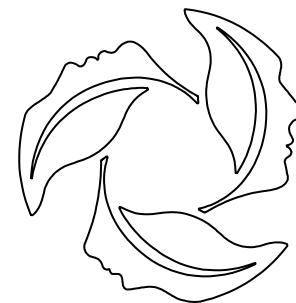


The Importance of Clinical Trials & Image Guidance In Radiation Therapy



Andrew Bayley

Princess Margaret Hospital

University Health Network

"AWARENESS IS PROGRESS"



Disclaimer

Our discussion is an overview.

Some of things we talk about today are well established knowledge and facts.

Other things we talk about tonight will be my personal opinions and observations!

Always discuss your particular situation with the cancer specialist of your choice as this talk is not an endorsement or recommendation about any particular treatment or medicine



The Importance of Clinical Trials



Andrew Bayley

Princess Margaret Hospital

University Health Network

The Importance of Clinical Trials

Why are there clinical trials?

Basics of Clinical Trials and Types of Clinical Trials

Why would you want to participate in a Clinical Trial and can I participate in a clinical trial?

Moral and Ethical Responsibilities of Clinical Investigators

Who decides on what the trial studies?

Some of the Important Clinical Trials in the past



The Importance of Clinical Trials

Why are there clinical trials?

Clinical trials test whether new techniques and promising approaches to cancer prevention, diagnosis and treatment are effective and safe

Almost all of current treatments were proven in clinical trials prior to becoming “standard therapies”

Clinical trials are final stage of the cancer research process



The Importance of Clinical Trials

Why are there clinical trials?

Comparing similar groups of people taking different treatments for the same type of cancer is another way to make sure that study results are real and caused by the treatment rather than by chance or other factors.

Comparing treatments with each other often shows clearly which one is more effective or has fewer side effects

If the new approach is a good one then we know which group of people who will benefit so that it can be used widespread



The Importance of Clinical Trials

Types of Clinical Trials

Type of Clinical Trial	What is it Studying?
Prevention	improve ways to prevent cancer from starting in first place or recurring after treatment eg lifestyle medicine vitamins
Screening	ways to detect cancer early
Diagnostic	tests or procedures to detect cancer in a better or safer way,
Treatment	new drugs or new treatments or new techniques in radiation or surgery test new ways of using standard treatments
Supportive care	Quality of life, reduce impact of cancer on patients or their families, improve comfort of patients



The Importance of Clinical Trials

Pre-clinical, Phase I, II, III, IV Trials

Pre-clinical test new ideas in laboratory, human cells in test tubes or on animals

Phase I dose of radiation over how long
study how a new drug should be delivered
how should it be taken how much is safe, side effects

Phase II dose of radiation / dose of radiation per day
drug how well does it work and safety of drugs

Phase III test new treatment against standard treatment
assigned to a group via randomization
e.g. radiation versus radiation + hormone therapy



The Importance of Clinical Trials

Pre-clinical, Phase I, II, III, IV Trials

Phase IV new treatment that is effective may become a standard treatment, the new treatment is studied over a longer period of time to see if there are other side effects or sometimes to use in other groups of people or other disease



The Importance of Clinical Trials

Why would you want to participate in a clinical trial?

Benefits:

Access to new treatments or drugs before they become widely available. If the treatment is found to be effective, one of the first ones to benefit

Health care provided by leading experts in cancer treatment & research

Close monitoring of your care and often more follow-up visits or tests

Opportunity to help make a very important contribution to cancer research and to help every man that comes after you



The Importance of Clinical Trials

Why would you **not** want to participate in a clinical trial?

Risks:

New treatments or drugs have side effects risks unknown to doctors

New treatments or drugs may be ineffective, less effective than current standard treatments

Even if new approach works, it may not work for you

Cannot choose the treatment arm

I don't want to be a "guinea pig"



The Importance of Clinical Trials

Ethical Responsibilities of Clinical Investigators

Clinical investigators undergo rigorous training in ethics of clinical trials

Research Ethics Boards (Tri-Council Statement)

group of health professionals and lay people carefully review and evaluate all clinical trials to ensure: need for the study, ensure people participating are protected, making sure the benefits of the study outweigh the risk

Health Canada

reviews all clinical trials with investigational devices or drugs to make sure that trials are properly designed and carried out without excessive risk



The Importance of Clinical Trials

Ethical Responsibilities of Clinical Investigators

Informed Consent Process

Your right and my responsibility to make sure you have enough information to make an informed and educated decision about taking part

Informed consent includes the following information:

A description of the clinical trial, why are investigators studying this

How many people will be in the trial

The treatments and tests involved

Potential benefits / potential risks

Known side effects of the treatment(s)

Alternative treatment that are available may benefit you

A statement about confidentiality of information



The Importance of Clinical Trials

Can I participate in a Clinical Trial?

YES!!!!



The Importance of Clinical Trials

Can I participate in a Clinical Trial?

Eligibility Criteria:

make sure study participants are alike in the same key ways

Age, Gender,

Type and Stage of Cancer,

Health status and other medical problems

Previous cancer or cancer treatment

Criteria help us know who will benefit most from a particular type of treatment and also who should not have the treatment



The Importance of Clinical Trials

Who decides on what the trial studies?

- Phase III usually a group of internationally known and respected experts agree on important research questions
- Phase I/II often a national cancer body or a large cancer centre with many patients
- Preclinical Clinician Scientist / laboratory researcher groups of laboratory researchers



The Importance of Clinical Trials

Who decides on what the trial studies? **even get automatic notification

National Cancer Institute of Canada Clinical Trials Group
(NCIC CTG)

www.ctg.queensu.ca/trials/default.html

Ontario Cancer Research Network (OCRN)

www.OntarioCancerTrials.ca

National Cancer Institute (NCI)

www.cancer.gov/search/clinical_trials/search_clinicaltrialsadvanced.aspx



The Importance of Clinical Trials

Some important trials of the past and present??

Low Risk Disease at Diagnosis

Intermediate Risk Disease at Diagnosis

High Risk Disease at Diagnosis

Metastatic Setting



Results of RT in 2-D era using doses of RT as high as could safely be given

- Low risk
 - Approximately 60% disease free at 10 yrs
- Intermediate Risk
 - Approximately 40% disease free at 10 yrs
- High Risk
 - Approximately 20% disease free at 10 yrs



How Can we improve Radiation Treatment results in Prostate Cancer

Increase the dose of radiation to the prostate while protecting the normal tissues around it.

Use other treatments with radiation to kill cancer cells - hormone treatment



The Importance of Clinical Trials

Some important trials of the past and present??

Bill-Axelsson N Engl J Med 2005; 352:1977-1984, May
12 2005

Radical Prostatectomy versus Watchful Waiting in
Early Prostate Cancer

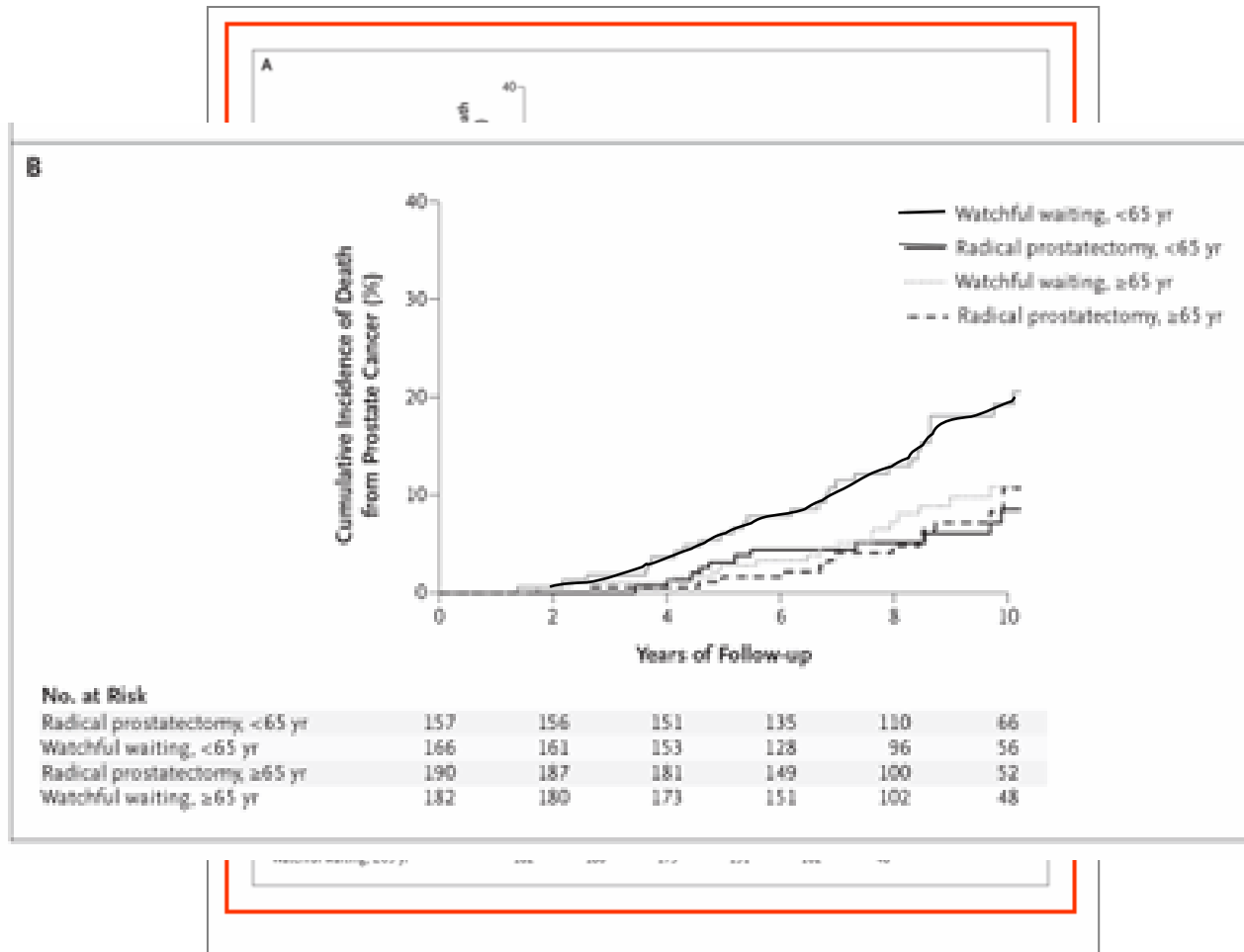
Oct. 1989 Feb 1999, 695 men with early prostate
cancer (mean age, 64.7 years) were randomly
assigned to radical prostatectomy or watchful
waiting

Primary end point was death due to prostate cancer 

The Importance of Clinical Trials

Some important trials of the past and present??

Bill-Axelsson N Engl J Med 2005; 352:1977-1984, May 12 2005



The Importance of Clinical Trials

Some important trials of the past and present??

Bill-Axelson N Engl J Med 2005; 352:1977-1984, May 12 2005

Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

Local Treatment

Conclusions ~~Radical prostatectomy~~ reduces disease-specific mortality, overall mortality, and the risks of metastasis and local progression. The absolute reduction in the risk of death after 10 years is small, but the reductions in the risks of metastasis and local tumor progression are substantial

Since, in absolute terms, the reduction in mortality is moderate, clinical decision making and patient counseling will remain difficult.



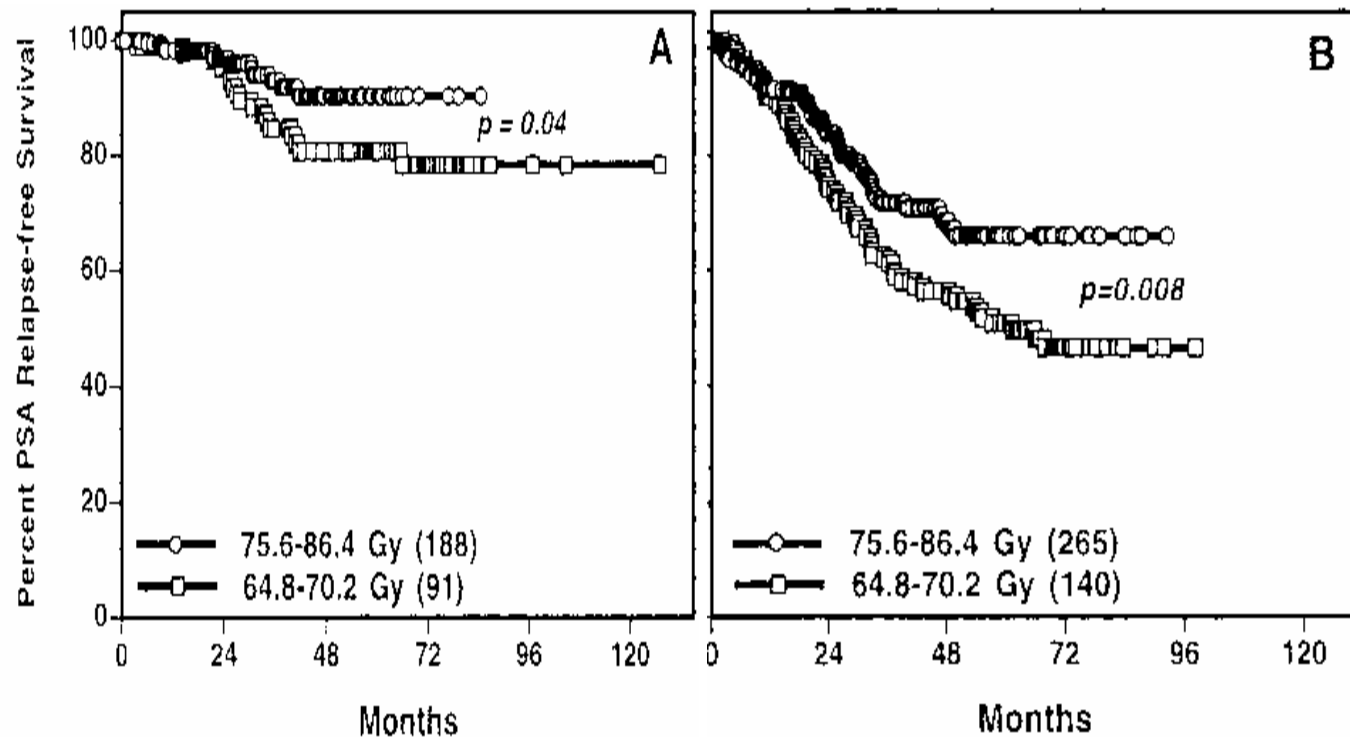
The Importance of Clinical Trials

Some important trials of the past and present??

Clinical Examples: Improved results with dose escalation

Good risk

Intermediate risk



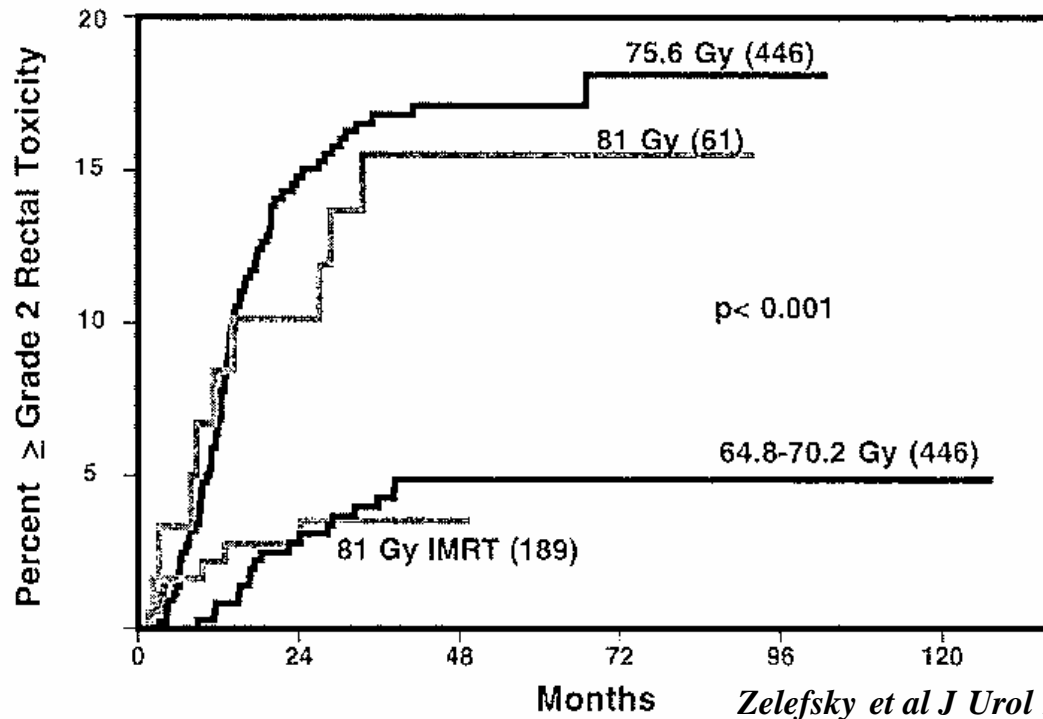
Zelevsky et al J Urol 2001



The Importance of Clinical Trials

Some important trials of the past and present??

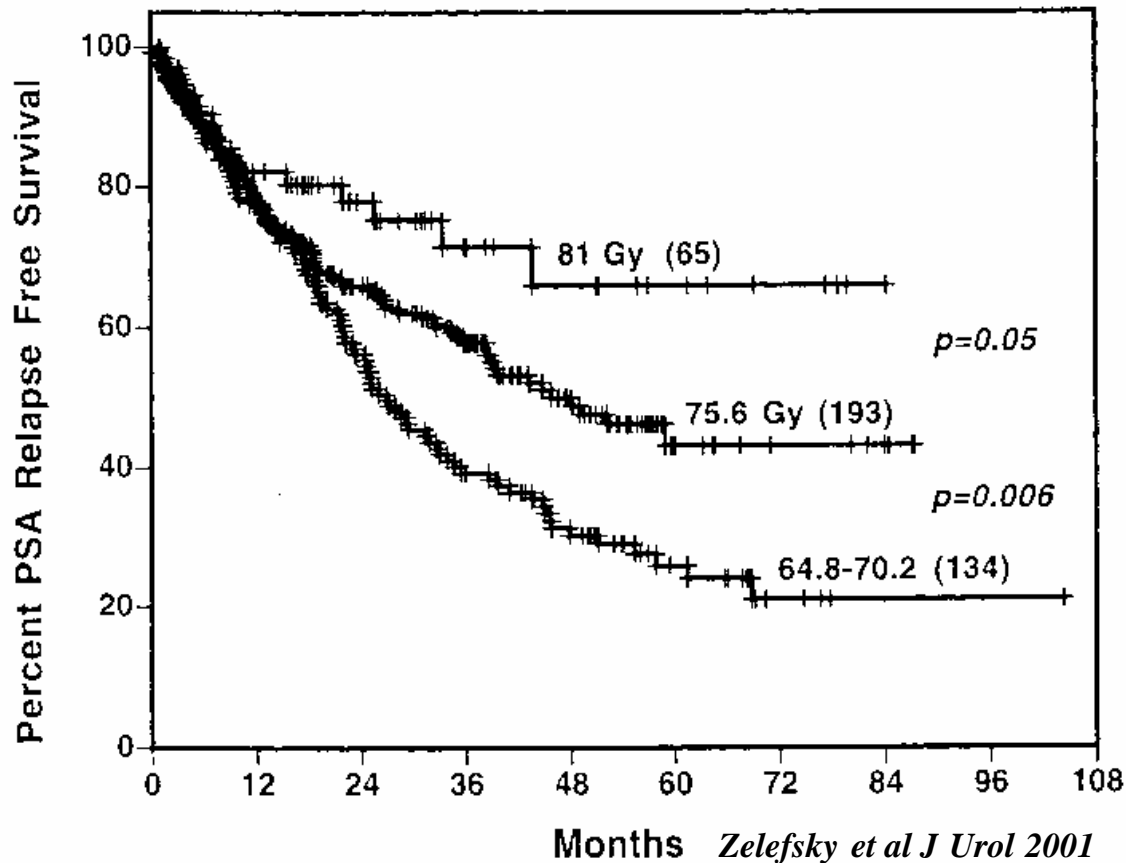
Clinical Examples: Prostate IMRT Toxicity



The Importance of Clinical Trials

Some important trials of the past and present??

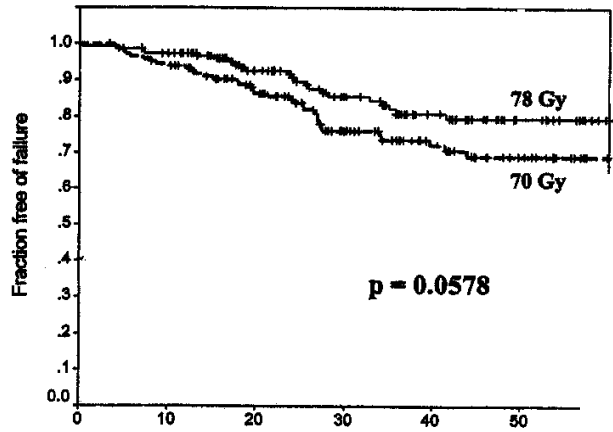
Clinical Examples: Improved Results with Dose Escalation
High risk



The Importance of Clinical Trials

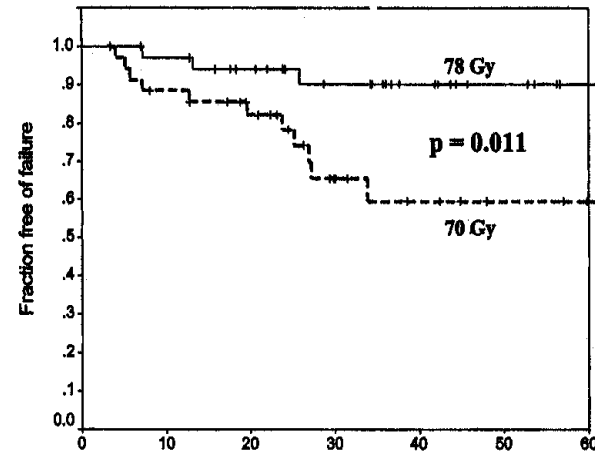
Some important trials of the past and present??

Months	0	10	20	30	40	50	60
70 Gy	150	137	106	71	49	32	16
78 Gy	151	144	106	77	54	31	15



All patients

Months	0	10	20	30	40	50	60
70 Gy	36	30	24	13	9	6	4
78 Gy	36	34	29	22	15	10	6



T1T2 PSA > 10

Months after radiotherapy

Pollack et al, JCO 2000



PMH 99-07 TRIAL P. Warde PI

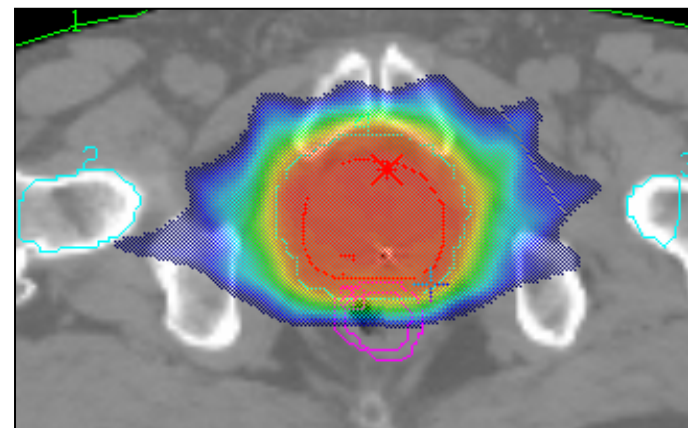
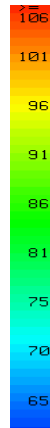
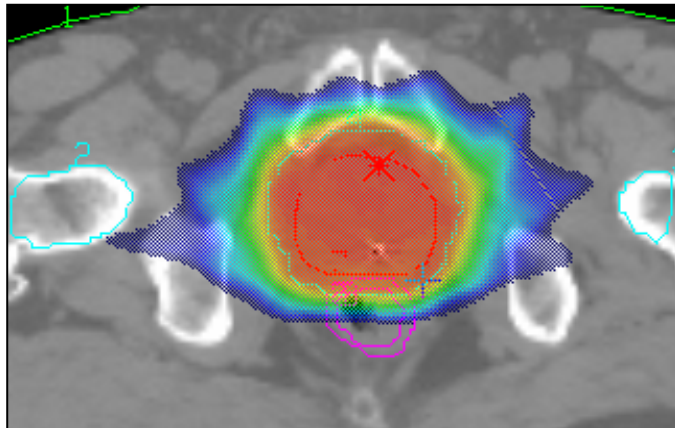
Phase II trial of dose escalation – Catton et al

ALL intermediate risk prostate patients who are having radiation therapy receive dose escalation at PMH
Approx 250-300 new patients per yr

IMRT

VS

5 MONTHS OF
BICULTAMIDE +IMRT



COMING SOON ACROSS CANADA

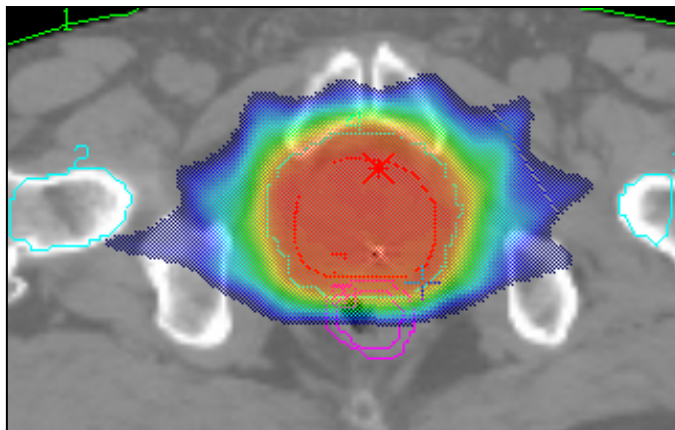
Intermediate risk prostate patients

OCO Group

STANDARD

78Gy in 39F

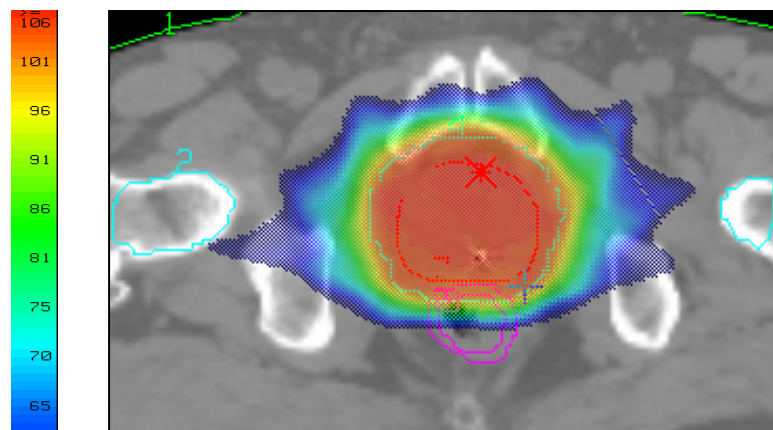
IMRT 3D CONFORMAL



HYPOFRACTIONATION

60Gy in 20F

IMRT 3D CONFORMAL



The Importance of Clinical Trials

Some important trials of the past and present??

Bolla et al N Engl J Med 1997; 337:295-300, Jul 31, 1997

From 1987 to 1995, 415 patients with locally advanced prostate cancer ** long time and a lot of men

In past, only 20% of men were disease free at 10yrs

Radiation to
Pelvis and prostate

vs

Radiation to
Pelvis and prostate
And
Goserelin (hormone)



The Importance of Clinical Trials

Some important trials of the past and present??

Bolla et al N Engl J Med 1997; 337:295-300, Jul 31, 1997

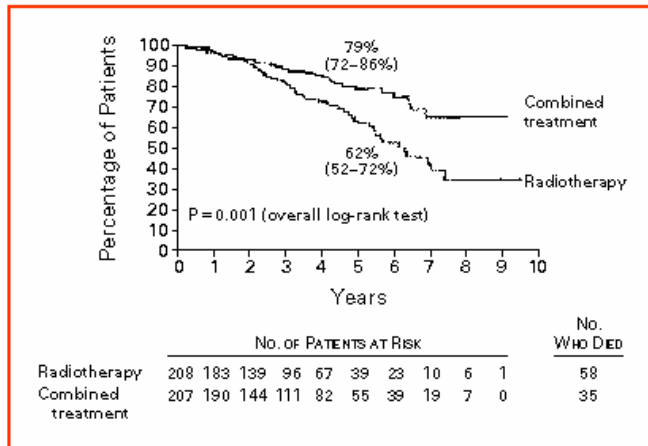


Figure 1. Kaplan-Meier Estimate of Overall Survival.

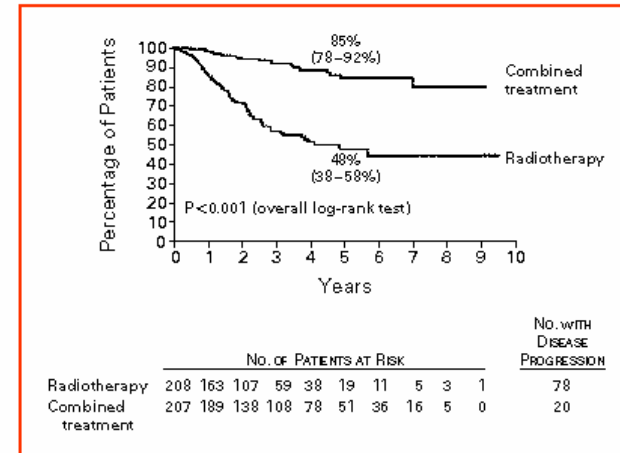


Figure 2. Kaplan-Meier Estimate of the Disease-free Interval.

Conclusions Adjuvant treatment with goserelin, when started simultaneously with external irradiation, improves local control and survival in patients with locally advanced prostate cancer



The Importance of Clinical Trials

Some more clinical trials at PMH across Canada across the world

Advanced Disease or Metastatic Setting

NCIC PR-7 AND PR-8 Trial continuous vs intermittent hormone therapy QOL and survival

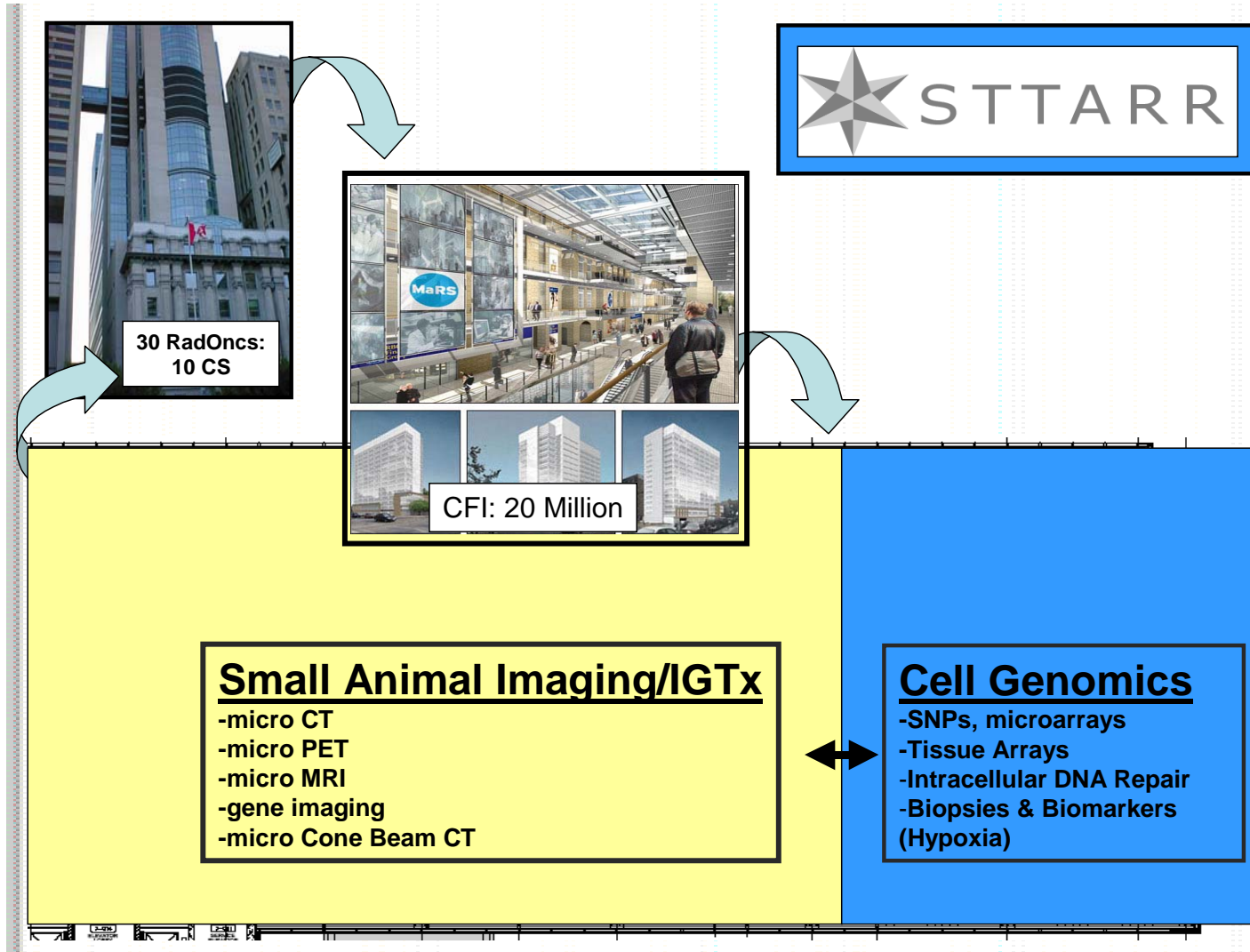
Hormone therapy side effects: prevent bone loss, decrease hot flushes, QOL

MRI study to see if can find local recurrence in prostate better using MRI then might be able to investigate other local therapy



The Importance of Clinical Trials

What about the benchtop laboratory???

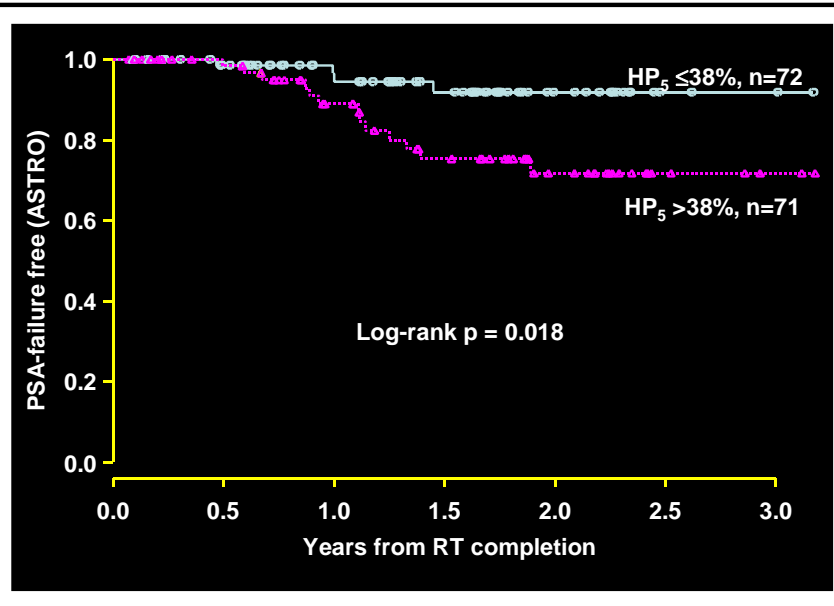
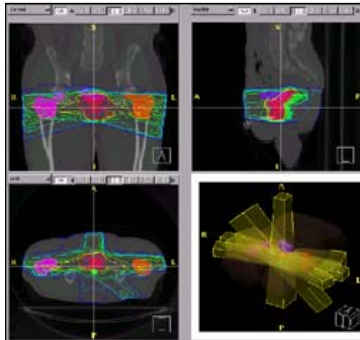


The Importance of Clinical Trials

What about the benchtop laboratory???

Hypoxia Predicts For Poor Outcome Following Prostate 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



Slide courtesy Dr. M. Milosevic

Risk Groupings and Prognostic Factors

PROGNOSTIC FACTORS

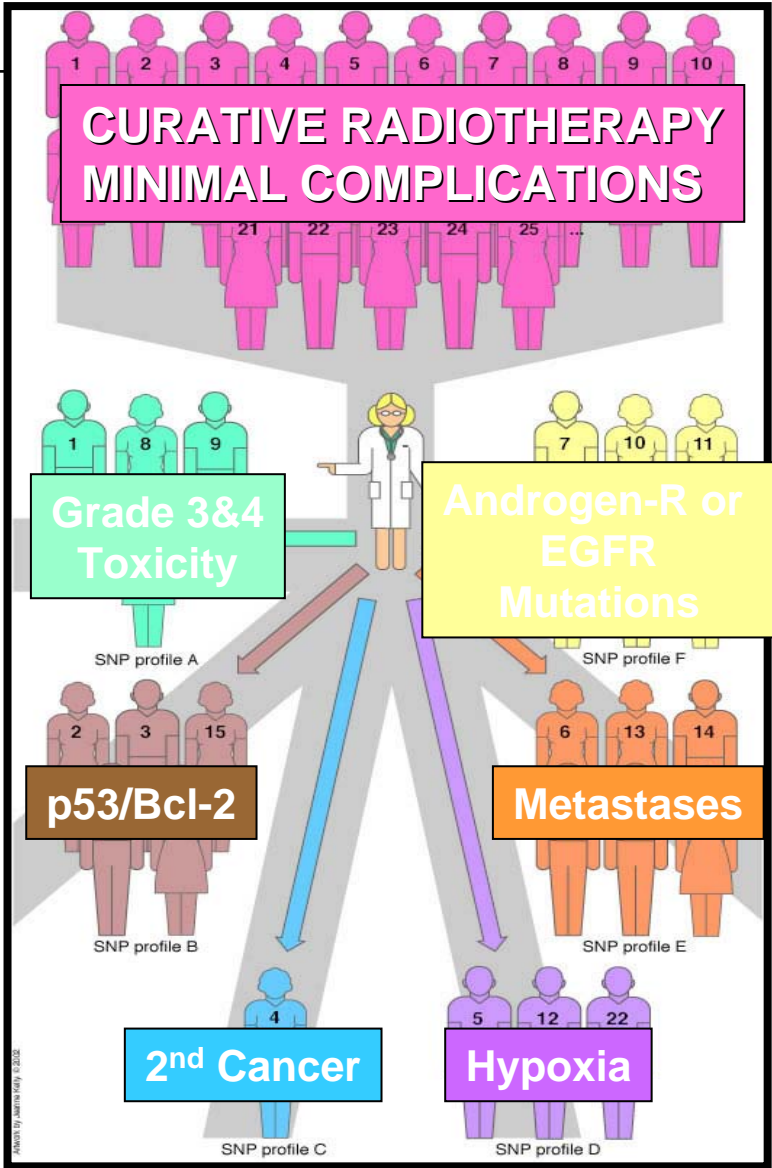
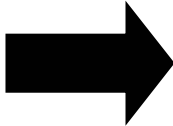
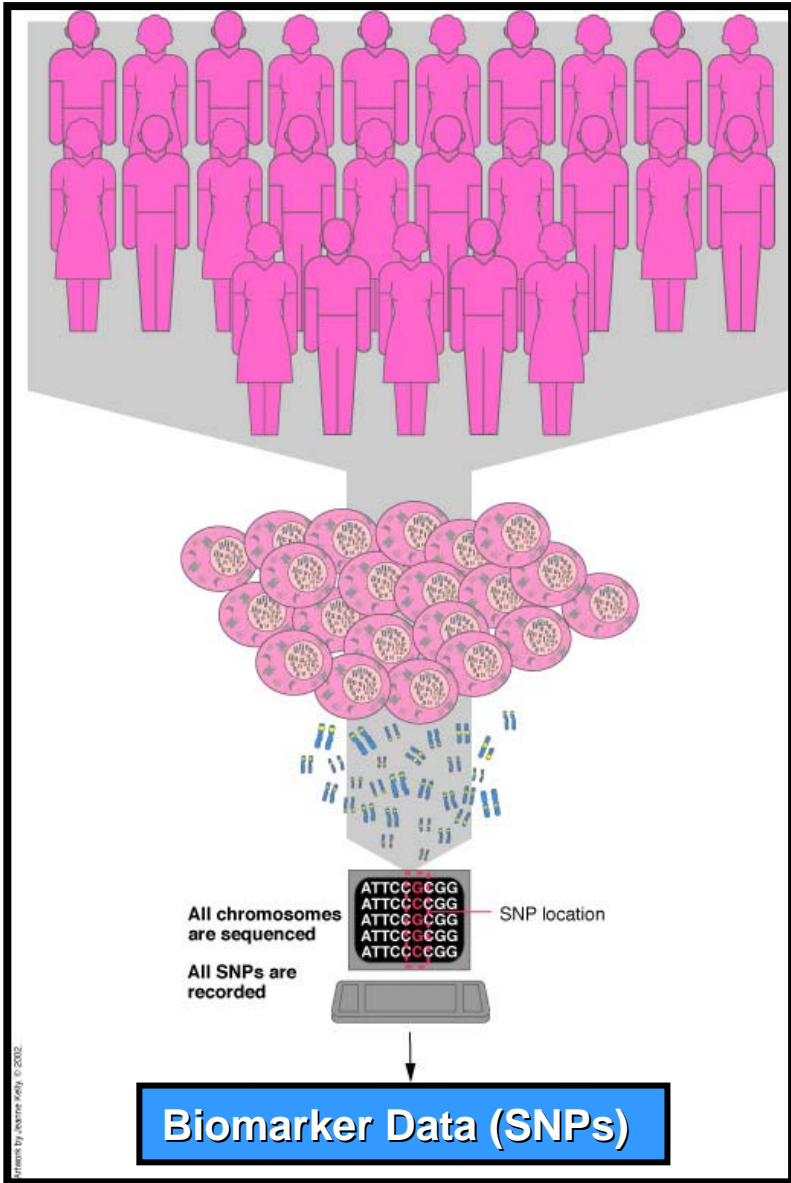
- Traditional: T-stage, PSA, Gleason Score
- Newer: Percent Positive Biopsies, Ki-67, PSA DT < 10 months
- Promising: **p53**, BAX-BCL2, EGFR,MDM2, SURVIVIN, **p16^{INK4a}**, **Hypoxia**, **Repair**

RISK GROUPS

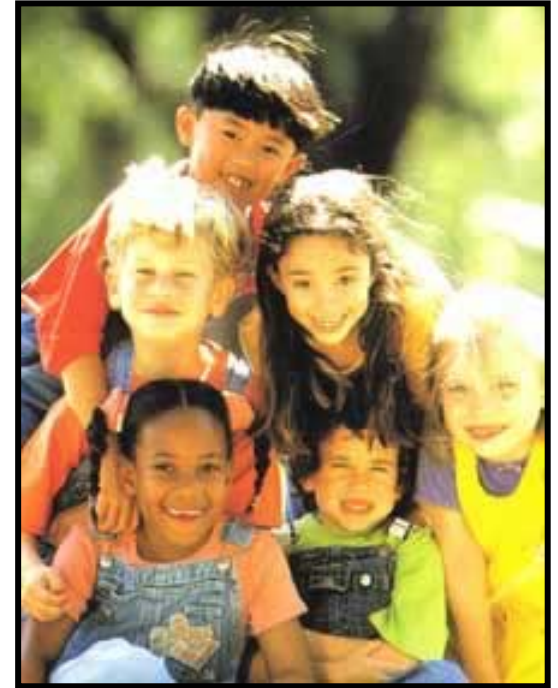
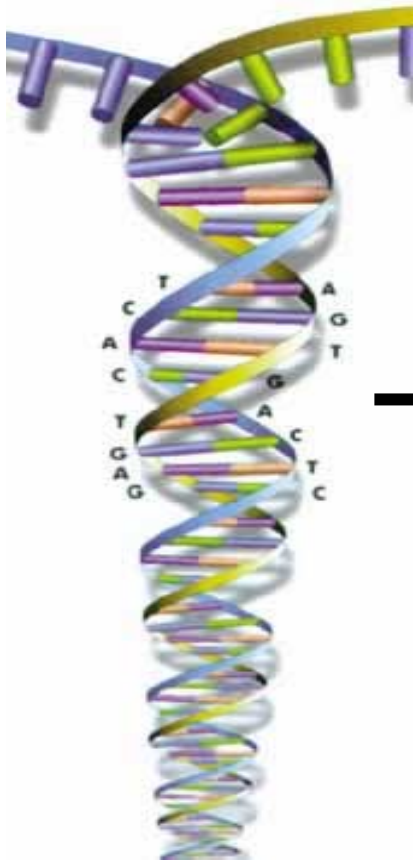
- LOW: T1/T2; PSA <10; GS 4-6 (*Brachy, EBRT; Surgery, WW*)
- INTERMEDIATE: T1/T2; GS 7; PSA 10-20 (*Brachy/EBRT +/- Hormones; Surgery, WW*)
- HIGH: PSA > 20; GS 8-10; T3-T4 (*EBRT + Hormones +/- Chemo; rarely surgery*)



KEY CONCEPT: Individualization



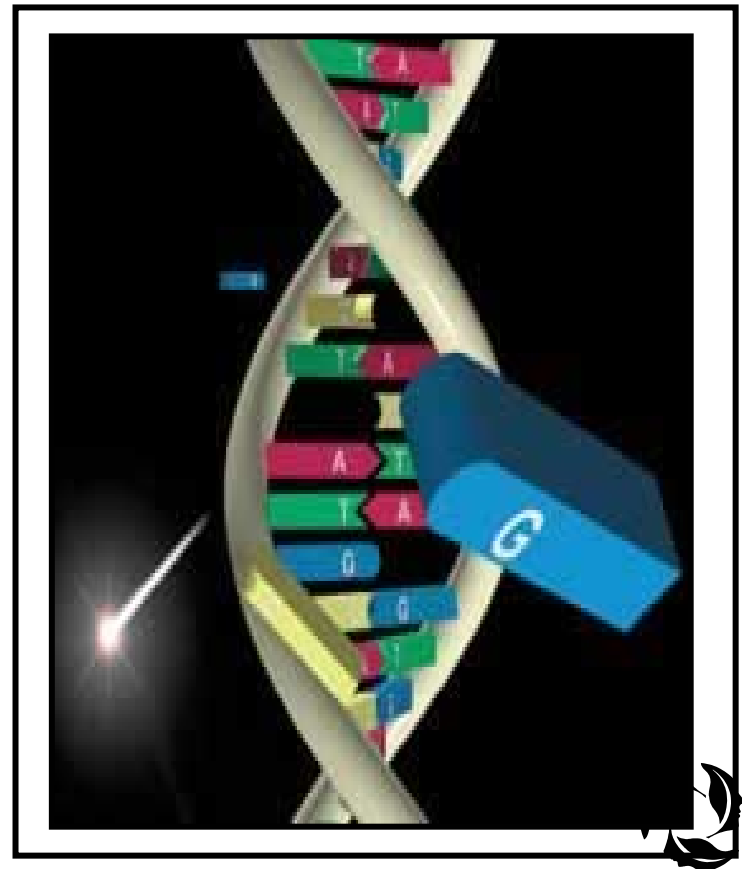
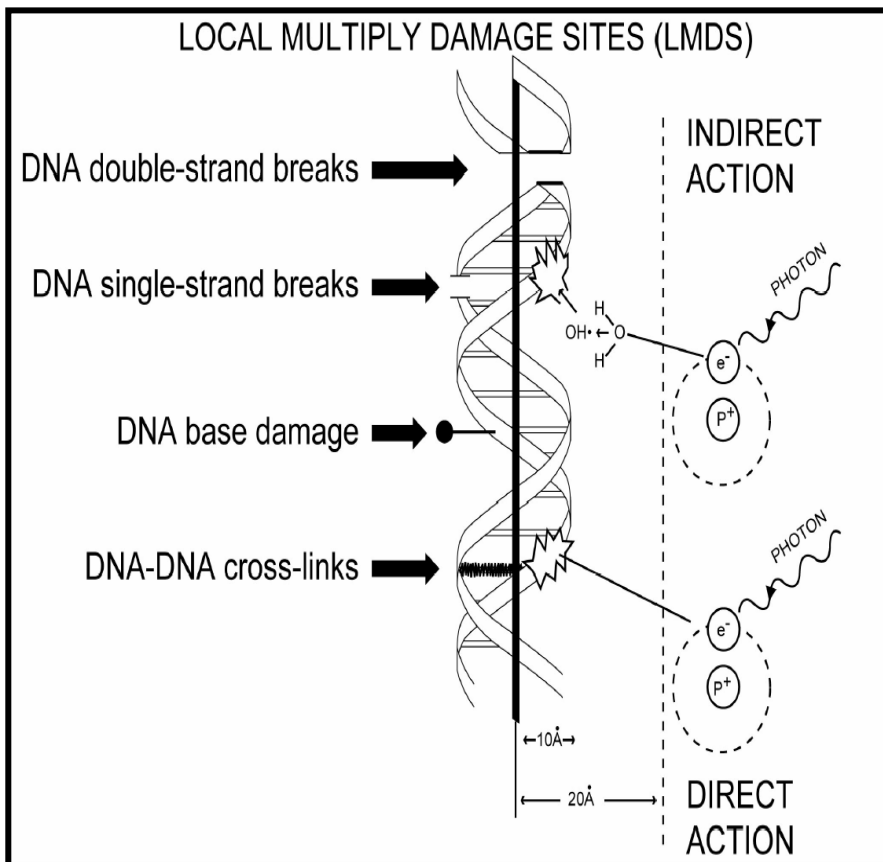
The Genetic Code: The Source of Diversity Between Individuals



However, the letters (bases) of the code can be scrambled or mutated in cancer cells and alter the cell's behaviour

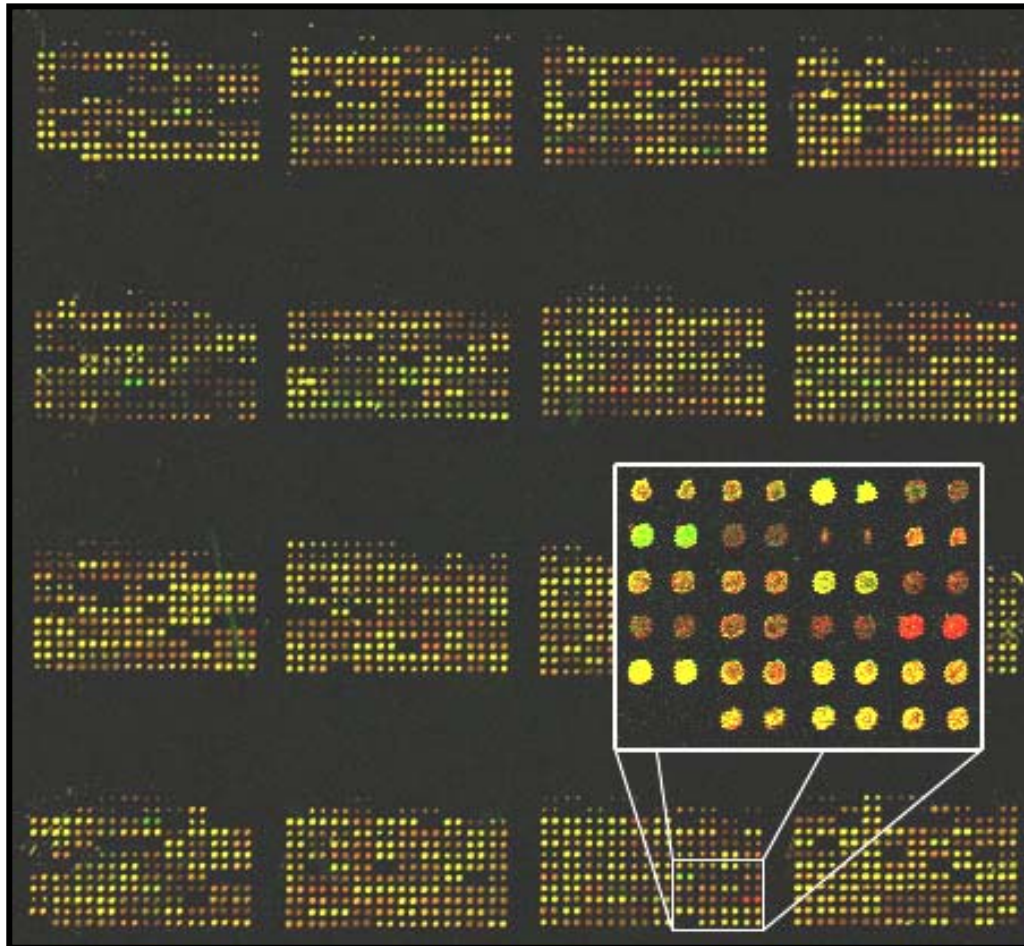


DNA Breaks: A Way To Kill Cancer Cells With Radiotherapy



Slide courtesy Dr. R. Bristow

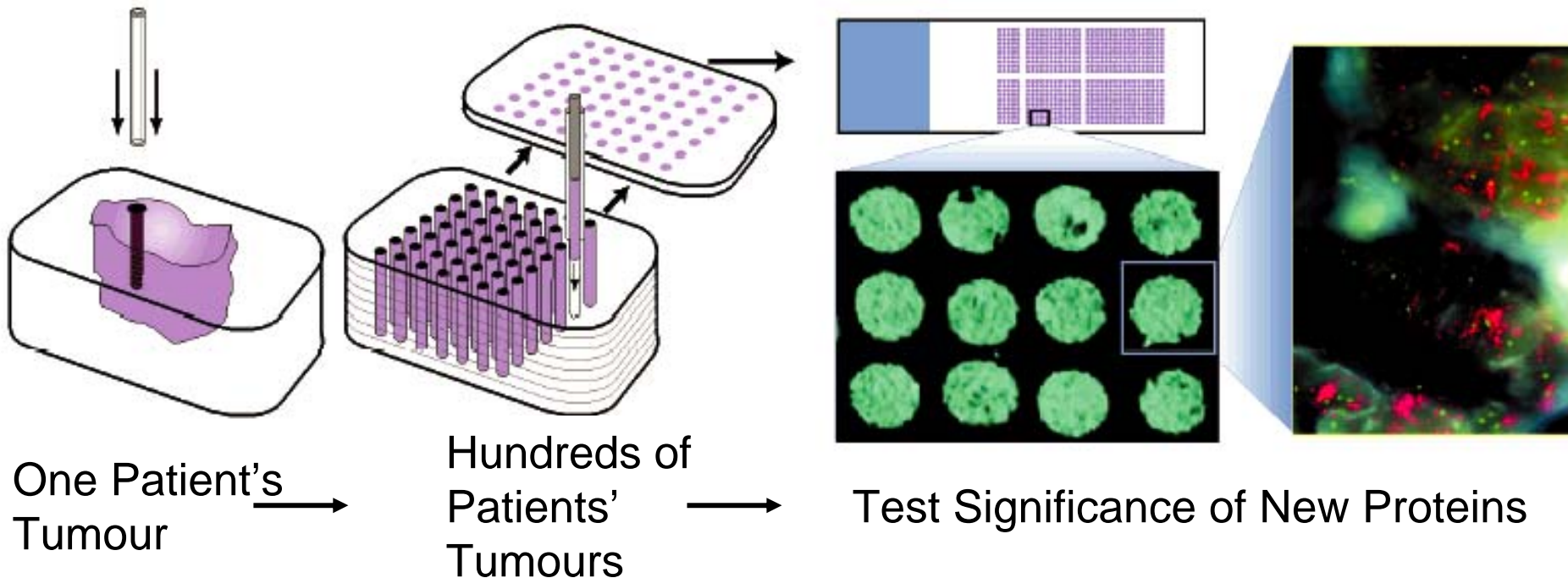
DNA Microarrays: Thousands of genes can be tested at once per patient! (Hepsin, PIM1, AMACR, MTA1)



Gives extra information beyond Gleason score and PSA-an individual signature!



Prostate Tissue Arrays: New Test for Proteins in Many Patients



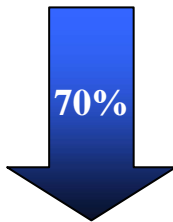
Slide courtesy Dr. R. Bristow



Prostate High Precision RT

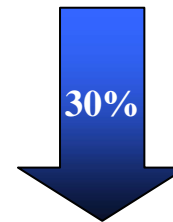
Clinical Impact of Individualized Biomarkers

Success Predictors



High-Dose, Conformal
Radiotherapy or
Brachytherapy

Failure Predictors



Send to surgery
OR
-Target hypoxia
-Target p53 /apoptosis
-Target metastases

The basis for the determination of a “molecular therapeutic ratio” for individual patients treated at PMH-UHN.

