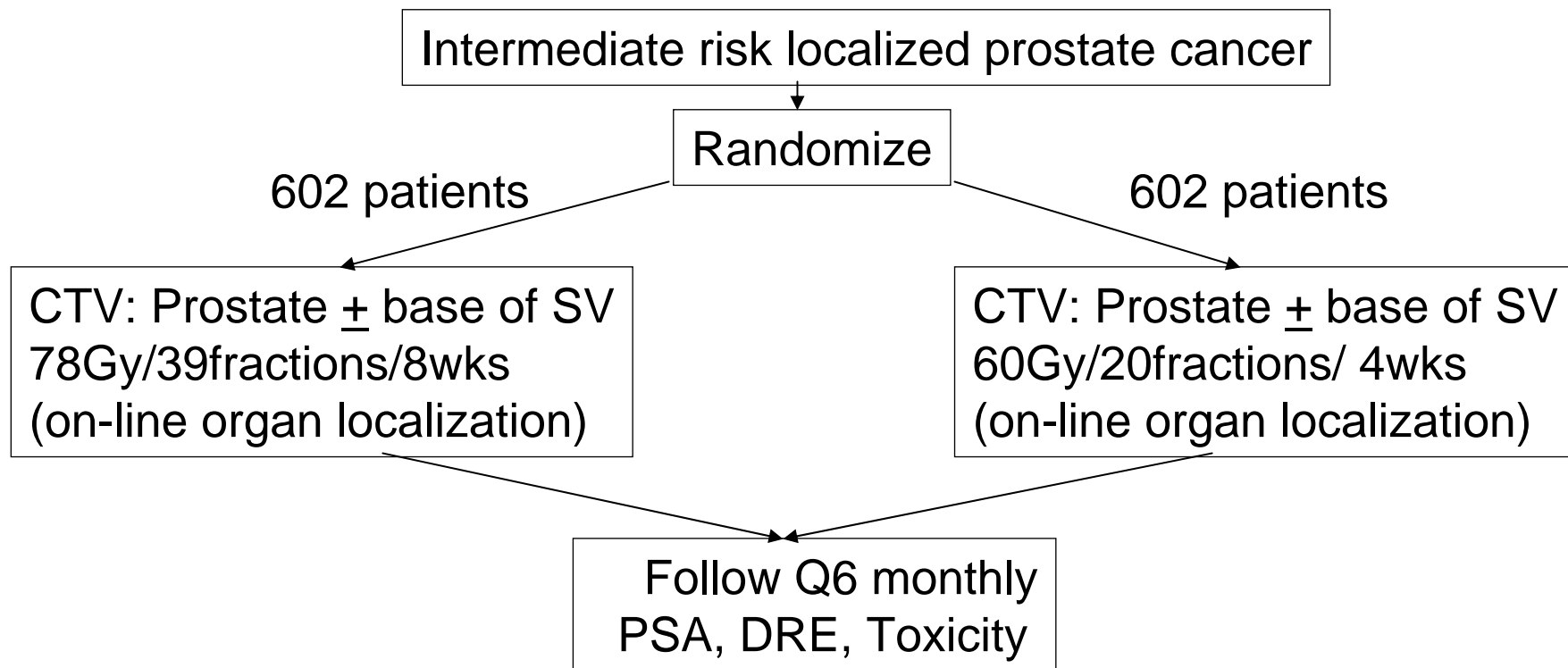
Daily CT Image Guidance

Cone-beam CT
(CBCT) + soft
tissue



A randomized trial of a shorter fractionation schedule for localized intermediate risk prostate cancer.

Sponsor: Ontario Clinical Oncology Group (OCOG)



Primary endpoint:

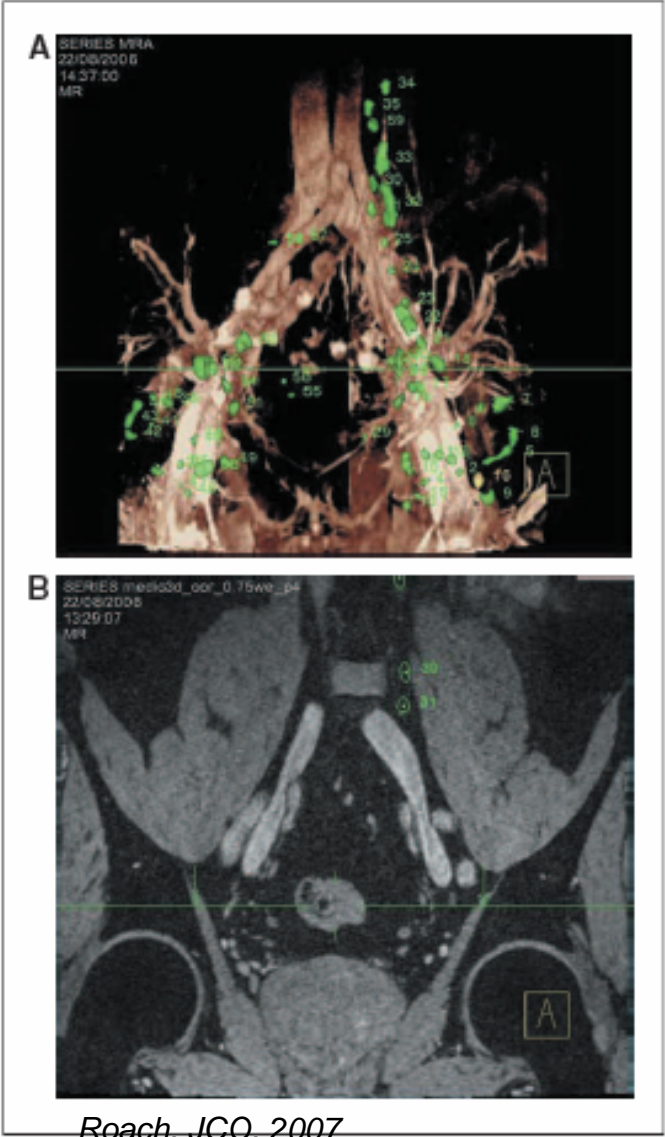
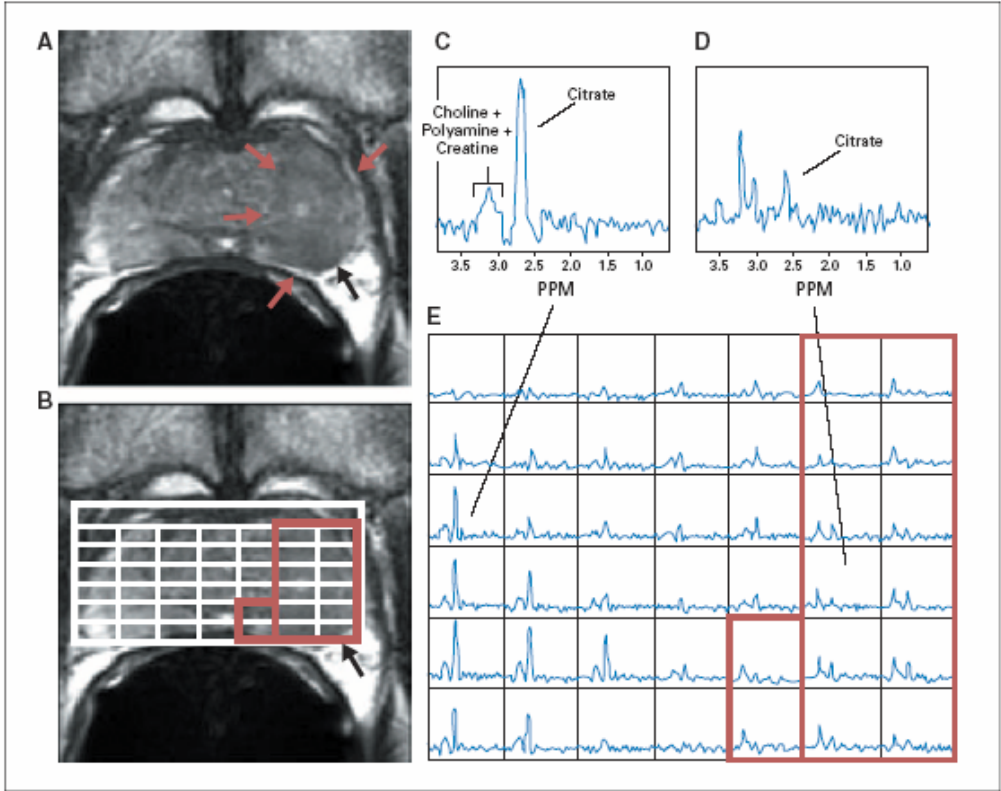
5-year bRFR

Non-inferiority design

Secondary endpoints:

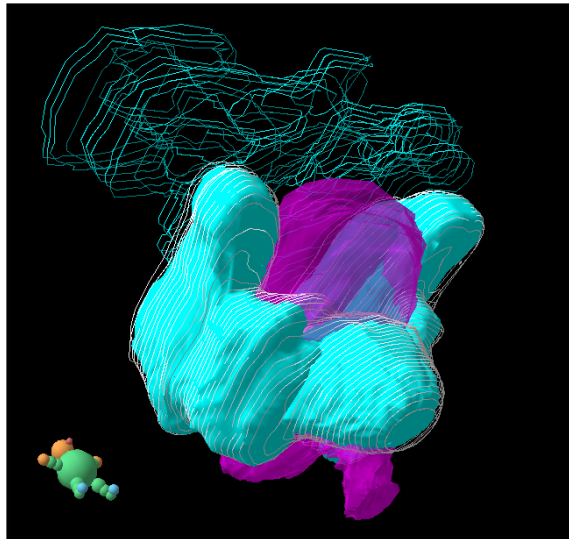
1. Biochemical-Clinical Failure (BCF)
2. Prostate Cancer Specific Survival
3. Toxicity
4. Quality of Life (EPIC and SCF-12)

Patient-Unique Tissue Anatomy And Physiology



PMH Precision-Guided Therapy

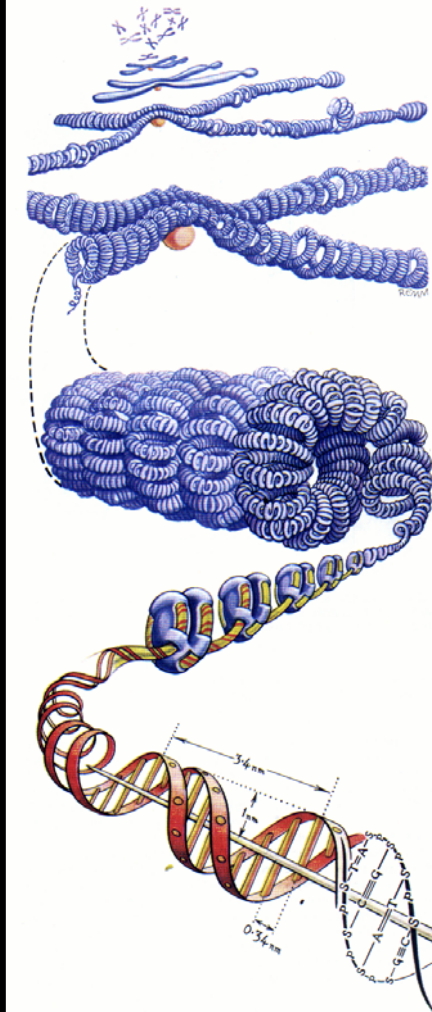
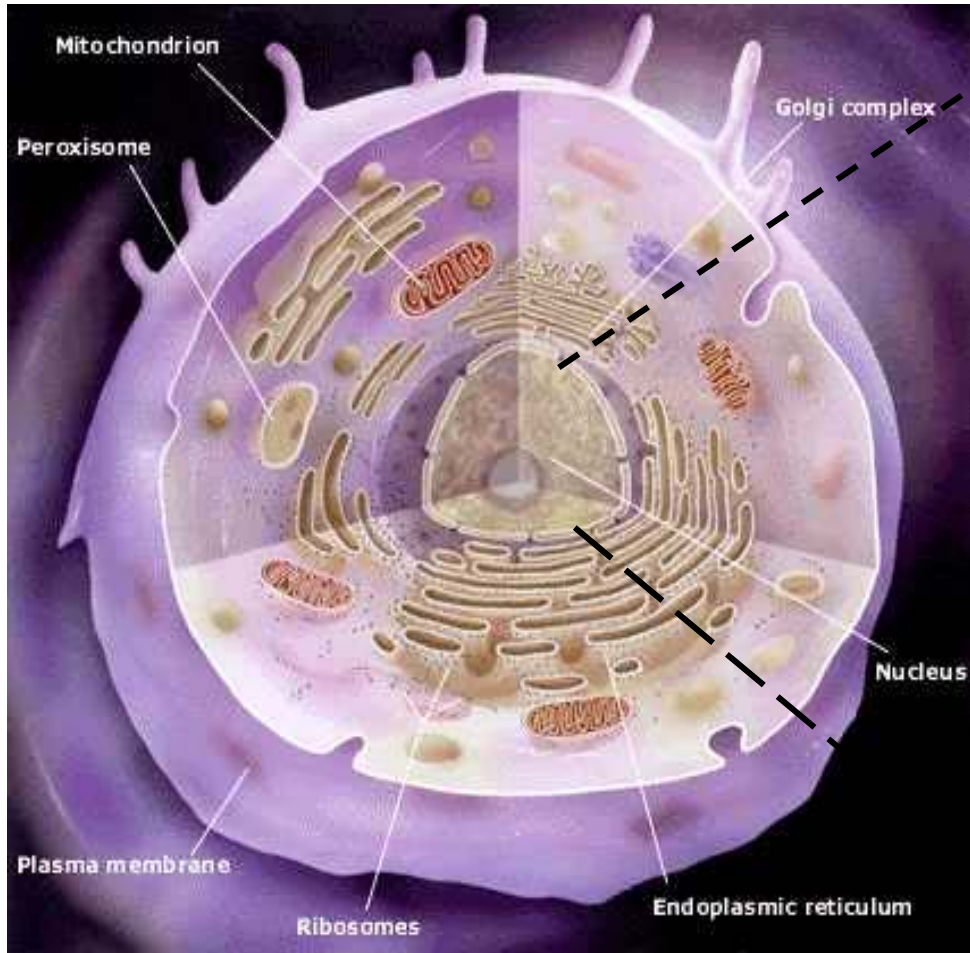
- **New PHYSICAL techniques are being developed in an attempt to lessen the damage to surrounding tissue**
 - such as 3-dimensional conformal radiation therapy (3-D CRT)



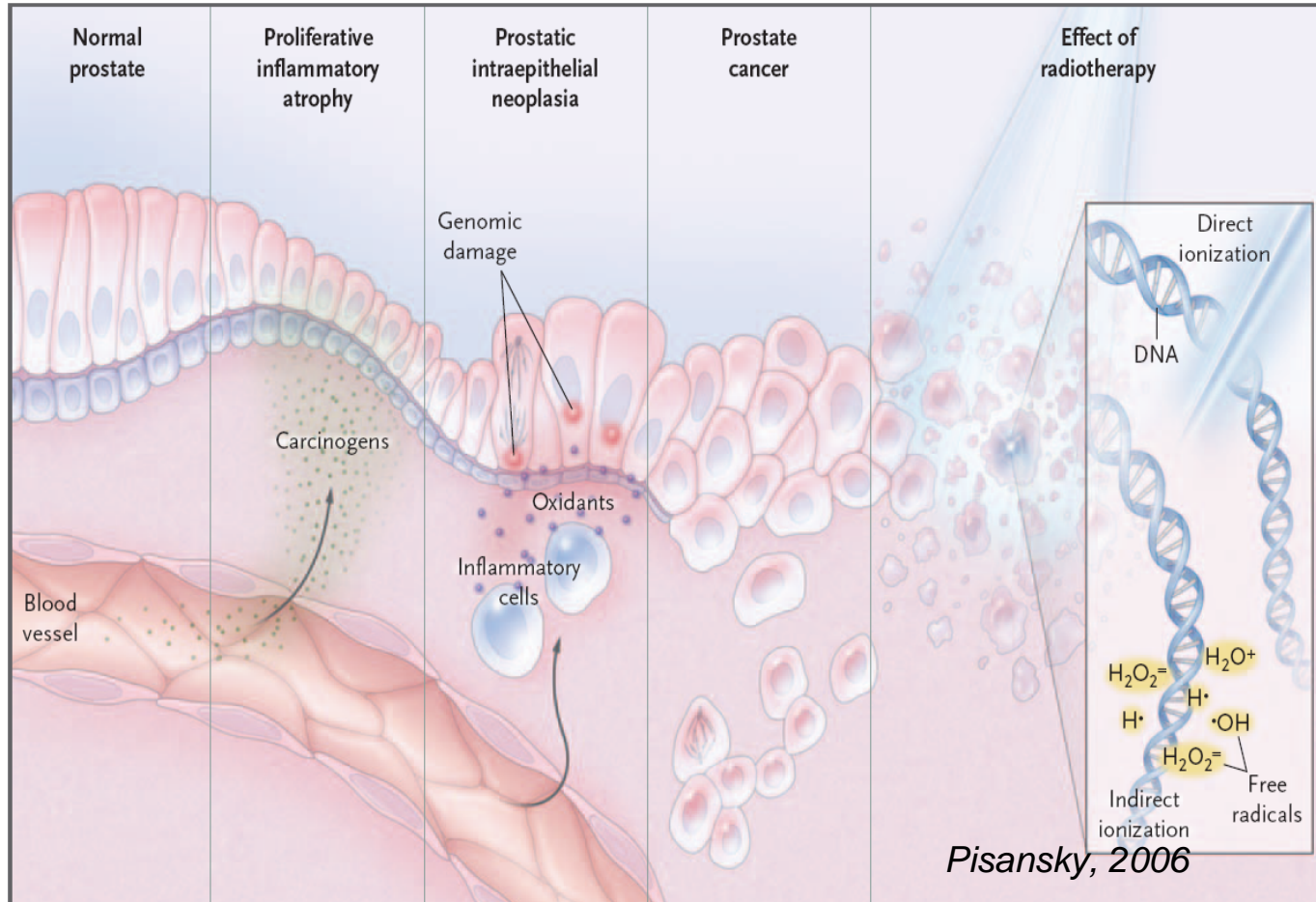
Great ! Now add Biological Precision !!



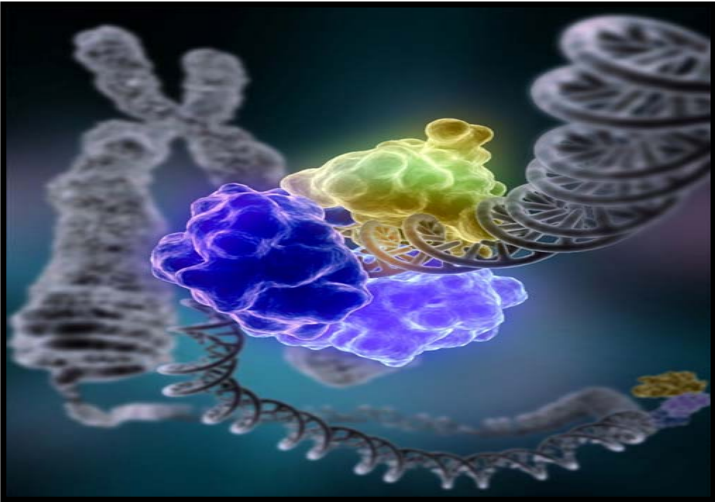
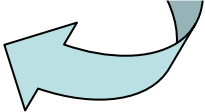
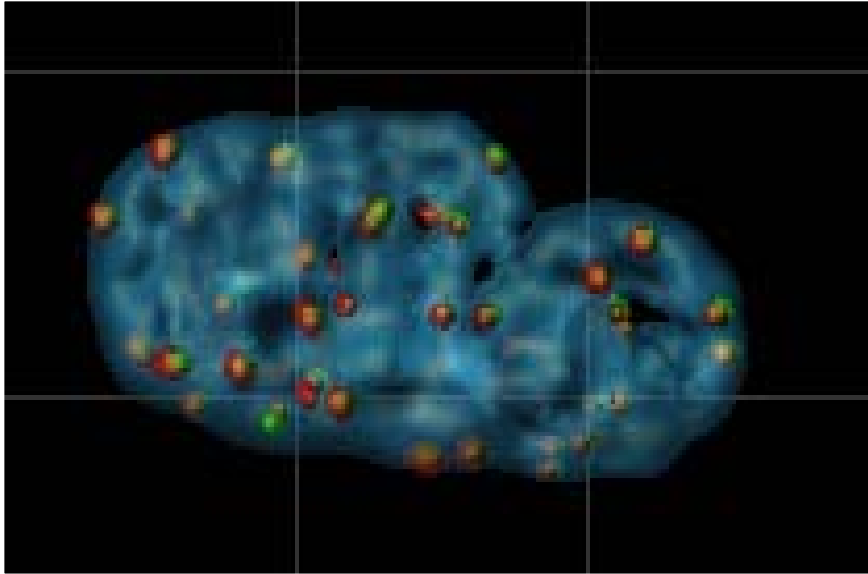
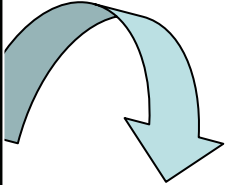
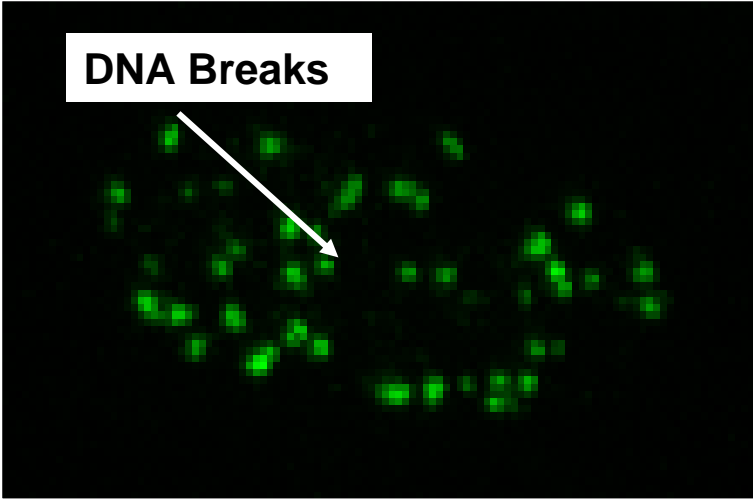
The Cell's Chromosomes and DNA Hold Important Information



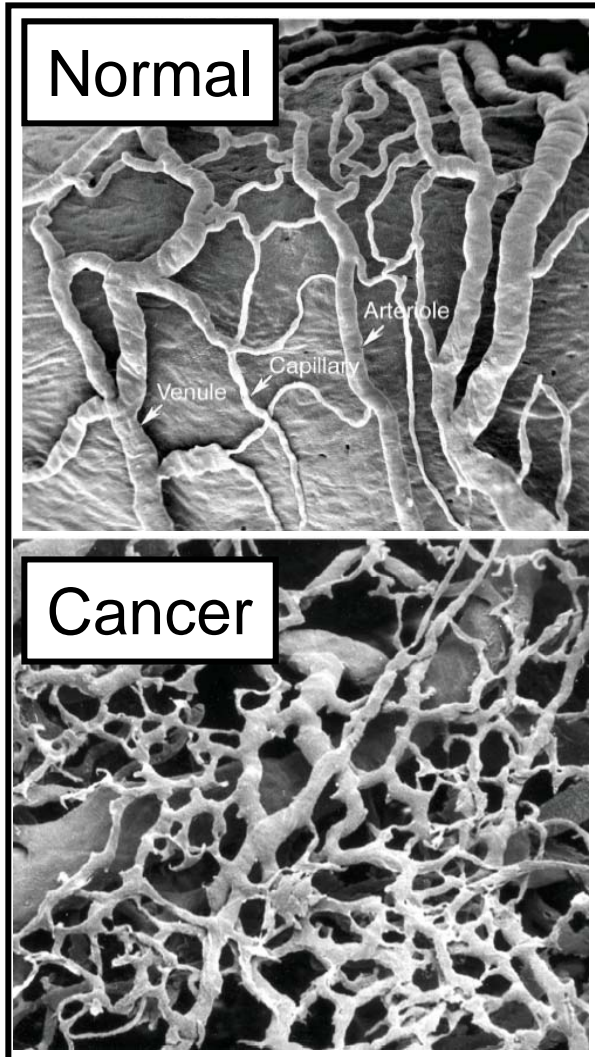
DNA Breaks: A Way To Kill Cancer Cells With Therapy



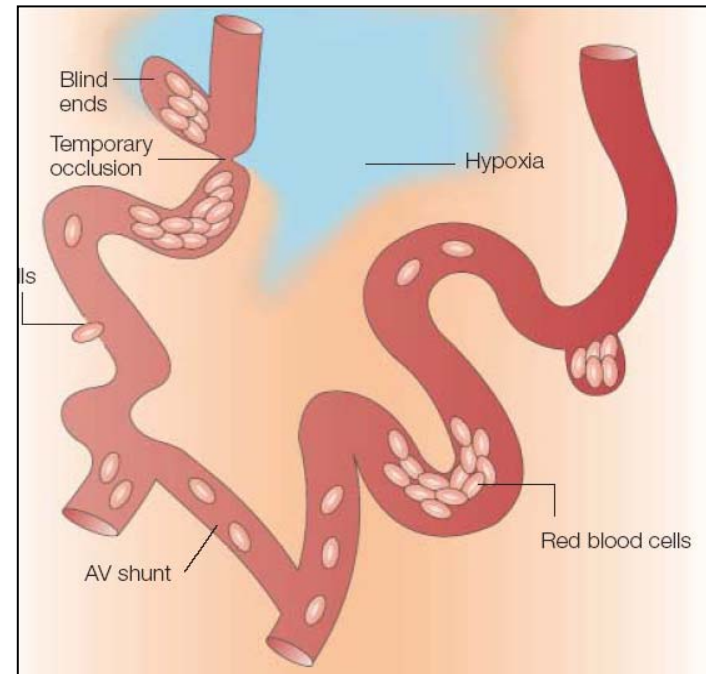
Measuring Radiotherapy-Induced DNA Breaks



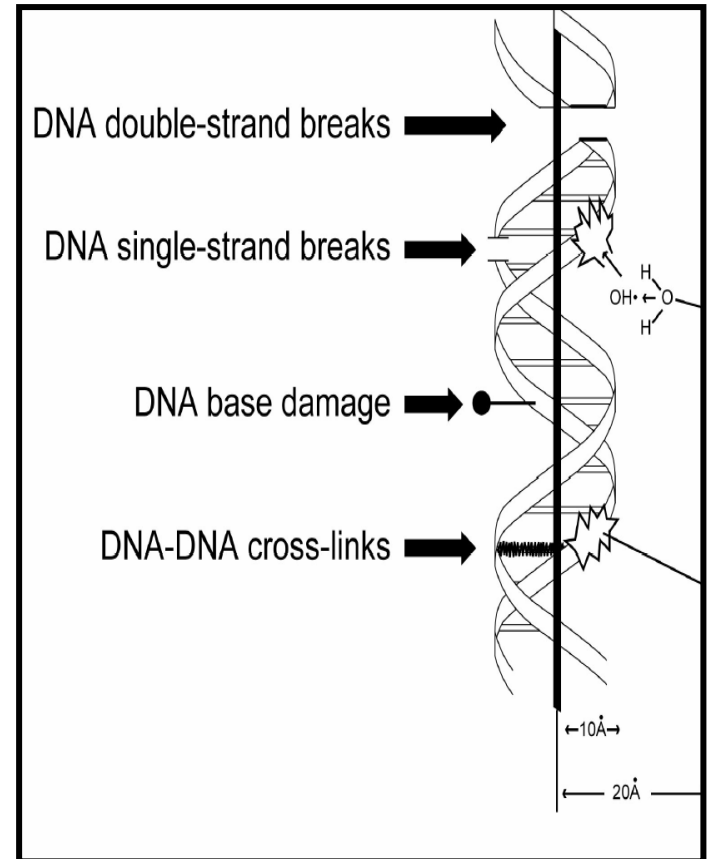
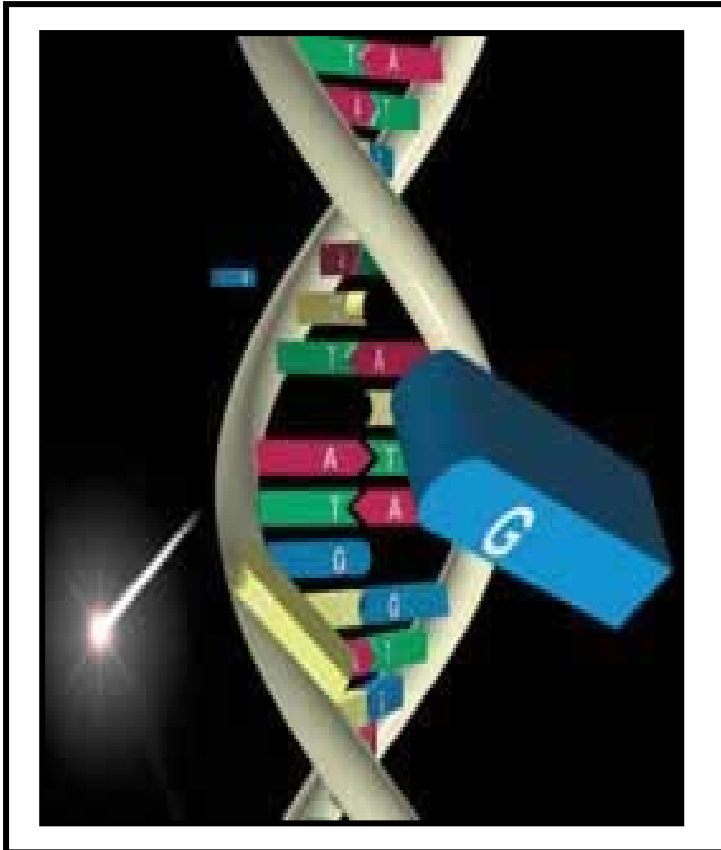
Aggressive Cells Develop in Poorly-Oxygenated (Hypoxic) Prostate Cancer Cells: Why ?



Cancer Hypoxia is linked to increased metastatic spread, chromosomal instability and resistance to chemo- and radiotherapy.
How/Why?

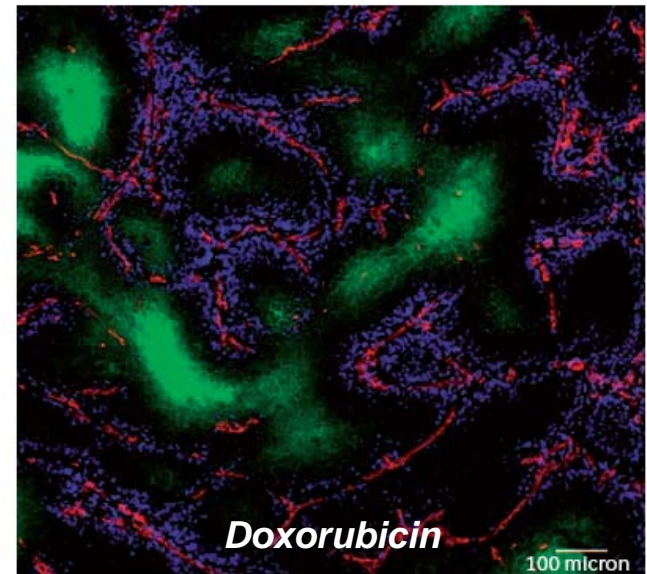
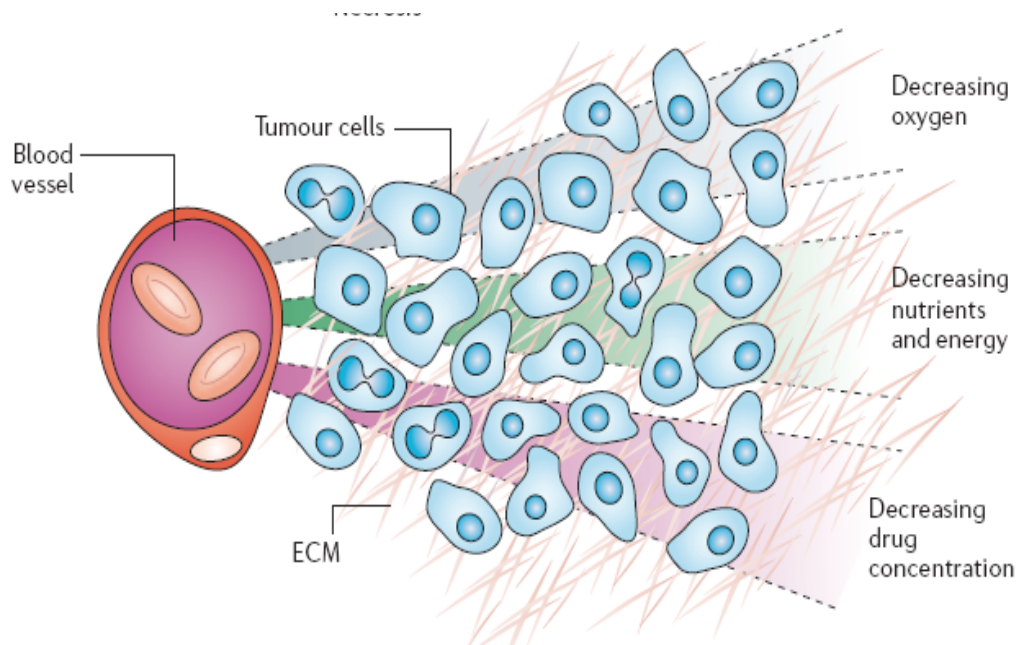


DNA Breaks & O₂: A Way To Kill Cancer Cells With Therapy



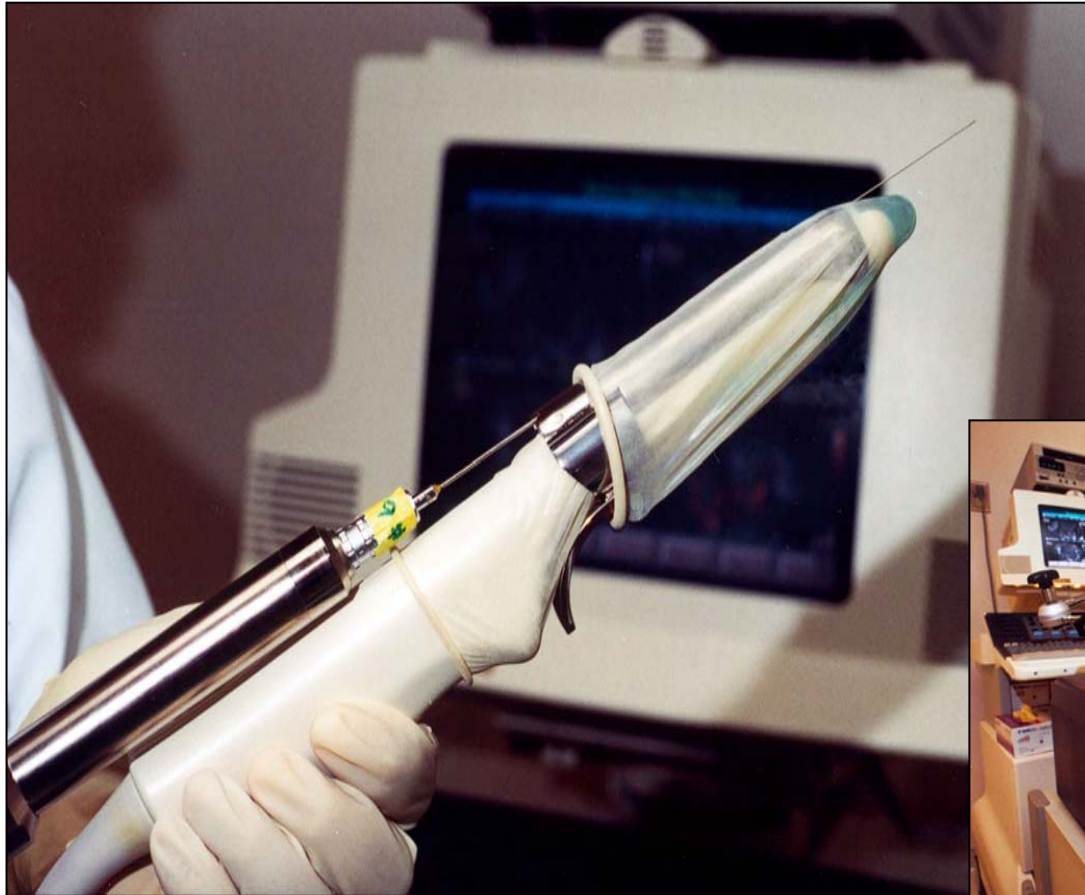
DNA-dsb Oxygen Enhancement Ratio (OER) = Hypoxic cells 2-3x more resistant

Chemotherapy: Decreased Penetration and Non-cycling Cells



Minchinton and Tannock, Nat Rev Can, 2006

Measuring Oxygenation: Eppendorf pO₂ Probe



Prostate: trans-rectal *Eppendorf*
Electrode & biopsies

Bristow-Brampton-2009



Prostate Patient pO₂ Data

Table 1. Characteristics of patients with prostate cancer oxygen measurement

	Patients with oxygen measurements prior to treatment only	Patients with oxygen measurements both pre- and post-androgen withdrawal
<i>n</i>	226	22
Age*	71 (55–82)	71 (55–79)
T category †		
T ₁	87 (39%)	12 (54%)
T ₂	135 (60%)	10 (46%)
T ₃	4 (2%)	
Gleason score		
6	67 (30%)	3 (14%)
7	146 (65%)	18 (82%)
8, 9	13 (6%)	1 (4%)
PSA* ‡ (ng/mL)	8.0 (0.9–33)	7.8 (3.3–30)
Prostatic volume* ‡ (cm ³)	40 (13–179)	37 (23–171)
Grand median pO ₂ * ‡ (mm Hg)	6.8 (0–75)	5.5 (1.8–61)
Median HP ₅ * ‡ (%)	33 (0–100)	46 (0–93)

*Median and range.

†Clinical T category. All patients were clinically N₀, M₀ (UICC-TNM Classification, 6th Edition, 2002).

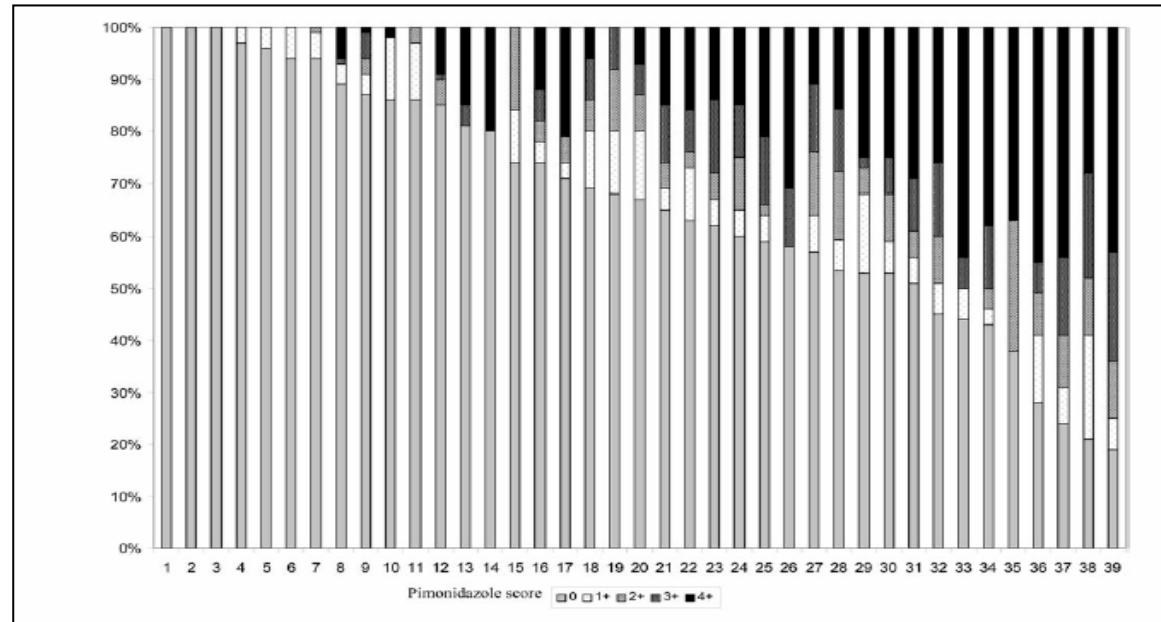
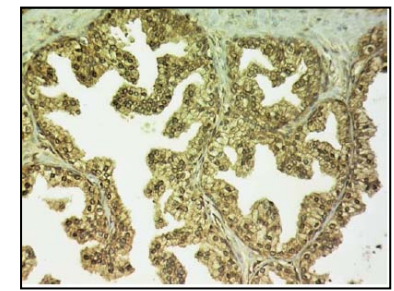
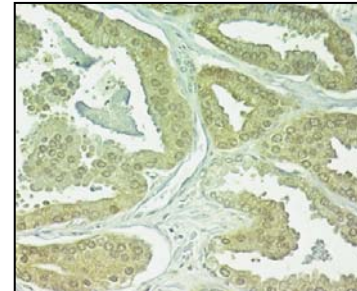
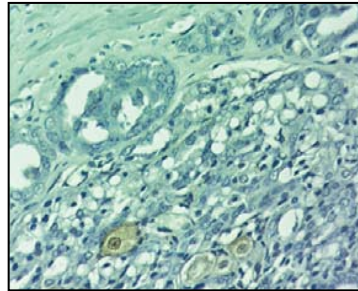
‡Values prior to androgen withdrawal.

Pimonidazole Staining in Prostate Cancer

Correlations only with GS; not PSA/vascularity/T (Carnell et al; 2006)

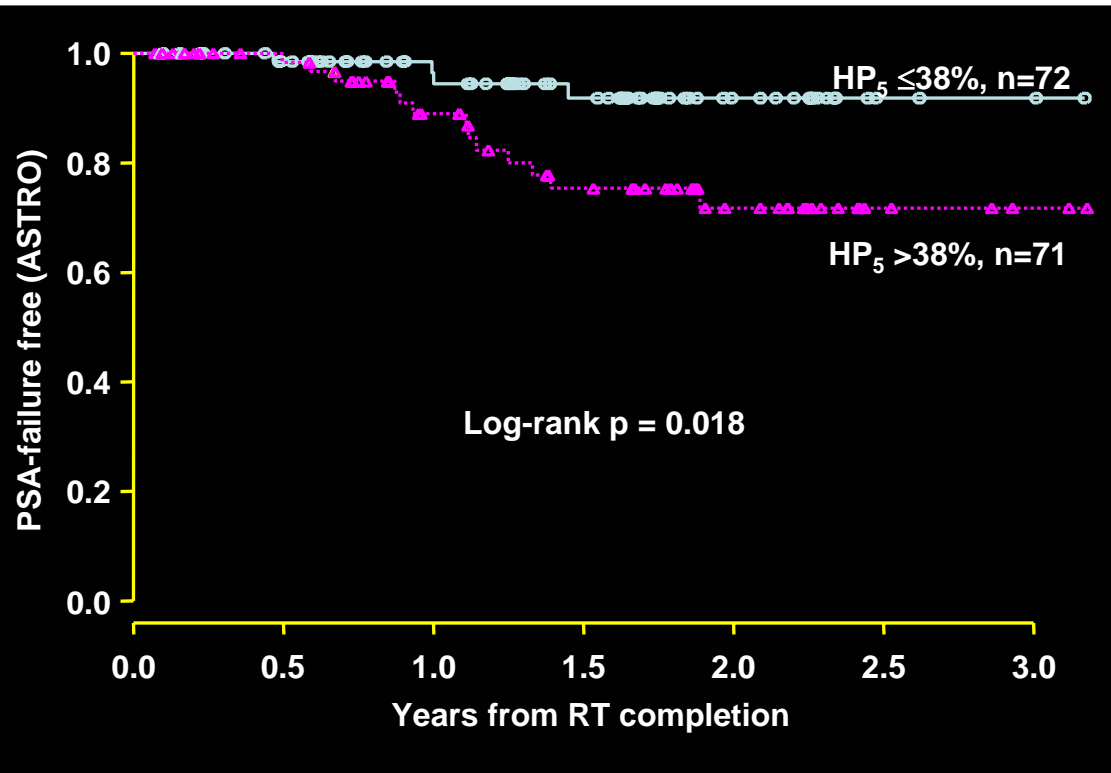
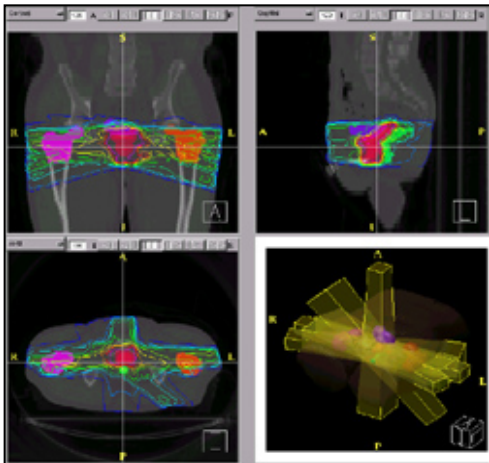
Table 1. Patient characteristics

Characteristic	Value
Patients	37
Clinical stage at presentation*	
T1cNOM0	11
T2aNOM0	2
T2bNOM0	17
T2cNOM0	2
T3aNOM0	0
T3bNOM0	5
Pathological stage at surgery*	
T2aNOM0	1
T2bNOM0	10
T2cNOM0	11
T3aNOM0	12
T3bNOM0	2
T3aN1M0	0
T3bN1M0	1
Gleason score at biopsy	
Low (2-4)	5
Moderate (5-6)	14
High (7-10)	17
Ungraded	1
Gleason score of prostatectomy	
Low (2-4)	0
Moderate (5-6)	14
High (7-10)	25
Age (y)	
Median	69
Range	49-83
PSA (ng/mL)	
Median	8.35
Range	3.53-39.1



Hypoxia (Eppendorf pO₂) Predicts For Biochemical Relapse Post-Radiotherapy

- pO₂ taken when placing fiducial markers for plan
- Dose: 75.6-79.8 Gy
- Intermediate Risk (T1/T2; GS7, PSA 10-20)



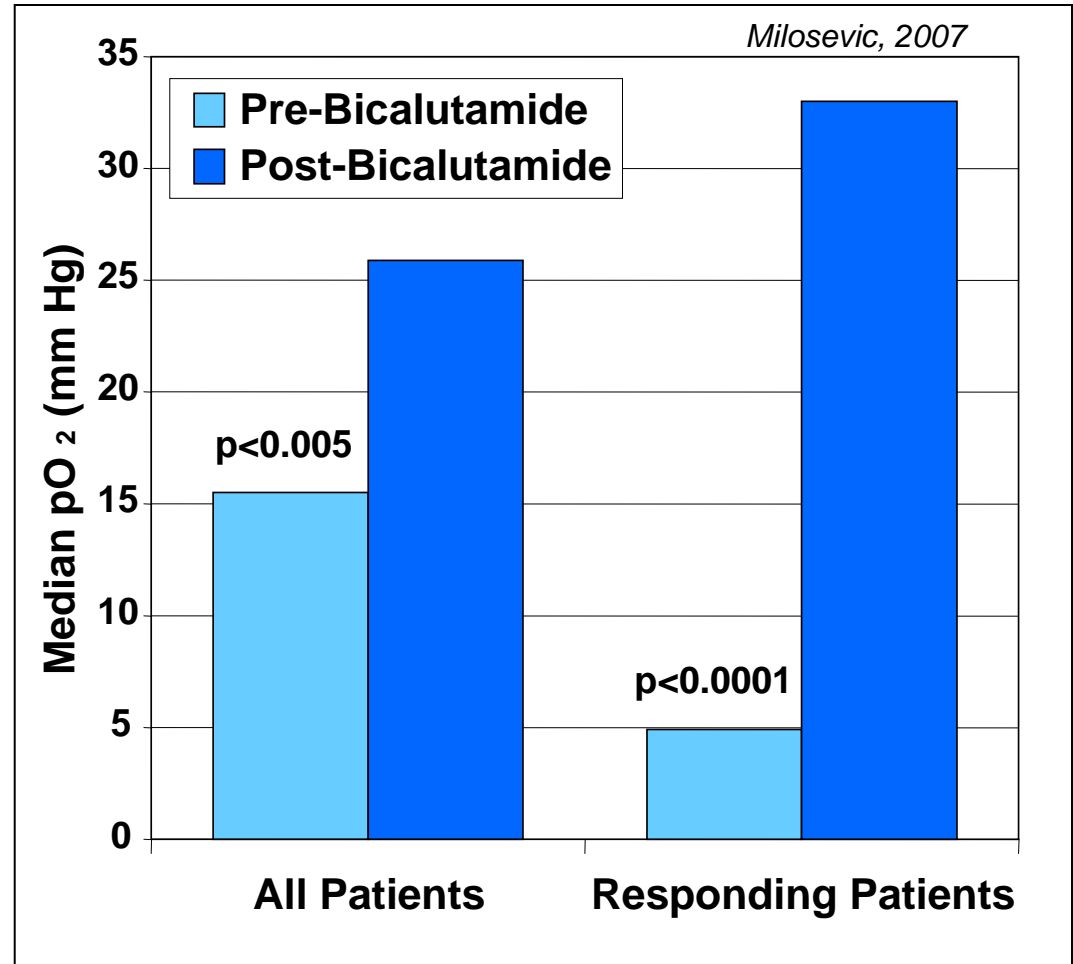
Milosevic and colleagues; PMH-2005



Neoadjuvant Casodex (Bicalutamide) Reduces Prostate Hypoxia

No relationship to:

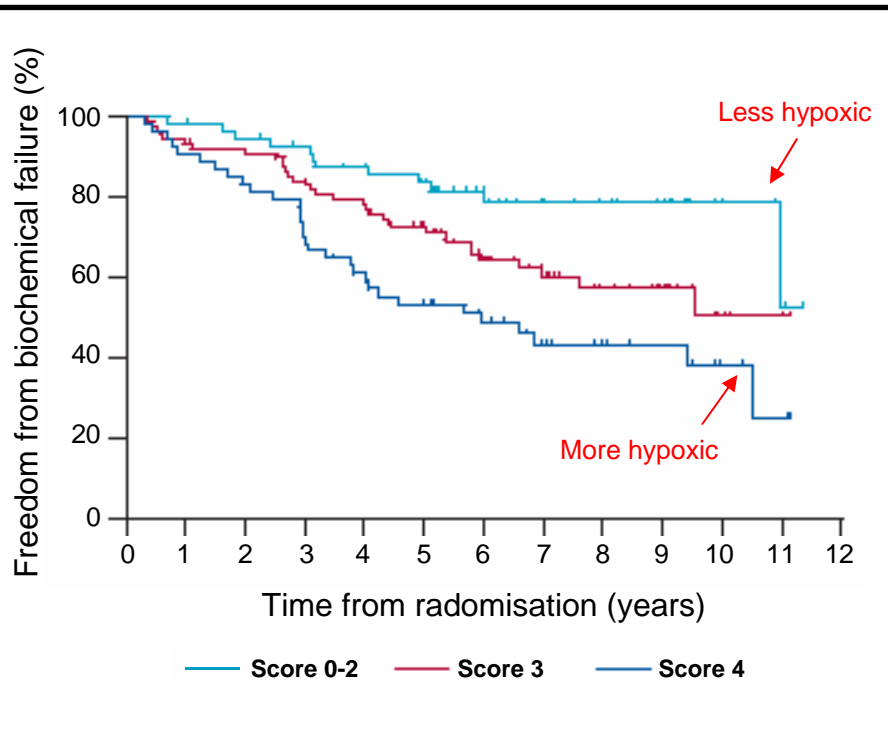
- T-Category
- Gleason score
- PSA
- Change in PSA
- Duration of bicalutamide



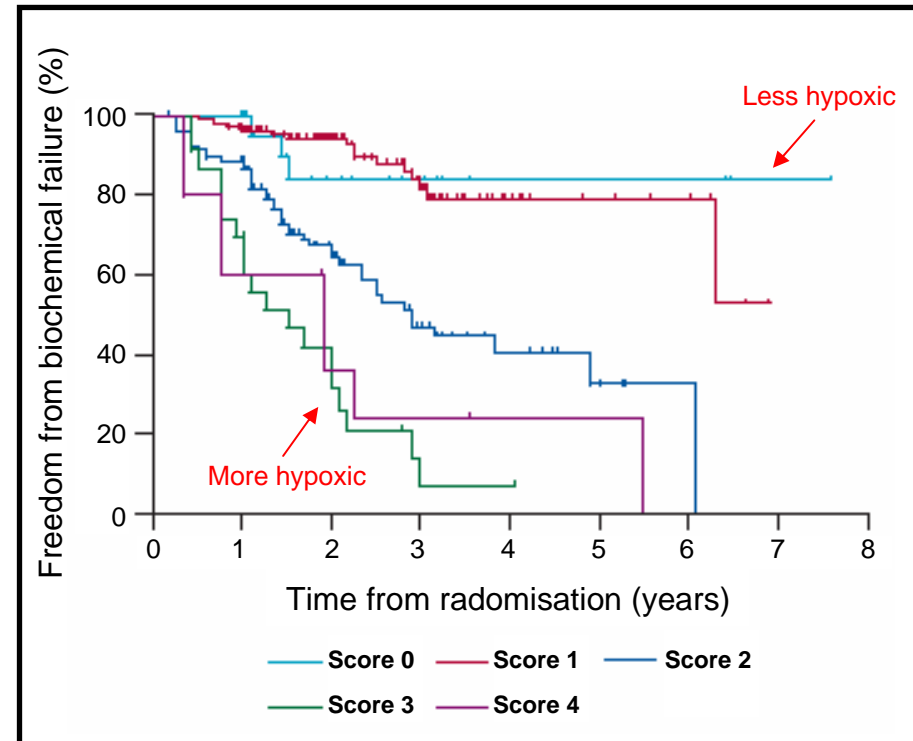
May explain combination therapy success in high-risk CaP

Hypoxia is a negative clinical prognostic factor

Radiotherapy



Radical Prostatectomy



- Prostate tumours with increased HIF1 have higher relapse
- Potentially a local and systemic problem (cervix, HEENT, breast, sarcoma, etc.)

Bristow-Brampton-2009

(adapted from Vergis et al.; Lancet Oncol, 2008)



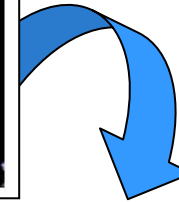
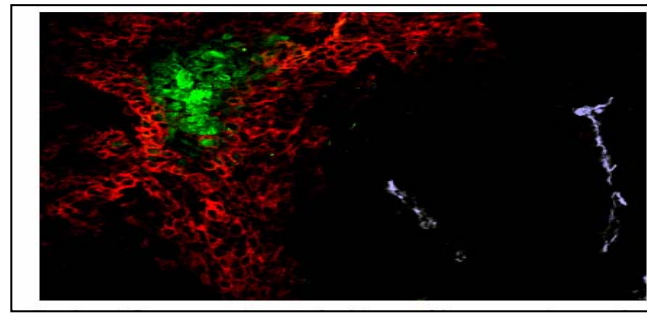


Table 1 – Therapeutic mechanisms to overcome hypoxia

Aim	Treatment strategy	Currently	References
Increasing oxygen supply	ARCON (carbogen and nicotinamide)	In a phase III trial for carcinomas of the larynx and bladder	[14,45]
	Hyperbaric oxygen	Has been investigated in a phase III trial, but is currently not in use for this purpose	[15]
	Blood transfusion/erythropoietin	Has been tested in phase III trials. Results have been contradictory and inconclusive. Needs to be investigated	[33–35,123,124]
Mimic oxygen	Hypoxic cell sensitisers (nimorazole)	Has been tested in a phase III trial, but is currently only in practice in Denmark	[16]
Targeting hypoxic cells	Hypoxic cytotoxins (tirapazamine)	In a phase III trial, no results have been published	[55,56,58]
	Gene therapy	Has only been investigated in laboratory settings, no results from clinical trials yet	[53]
Targeting tumour microenvironment	Anti-angiogenesis (VEGF)	Under investigation in a phase III trial	[53]
	Inhibiting biological response pathways (HIF-1, MAPK, PI3K)	Under investigation in phase I and II trials	[59–61]

ARCON, accelerated radiotherapy combined with carbogen and nicotinamide; VEGF, vascular endothelial growth factor; HIF-1, hypoxia-inducible factor-1; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase.

van der Kogel and colleagues; 2007

Hypoxia & Prostate Biology

- Androgens can cause increased systemic spread
- Hypoxia can up-regulate PSA
- Hypoxia can associate with genetic alterations
- Hypoxia can modify treatment responses to chemotherapy, radiotherapy and AD (pre-clinical and clinical)
- Hypoxia may select for hormone-resistant disease

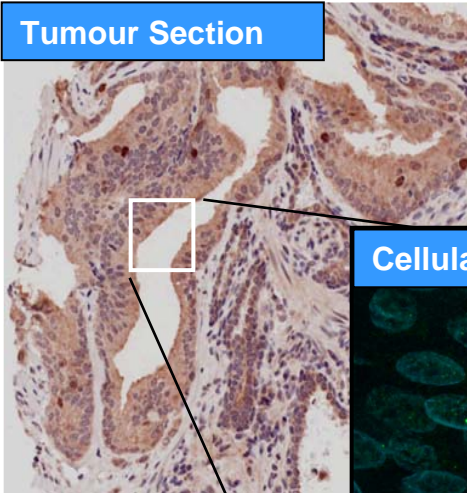
“Need effective measurements of hypoxia to individualize findings to specific patient prognosis and treatments”

Microenvironmental Overlay For Screens and Assays to Reduce “Noise/Signal” in Hits/Biomarkers

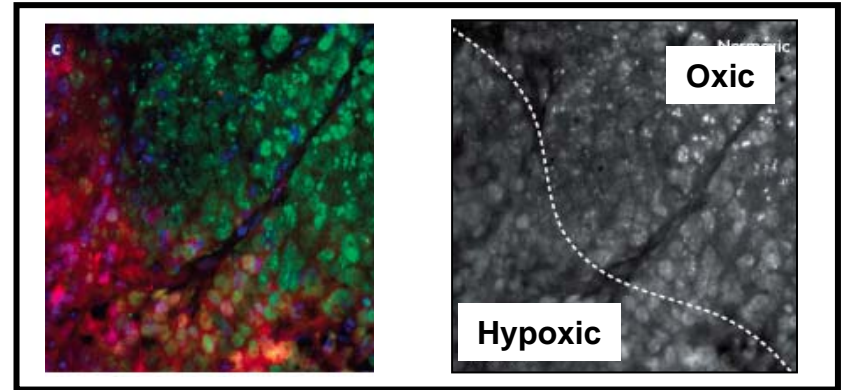
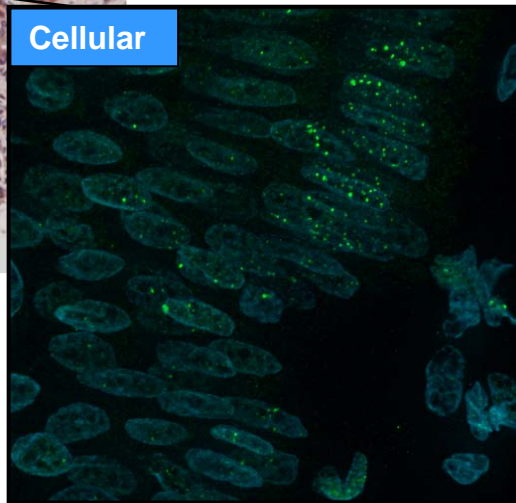
E.G. siRNA/Chemical Screens & Novel Agent Testing In Vitro: Are They The Best Hits ?
(Transcription, Translation, Kinase Activity, EGFR, AR)

Int Risk CaP Example:
Frozen-paraffin cores: ~270 men
pO₂ measurements
CGH-RNA-TMA
XRT Outcome data

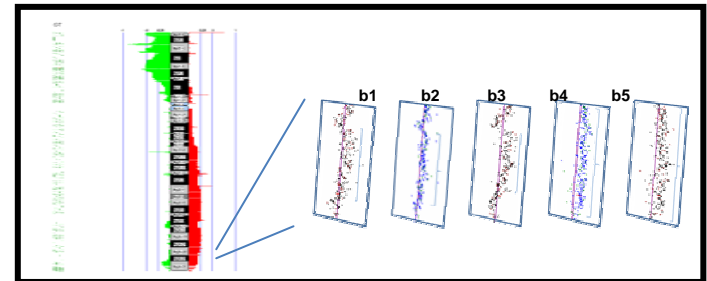
Tumour Section

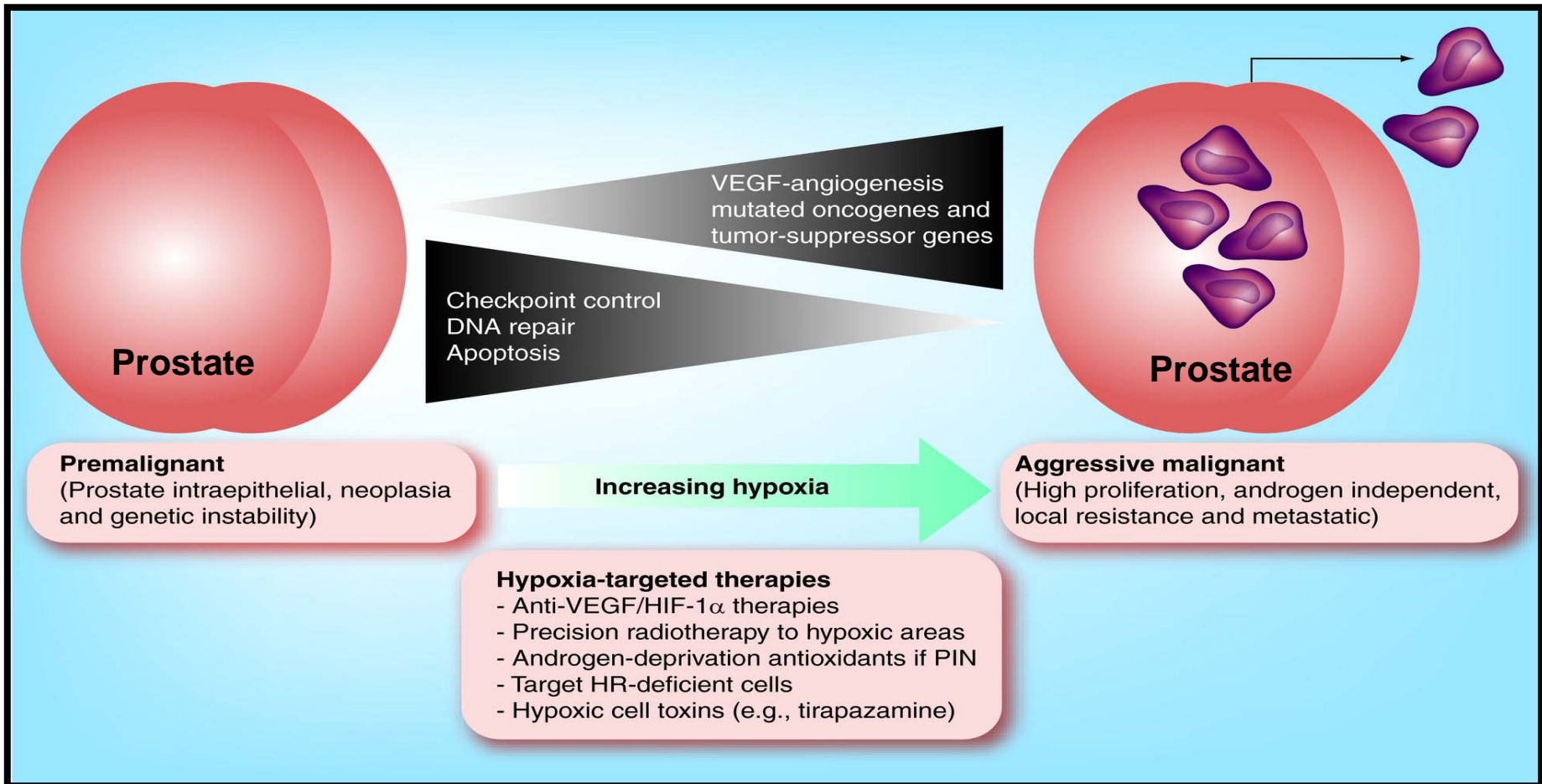


Cellular



EF5, Pimo
CAIX, HIF1





(Chan et al.; *Future Oncol*, 2007)

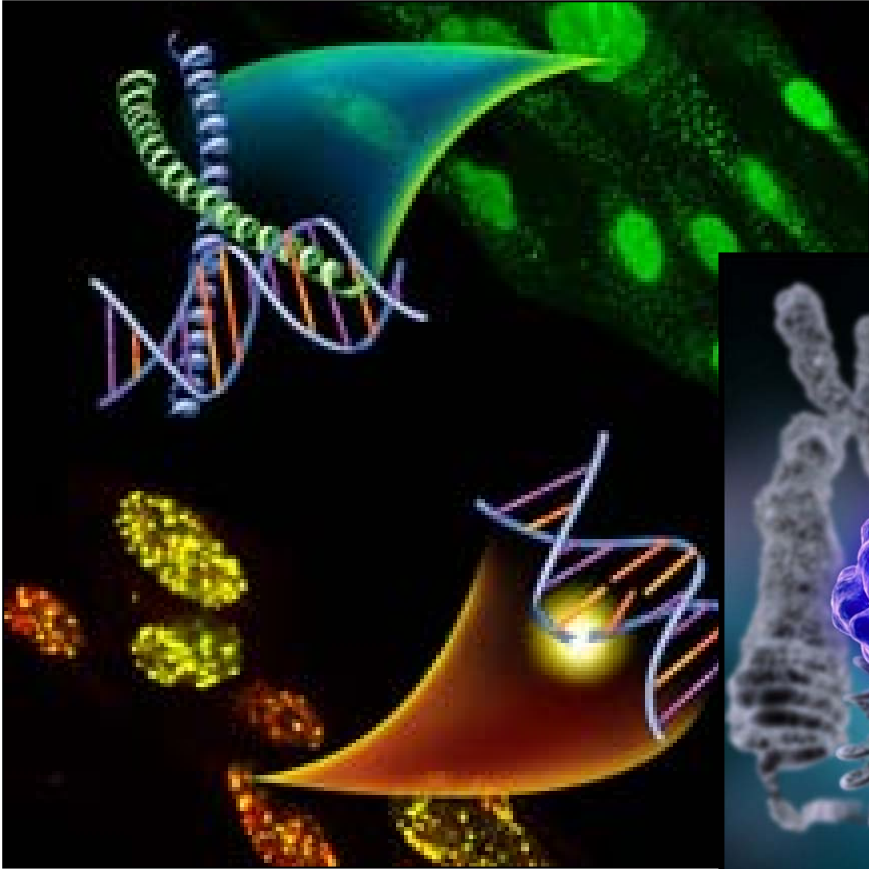


CLINICAL AND EXPERIMENTAL STUDIES IN HYPOXIA RESEARCH

- **New studies and treatments against hypoxic prostate cancer cells**
 - In the next 5 years, we are going to measure hypoxic states in normal, pre-malignant and malignant prostate cancer to try and predict the risk of prostate cancer (Familial Prostate Clinic)
 - We are also attempting to measure relative hypoxic cells in existing tumours within individual men to predict their response to cancer therapy
- **New treatments:**
 - We are developing ways to reduce the level of hypoxia within tumours to improve therapy response
 - We can combine these with precision radiotherapy



HOPE FOR THE FUTURE: PREVENTION AND PRECISION





**Genetic instability
DNA Repair**



**Translation
mTOR/PERK/UPR**



**Metabolic Imaging &
Novel Trials**



**4-D Tracking
Multi-imaging**



**Metastasis and MET
FAK and Stem cells**



The Bristow Lab

PMH-Terry Fox Hypoxia PPG Team
(Hill, Hedley (DDP), Milosevic, Yeung, Fyles)
Radiation Medicine Program
PMH Prostate Program

Bristow Lab: Farid Jalali, Alice Meng, Rong Fan (former), Shahnaz Al-Rashid, TS Kumaravel (former), Oliver Faulhaber (Former), Helen Zhao, Carla Coackley, Tien Phan, Jamil Sawani, Norman Chan, Ramya Kumareswaran, Mike Fraser, Mohsin Ali, Kaisa Luoto, Nirmal Boghal, Stanley Liu, Adrian Ishkanian, Danny Vesprini



THE Prostate CENTRE

University Health Network • Princess Margaret Hospital



Princess Margaret Hospital
University Health Network



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