Diagnosis and Management of Prostate Cancer

Rod Studd
Urologist
CCDHB
Urology Care Wellington

Summary

1. Diagnostic Workup

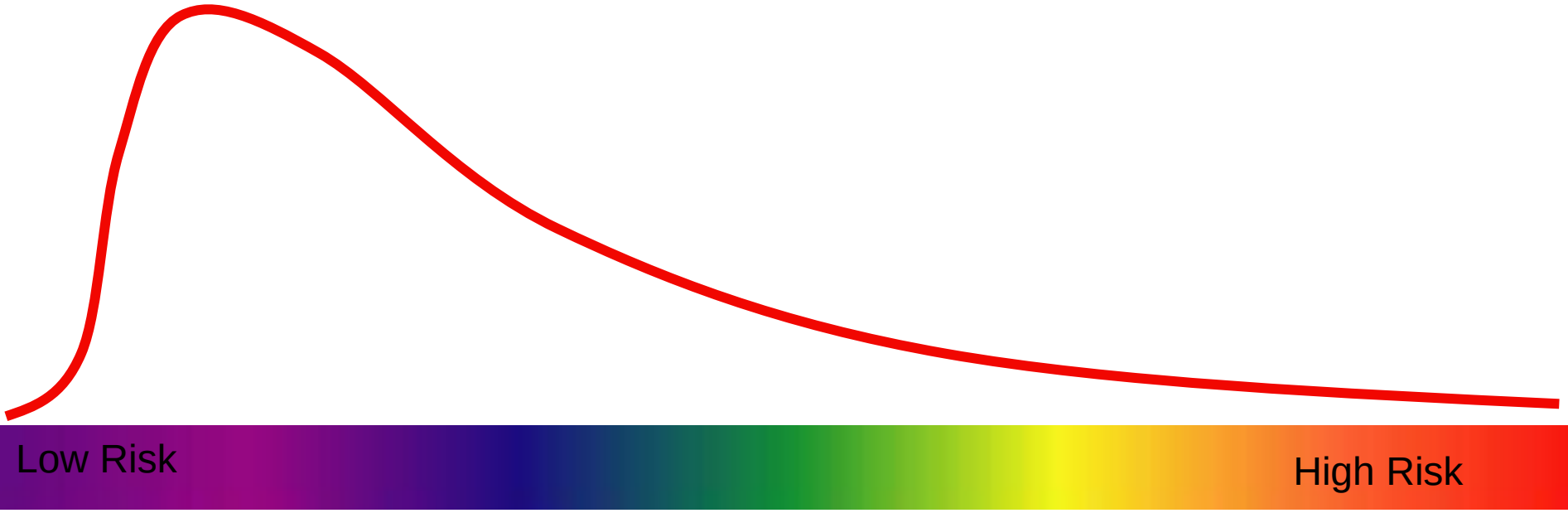
   pre-biopsy MRI, prostate biopsy techniques, minimizing biopsy risk, staging scans

2. Risk Adjusted Management
   - Watchful waiting
   - Active Surveillance
   - Surgical Management – the pro's and con's

   (Scott to cover primary radiotherapy, adjuvant and salvage radiotherapy)

Prostate Cancer,

a spectrum of disease



Most prostate cancers provide just a small threat to the man

Growing old is invariably fatal while prostate cancer is only sometimes so.

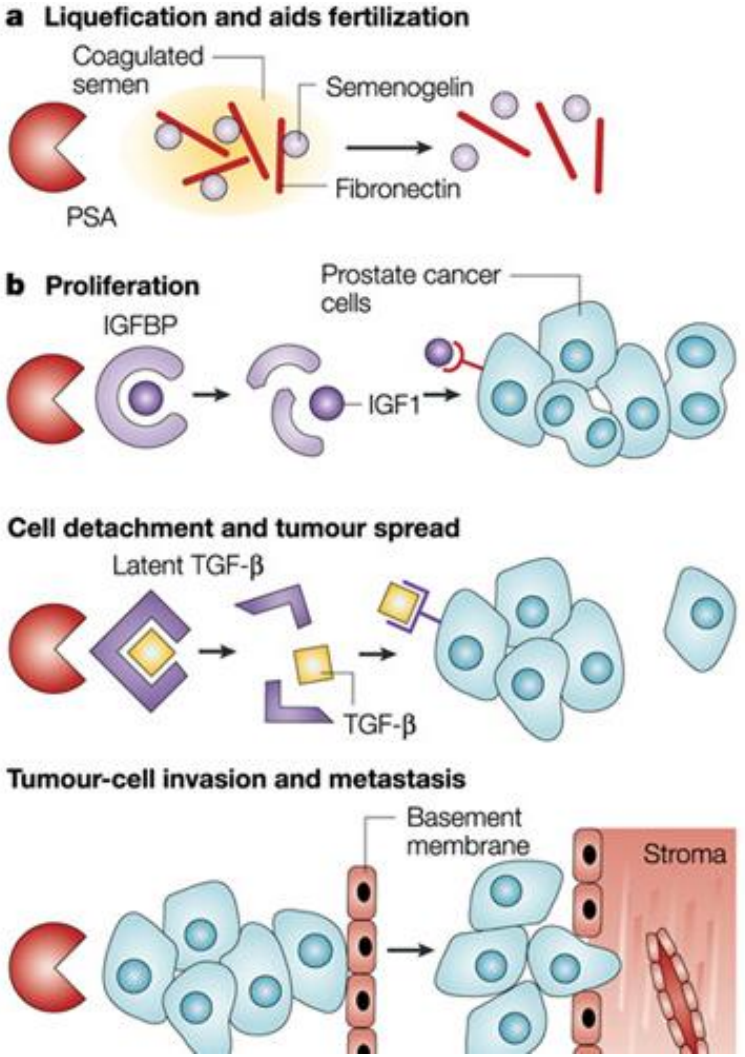
4 Rules of Thumb for Improving the Balance of Harm versus Benefit

1. Inform the man: Disease threat, Benefit and Risks of the Tests and the Treatment
2. Screen the right people
3. Biopsy the right people
4. Treat the right people

DIAGNOSTIC WORKUP

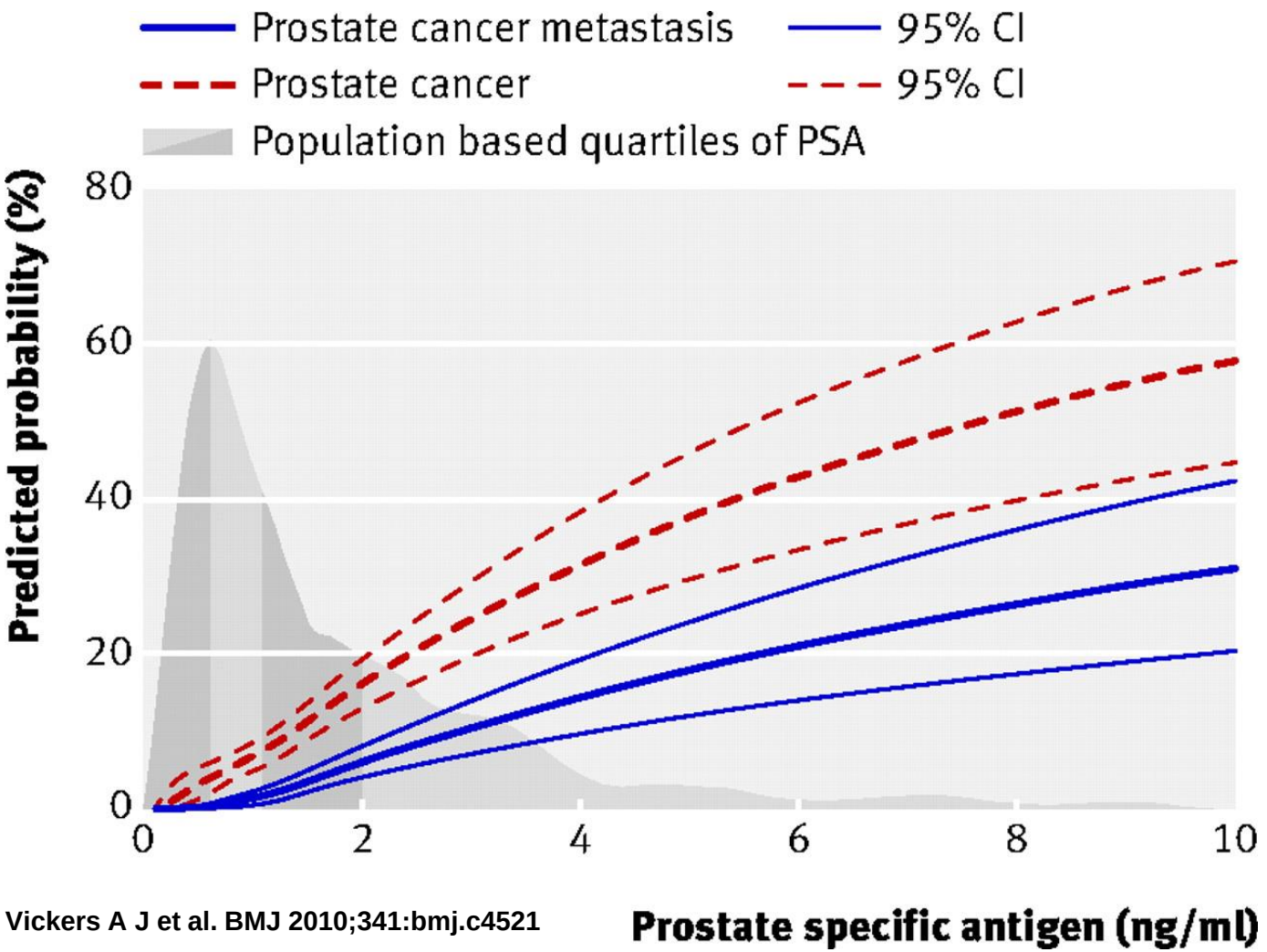
PSA

- A Serine protease enzyme
- Produced by epithelium of the prostate gland
- Liquefies the ejaculate
- Rises with prostate size, inflammation and cancer
- 5-7 year lead time in diagnosis of cancer
- Also has a role in cancer proliferation and metastasis



There is a direct relationship between PSA level and risk of prostate cancer

Fig 1 Lifetime risk of clinically diagnosed prostate cancer or prostate cancer metastasis.



Vickers A J et al. BMJ 2010;341:bmj.c4521

BMJ

The DRE

- Worth incorporating into your clinical evaluation as some benefits:
  - Allows assessment of prostate size
  - Presence of a nodule will lower your threshold for referral
  - There are some cancers – usually HIGH grade which do not produce much PSA. DRE may find these

However:

- Less sensitive than PSA
- The ERSPC did not use DRE, just PSA..
- Unpleasant!

What is the Trigger for Further Evaluation? Key Points

- PSA can be elevated for several reasons: physiologic variation often occurs - up to 20% of elevated values will return to baseline within 1 year – REPEAT THE TEST
- Consider age, prostate volume, nodularity and possibility of inflammation to determine need for biopsy – CHECK UTI HISTORY, DO MSU
- NO evidence for use of antibiotics to reduce PSA in assymptomatic men
- 3ng/mL was the trigger in the ERSPC

I generally use the age specific reference ranges:

- 40's: median 0.7ng/mL. 95th centile 2.5ng/mL
- 50's : median 0.9ng/mL. 95th centile 3.5ng/mL
- 60's: median 1.2ng/mL. 95th centile 4.5ng/mL
- 70's: median 1.5ng/mL. 95th centile 6.5ng/mL

Diagnostic Workup

- Assume now that the man is suitable for PSA screening, has agreed to it and has two elevated PSA levels…

- What is the next step?

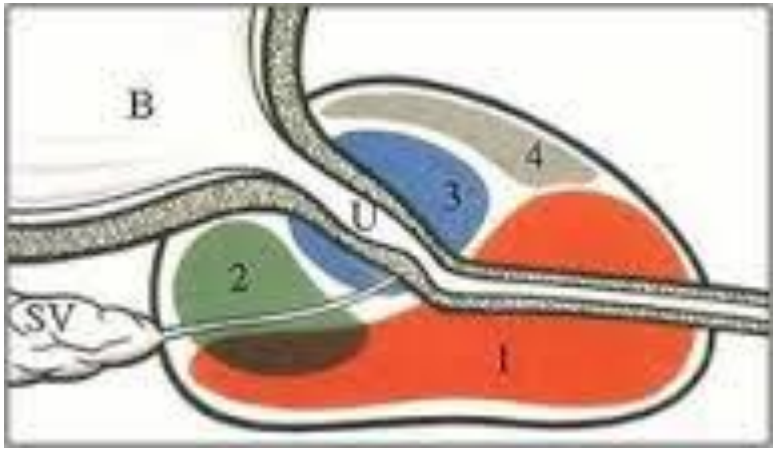
Biopsy or Multi-Parametric MRI scan?

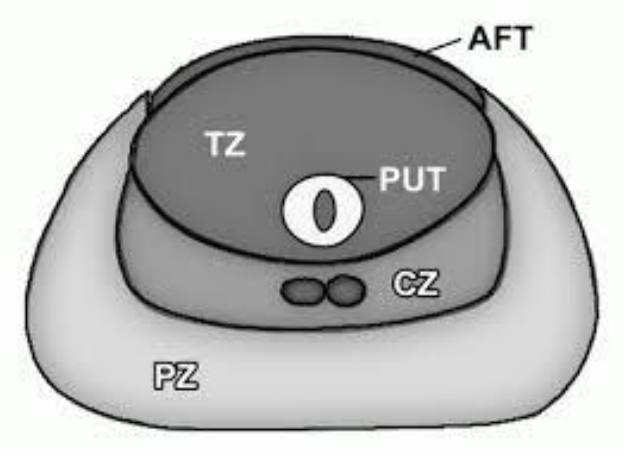
Biopsy

- Allows a definite diagnosis to be made & MRI cannot do this

But..

- invasive and has morbidity
- Usually ‘undirected’
- Anterior prostate relatively under-sampled with trans-rectal technique
- May detect insignificant cancers
- May miss significant cancers





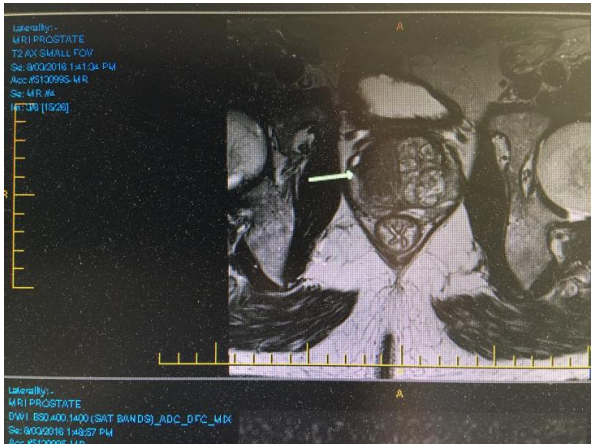
mpMRI

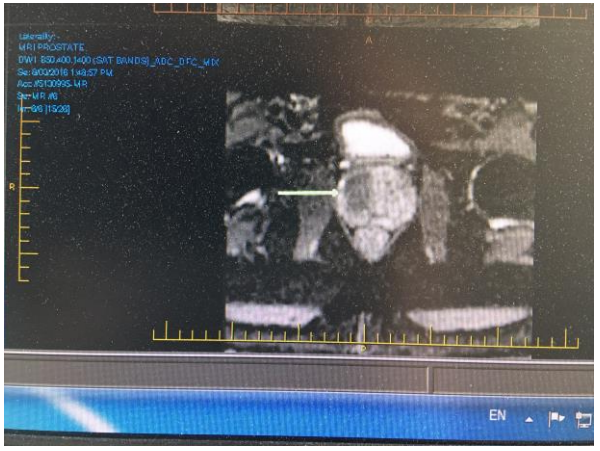
Combination of:

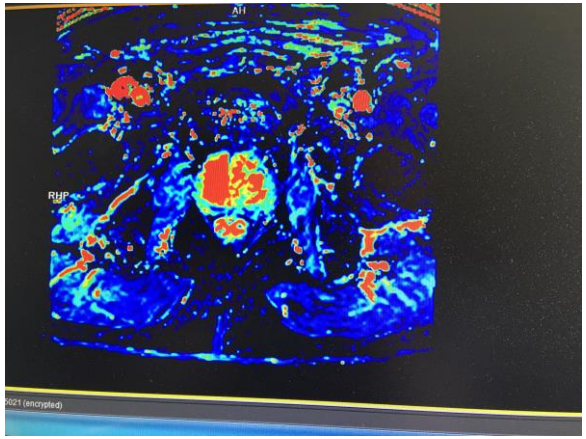
- High resolution T2 weighted images

And at least two functional MRI techniques:

- Diffusion weighted imaging (DWI)
- Dynamic contrast enhanced imaging (DCE)
- ADC maps







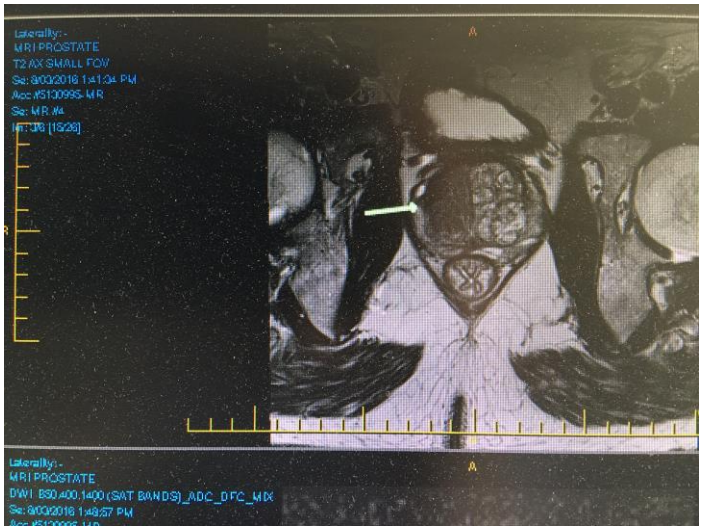
MRI Prostate

- High sensitivity for clinically significant disease
  - A negative MRI gives great confidence that we are not missing a life threatening cancer
- Low sensitivity for clinically insignificant disease
  - May therefore help reduce overtreatment
- Allows evaluation of the entire gland
- Potentially reduces the number of men needing biopsy by 50%
- An abnormality can be targeted by biopsy – usually transperineal which allows better targeting
- Reduces the diagnosis of low risk cancer by up to 90%
- I discuss this now with patients & suggest it to men with palpably normal glands & PSA elevation

MRI Abnormalities

PIRADS v2 reporting system 1-5 score

- 1. Very low (clinically significant cancer is highly unlikely to be present
- 2. Low (clinically sig cancer is unlikely to be present)
- 3. Intermediate (the presence of clinically significnt cancer is equivocal)
- 4. High (clinically significant cancer is likely to be present)
- 5. Very high (clinically significant cancer is highly likely to be present)

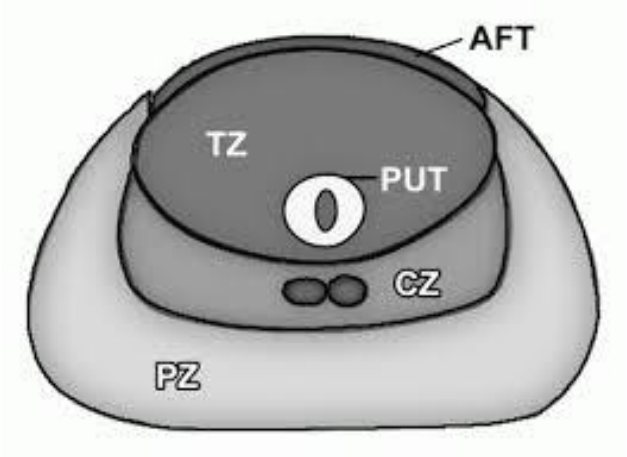


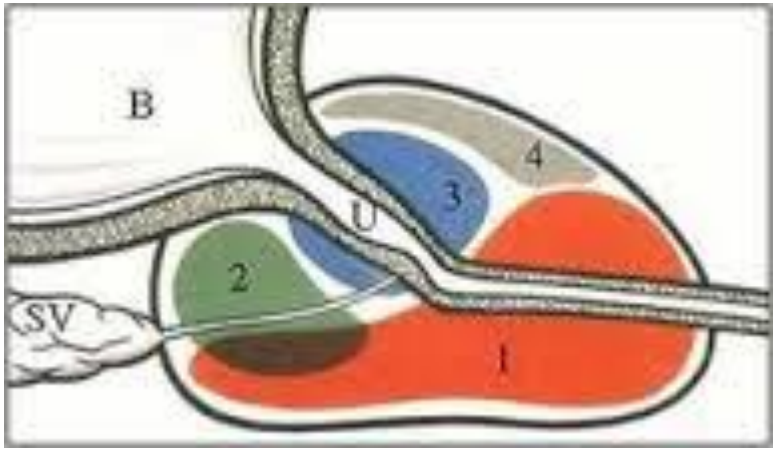
BIOPSY

Transrectal Biopsy

- The original and still the most prevalent technique
  - Quick & cheapest
  - No need for GA in >90%
- But..
  - Risk of sepsis
  - Under-sampling of anterior zone
  - Directed biopsies difficult

TRUS Biopsy Missed areas:





The Impact of Repeat Biopsies on Infectious Complications in Men with Prostate Cancer on Active Surveillance

Behfar Ehdaie,* Emily Vertosick,* Massimiliano Spaliviero,* Anna Giallo-Uvino,* Ying Taur,* Maryellen O'Sullivan,* Jennifer Livingston,* Pramod Sogani,* James Eastham,* Peter Scardino† and Karim Touijer*,‡

From the Urology Service, Sidney Kimmel Center for Prostate and Urologic Cancers (BE, MS, AG-U, MO, JL, PS, JE, PS, KT), Department of Epidemiology and Biostatistics (BE, EV), and Department of Medicine, Infectious Diseases Service (YT), Memorial Sloan-Kettering Cancer Center, and Department of Urology, Weill Medical College of Cornell University (PS, JE, PS, KT), New York, New York

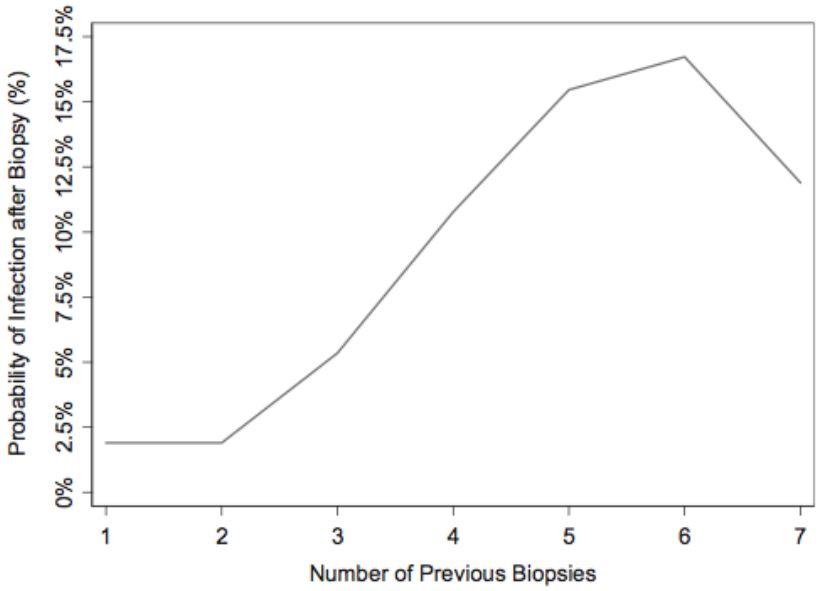


Figure 1. Risk of post-biopsy infection by number of previous biopsies.

fluoroquinolone prophylaxis

THE JOURNAL OF UROLOGY®© 2014 by AMERICAN UROLOGICAL ASSOCIATION EDUCATION AND RESEARCH, INC.http://dx.doi.org/10.1016/j.juro.2013.08.088 Vol. 191, 660-664,

REDUCING SEPSIS

ERTAPENEM FOR TRANSRECTAL ULTRASOUND GUIDED BIOPSY PROPHYLAXIS: INTERIM RESULTS

Dr Alice McLachlan

Capital and Coast DHB, Wellington, New Zealand

RESULTS

- August 2014 - July 2015
- 188 patients of required 326 ; 73% enrolment rate
- No cases of post TRUS biopsy sepsis

Antibiotic resistance pattern	PRE BIOPSY SWABS		POST BIOPSY SWABS
ESBL/AmpC production (From Oct 2014)	8/141	**5.7%**	Not assessed
Ciprofloxacin resistance (From June 2015)	**5/24**	**21%**	Not assessed
Carbapenem resistance	0/150	0%	**2/150 1.3%**

ERTAPENEM RESISTANT ORGANISMS

Two organisms *Enterobacter Cloacae*: reduced sensitivity to Ertapenem

- Minimally pathogenic bacterial species
- Resistance mechanism not easily spread
- Only affecting Ertapenem, not other carbapenems

The role of transperineal template prostate biopsies in prostate cancer diagnosis in biopsy naïve men with PSA less than 20 ng ml^{-1}

S Nafie, J K Mellon, J P Dormer and M A Khan

- 50 men with a benign DRE and PSA<20 had both a standard 12 core TRUS biopsy and a transperineal template biopsy

- Cancer detection Rate:

  TRUS 32%

  Transperineal 60%

Prostate Cancer and Prostatic Diseases **17**, 170-173 (June 2014

TRUS Versus Transperineal

TRUS

- The standard approach
- Office procedure
- X False negatives
- X Underestimation of Gleason score in 25%
- X Increasing infection

Transperineal Template

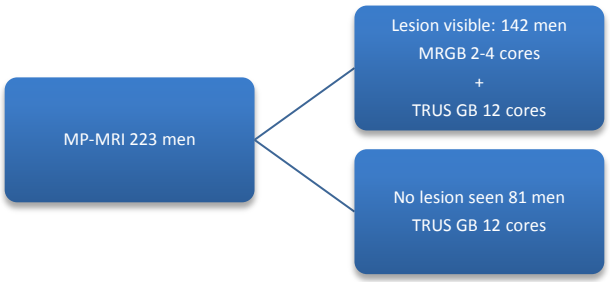
- Better access to entire gland especially anterior
- Many cores can be obtained
- Higher initial and repeat biopsy rates of cancer detection
- Reduced risk of underestimating disease volume and grade
- X GA
- X Cost
- X Equipment
- X Time
- X Retention

The Future is Directed Biopsy

- Techniques vary from:
  - ‘Cognitive’ guidance
  - MRI-USS fusion
  - MRI directed biopsy
- Practically in NZ
  - Transperineal biopsy using the brachytherapy set-up allows good ‘cognitive’ sampling

Prospective Study of Diagnostic Accuracy Comparing Prostate Cancer Detection by Transrectal Ultrasound–Guided Biopsy Versus Magnetic Resonance (MR) Imaging with Subsequent MR-guided Biopsy in Men Without Previous Prostate Biopsies

Morgan R. Pokorny[a], Maarten de Rooij[b, c], Earl Duncan[d], Fritz H. Schröder[e], Robert Parkinson[f], Jelle O. Barentsz[b], Leslie C. Thompson[a, d],



- MRGB Pathway Could:
  - **Reduce need for biopsy by 51%**
  - **Decreased diagnosis of LR CaP by 89.4%**
  - **Increased detection of intermediate/high grade disease by 17.7%**
  - NPV of TRUSGB for int/HR disease: 71.9%
  - **NPV of MRGB for int/HR disease 96.9%**

European Urology

Volume 66, Issue 1, July 2014, Pages 22–29

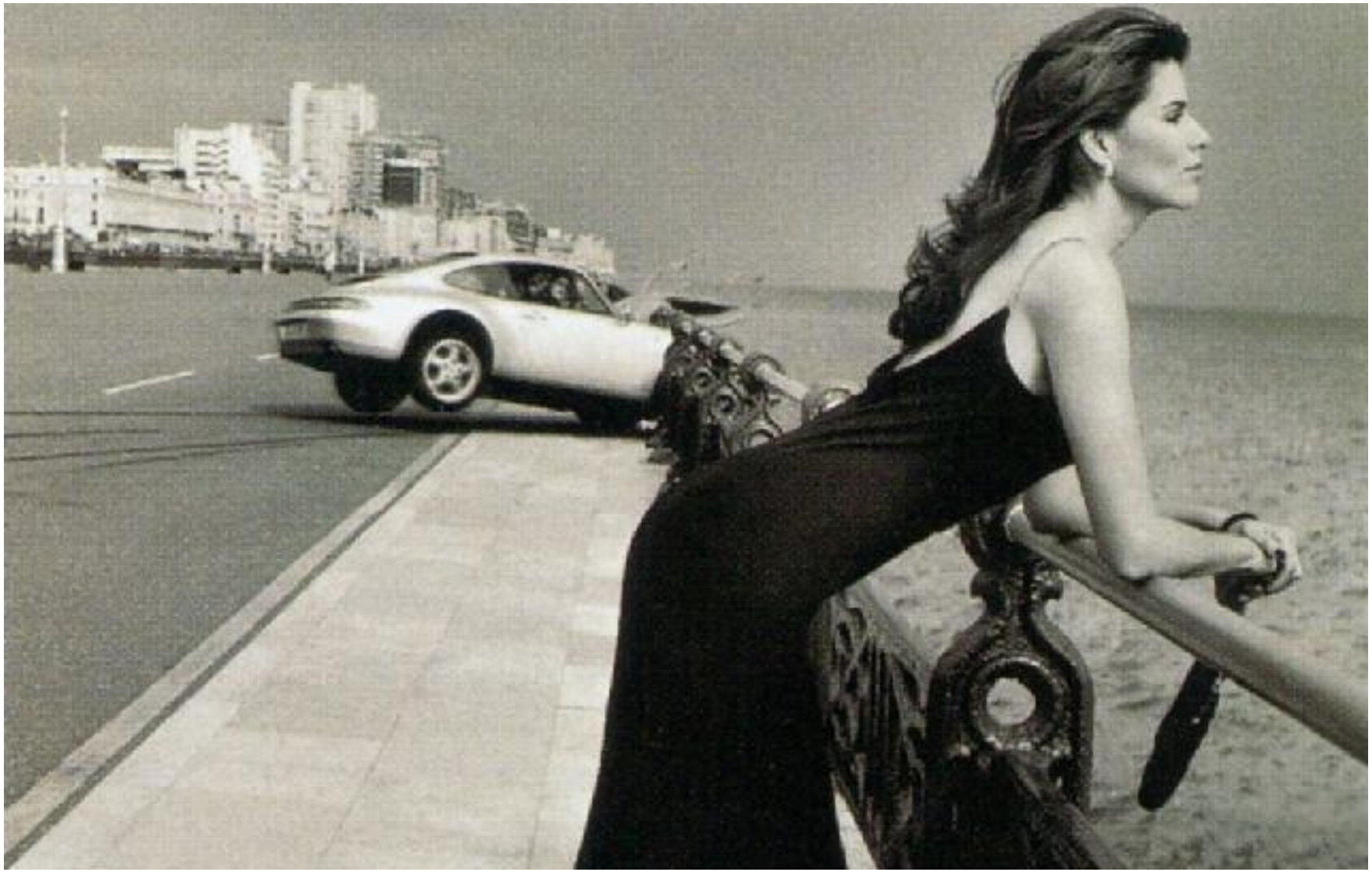
STAGING DISEASE

- Low Risk Disease: Gleason 6, PSA <10, Clinical Stage T1c, T2: No MRI or bone scan needed
- High Risk Disease: Gleason>7 or PSA>20 or clinical stage T3: MRI and bone scan
- Intermediate Risk Disease: Gleason 7 or PSA 10-20 or clinical stage T2b: selective use of MRI and bone scan for higher volume disease

Risk Adjusted Management of Prostate Cancer

MEANS MATCHING DISEASE THREAT TO MANAGEMENT

As we all know, prostate cancer is often slow growing and is *Not The Only Cause Of Death In Men*



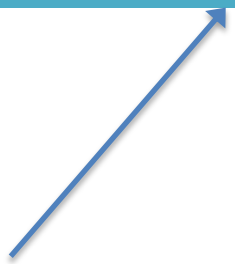
Impact of Co-morbidity on Mortality for T1c CaP if aged 66-74

Gleason	Co-Morbid	5 yr PCSM(%)	10 yr PCSM (%)	5 yr OM (%)	10 yr OM (%)
5-7	0	1.6	4.5	11.7	28.5
	1	1.1	2.0	25.3	50.5
	>1	4.3	5.3	42.5	53.1
8-10	0	13.6	25.7	26.4	55.0
	1	11.6	20.2	30.7	52.0
	>1	9.6	13.7	52.0	64.3

Even for aggressive CaP, twice as likely to die from other cause

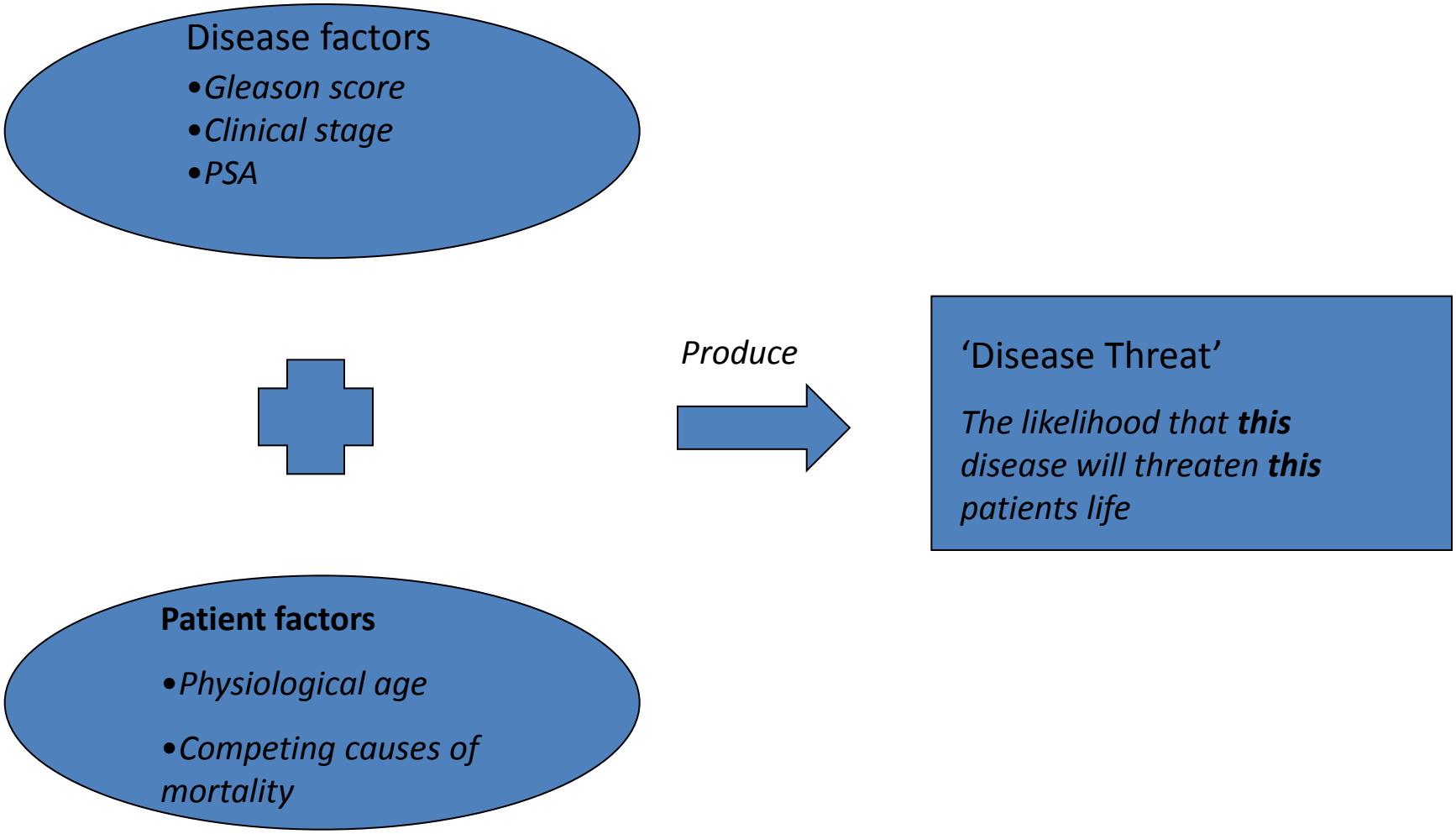
Impact of Co-morbidity on Mortality for T1c CaP if aged 66-74

Gleason	Co-Morbid	5 yr PCSM(%)	10 yr PCSM (%)	5 yr OM (%)	10 yr OM (%)
5-7	0	1.6	4.5	11.7	28.5
	1	1.1	2.0	25.3	50.5
	>1	4.3	5.3	42.5	53.1
8-10	0	13.6	25.7	26.4	55.0
	1	11.6	20.2	30.7	52.0
	>1	9.6	13.7	52.0	64.3



If co-morbidity 5 times as likely to die of other causes

We need to convey to the patient the threat that their disease is to them



There are usually three Management Options

1. Surveillance with a view to cure upon progression
(= Active surveillance)

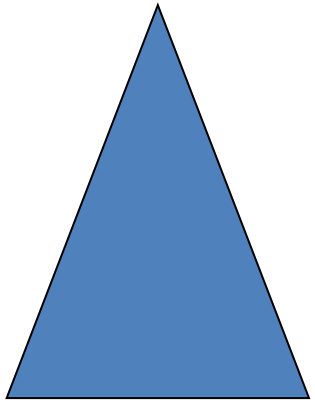
2. Surveillance with a view to androgen deprivation upon progression
(= Watchful Waiting)

2. Curative therapies
(= Surgery or Radiotherapy)

Whether to Pursue Cure?

Risk posed by disease and potential for cure

Potential Morbidity of Curative Therapy



ESTABLISHING DISEASE THREAT

What is the magnitude of the threat in

LOWER RISK DISEASE?

data from Sweden…

Outcomes in Localized Prostate Cancer: National Prostate Cancer Register of Sweden Follow-up Study

Pär Stattin, Erik Holmberg, Jan-Erik Johansson, Lars Holmberg, Jan Adolfsson, Jonas Hugosson; on behalf of the National Prostate Cancer Register (NPCR) of Sweden

Manuscript received October 26, 2009; revised April 6, 2010; accepted April 9, 2010. JNCI Vol. 102, Issue 13 | July 7, 2010

6849 men <70yrs with low to intermediate risk prostate cancer identified & linked to cause of death register

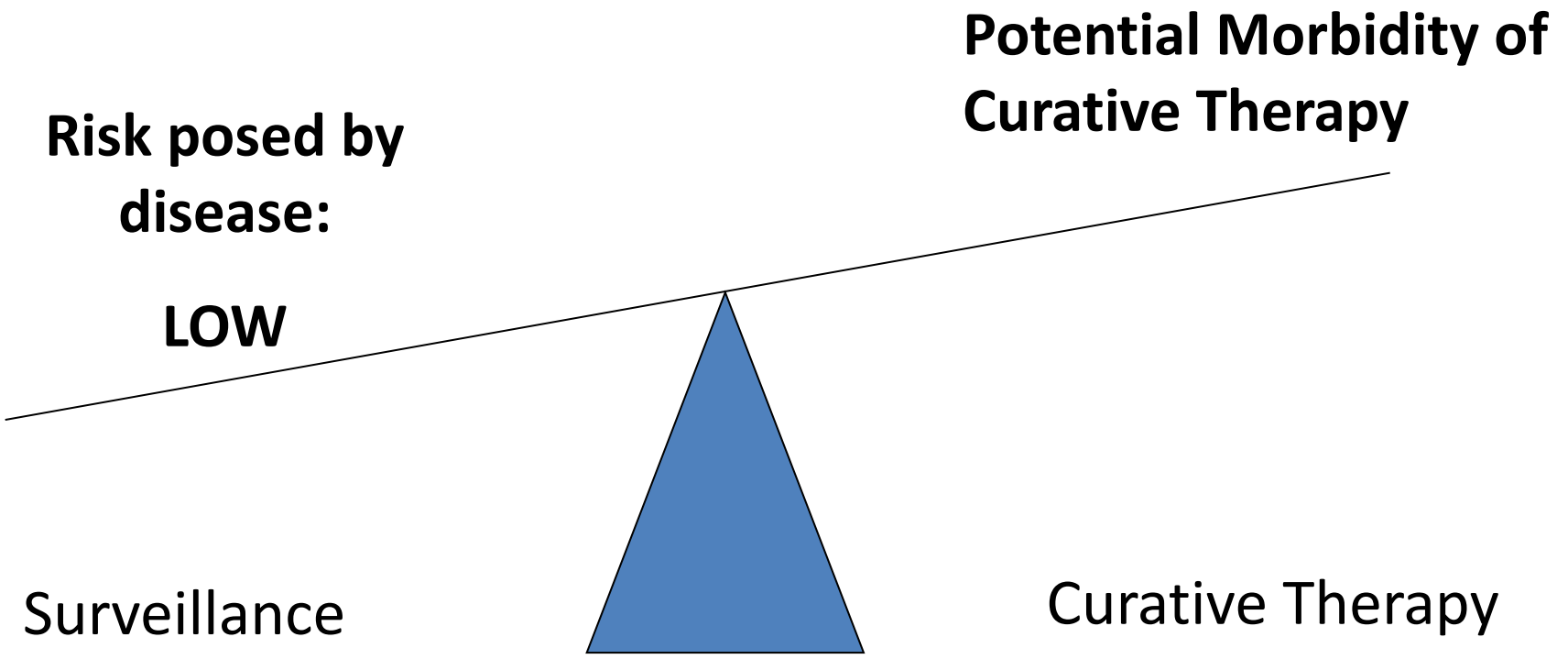
70% (4828) had curative therapy
30% (2021)began active surveillance

10 year risk of dying of prostate cancer in low to intermediate risk disease:

Surveillance:	***3.6% (for low risk this was 2.4%)***
Curative therapy:	***2.7%***

10 year risk of dying of competing causes on active surveillance 19.2%

Low Risk Disease



Active Surveillance

REVIEW & UPDATE

What's new in Active Surveillance?

1. Greater recognition of overtreatment problem & wider acceptance of surveillance
2. Better understanding of occult high grade disease

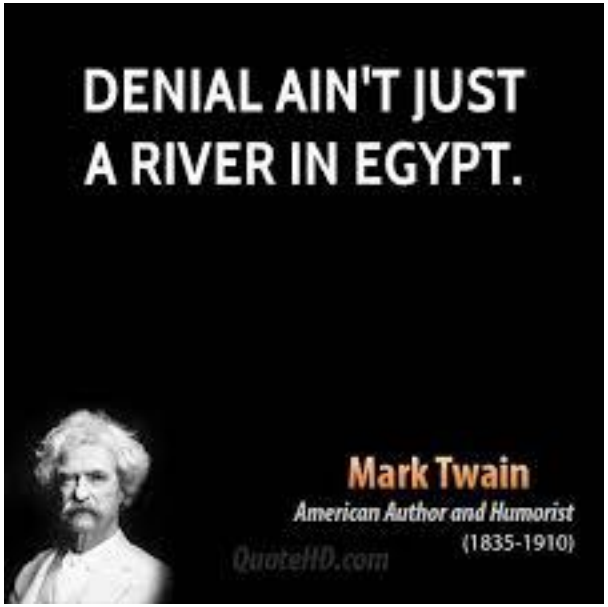
3. Better understanding of the flaws of PSA dynamics
4. Increasing data on multi-parametric MRI
5. Longer follow up of surveillance cohorts

US Preventive Services Task Force summary on PSA screening

- …small to no reduction in 10yr prostate cancer specific mortality: harms related to false-positive test results, subsequent evaluation, and therapy, including over-diagnosis and over-treatment
- The Task Force recommends AGAINST PSA-based screening….a Grade D recommendation

Response to USPSTF…

Head in sand, or reduce over-diagnosis & overtreatment



Over-diagnosis & Over-treatment

- A huge problem in modern medicine
- Mainly conditions where early detection is promoted
  - Breast cancer, thyroid cancer, lung cancer
- Clinically insignificant cancers found which pose no threat

Three factors promote over-diagnosis of cancer:

- Existence of a silent disease reservoir
- Activities leading to its detection
- Long natural history and hence limited cancer specific mortality

Prostate cancer fulfills these criteria!

Review Article JNCI 2010

Existence of a silent disease reservoir

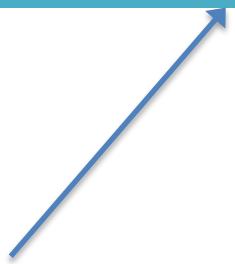
- Prevalence of CaP on Autopsy:

Age Range	
20-29	11%
30-39	31%
40-49	38%
50-59	44%
60-69	68%
70-79	68%

Powell J Urol 183 1792-6, 2010

Long natural history and hence limited cancer specific mortality

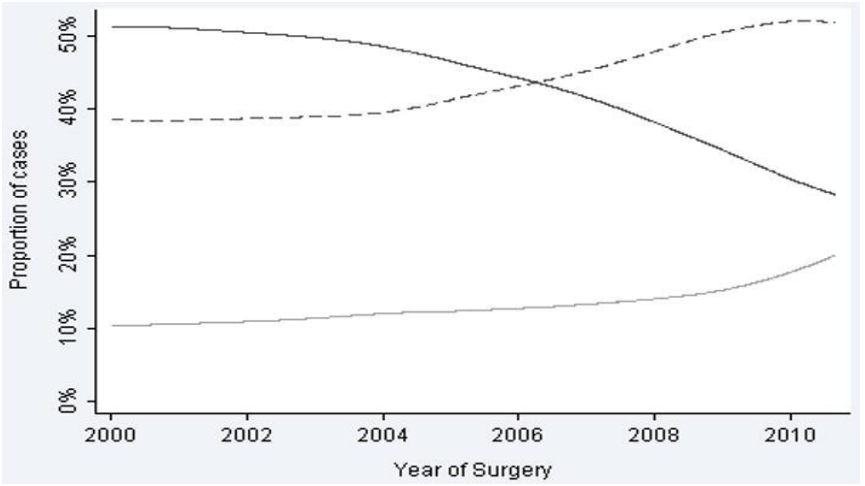
Gleason	Co-Morbid	5 yr PCSM(%)	10 yr PCSM (%)	5 yr OM (%)	10 yr OM (%)
5-7	0	1.6	4.5	11.7	28.5
	1	1.1	2.0	25.3	50.5
	>1	4.3	5.3	42.5	53.1
8-10	0	13.6	25.7	26.4	55.0
	1	11.6	20.2	30.7	52.0
	>1	9.6	13.7	52.0	64.3

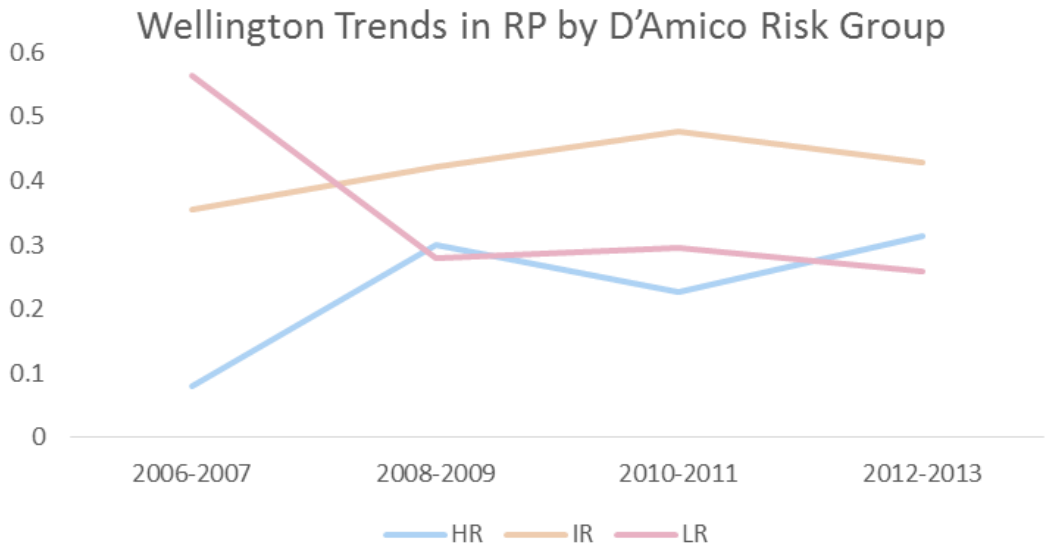


If co-morbidity 5 times as likely to die of other causes

Are we changing management?

. Trends in local practice match those seen internationally as illustrated by MSKCC data (solid line LR, dotted IR, light grey HR).





Localised prostate cancer management in Wellington - an evolving paradigm

Matthew Page, Daniel Marshall, Rod Studd

Wellington Regional Hospital, Wellington, NZ. Wakefield Private Hospital, Wellington, NZ. Southern Cross Private Hospital, Wellington NZ.

Rise of Active Surveillance in WGTN

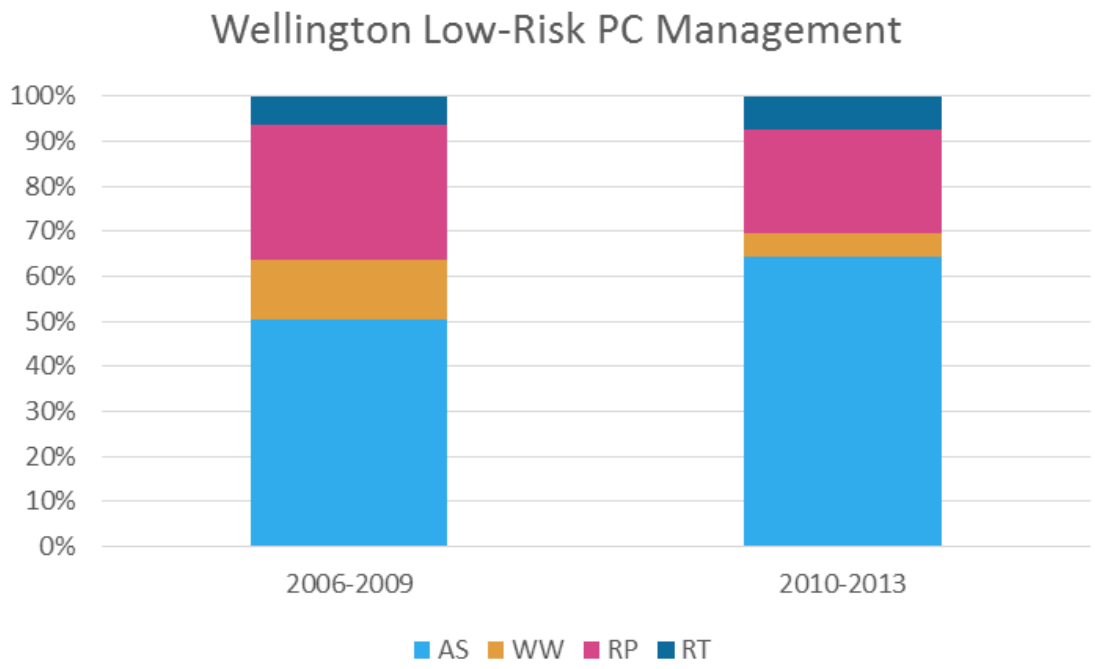


Fig. 2. Increase in AS (p<0.05) for low-risk disease with a corresponding decrease in surgical management of low-risk disease.

Localised prostate cancer management in Wellington - an evolving paradigm

Matthew Page, Daniel Marshall, Rod Studd

Wellington Regional Hospital, Wellington, NZ. Wakefield Private Hospital, Wellington, NZ. Southern Cross Private Hospital, Wellington NZ.

Active Surveillance Involves:

- Identification of men at low risk of disease progression

(Gleason <7, PSA <10, T2a or less, <3 cores positive, <50% of any one core +ve)

- Regular PSA, repeat biopsies
- Intervention if grade progression, stage progression or PSADT<3 yrs
- Up to 30% will eventually come to curative treatment

Follow-up

- PSA 4 monthly, annual review
- Biopsy 12 months after enrolment, then every 3-5 years. Stop at age 70 (convert to WW)
- Consider a mpMRI prior to first re-biopsy or if concerns about PSA increase or DRE changes

How should we define progression?

- Most use upgrade on re-biopsy
- PSA has limitations – lack of specificity

TABLE II. Progression Criteria Used in Active Surveillance

Publication	Gleason score[a]	Positive cores	Percentage cancer involvement per single core	Percentage positive biopsy cores	PSAdt (years)	PSAv (ng/ml/year)	cT[a]
Dall'Era [16]	Increase					>0.75	
Ercole [17]	Progression	Increase	Increase				Change
Klotz [18]	≥4 + 3				<3[b]		Increase cT
Soloway [19]	(Grade) >3	>2					
Tosoian [20]	>6	>2	>50				
Ischia [21]	Upgrade				[c]		Upstage
Bul [22][d]							
Godtman [23]	Upgrade				[c]		Upstage
Thomsen [24]	≥3 + 4	>3[e]			<3/5[f]		Increase cT
Selvadurai [25]	≥4 + 3			>50		>1	

Updated AS Outcomes

Active Surveillance for Clinically Localized Prostate Cancer—A Systematic Review

FREDERIK B. THOMSEN, MD,[1]* KLAUS BRASSO, MD, PhD,[1] LAURENCE H. KLOTZ, MD, FRCS(C),[2]
M. ANDREAS RØDER, MD, PhD,[1] KASPER D. BERG, MD,[1] AND PETER IVERSEN, MD[1]
[1]*Copenhagen Prostate Cancer Center, Department of Urology, Rigshospitalet, University of Copenhagen, Denmark*
[2]*Division of Urology, Department of Surgery, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada*

- 3550 patients
- Discontinuing AS:
  - At 5 years 33%
  - At ten years 55%
- Survival:
  - 96%-100% at ten years
  - Toronto series – CaP mortality from 3% at ten years to 8% at 15 years

J. Surg. Oncol. 2014;109:830–835

The Future of Active Surveillance

- Screening will be image/risk factor based, hence many fewer biopsies and fewer clinically insignificant cancers
- Avoid ‘cancer’ diagnosis in low risk patients
- In low risk disease: Imaging/biomarker to identify aggressive disease at diagnosis
  - Must be affordable, widely available and reproducible

CURATIVE THERAPY

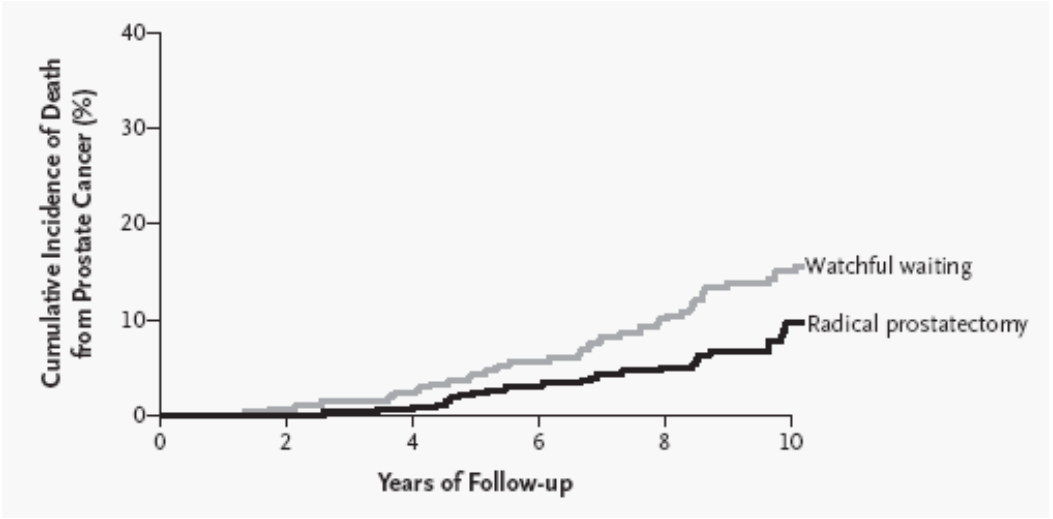
Risk of Mortality From Prostate Cancer Among Men in a Randomized Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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., and Jan-Erik Johansson, M.D., Ph.D., for the Scandinavian Prostate Cancer Group Study No. 4*



695 men randomised to surgery or delayed endocrine intervention

- 76% T2
- 11% had PSA detected disease

After median FU of 10.8yrs,

- 39% of men had died
- **7% absolute difference in survival for surgical group (14.4% vs 8.6%)**

The NEW ENGLAND JOURNAL of MEDICINE

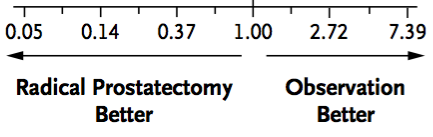
ESTABLISHED IN 1812 JULY 19, 2012 VOL. 367 NO. 3

Radical Prostatectomy versus Observation for Localized Prostate Cancer

Timothy J. Wilt, M.D., M.P.H., Michael K. Brawer, M.D., Karen M. Jones, M.S., Michael J. Barry, M.D.,

B **Death from Prostate Cancer**

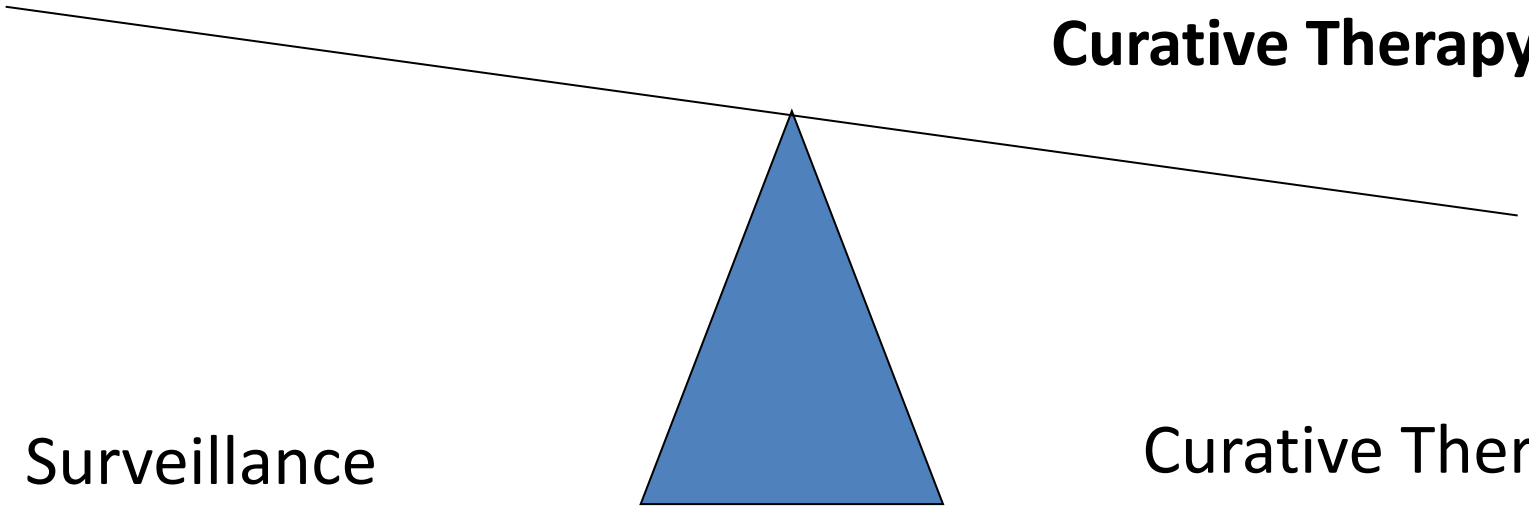
Subgroup	Observation	Radical Prostatectomy	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/total no.			
Overall	31/367	21/364	0.63 (0.36–1.09)	
Age				0.63
<65 yr	12/131	6/122	0.52 (0.20–1.39)	
≥65 yr	19/236	15/242	0.68 (0.34–1.33)	
Race				0.76
White	22/220	15/232	0.57 (0.30–1.10)	
Black	7/121	5/111	0.80 (0.25–2.54)	
Other	2/26	1/21	0.56 (0.05–6.17)	
Charlson score				0.63
0	19/220	14/224	0.69 (0.34–1.37)	
≥1	12/147	7/140	0.54 (0.21–1.38)	
Performance score				0.57
0	25/310	18/312	0.67 (0.37–1.23)	
1–4	6/57	3/52	0.41 (0.10–1.71)	
PSA				0.11
≤10	15/241	14/238	0.92 (0.44–1.91)	
>10	16/125	7/126	0.36 (0.15–0.89)	
Risk				0.11
Low	4/148	6/148	1.48 (0.42–5.24)	
Intermediate	13/120	6/129	0.50 (0.21–1.21)	
High	14/80	7/77	0.40 (0.16–1.00)	
Gleason score				0.57
<7	15/261	11/254	0.68 (0.31–1.49)	
≥7	15/86	10/98	0.51 (0.23–1.14)	



Higher Risk Disease

Risk posed by disease -HIGH'er

Potential Morbidity of Curative Therapy



Surveillance

Curative Therapy

If Treatment is Reasonable then How do We Decide Upon which Treatment?

- Disease Factors – local tumour stage – very advanced may indicate radiation preferable
- Patient Factors – personal preference, experience of friends, age, prostate size, urinary symptoms, colitis, anticoagulation
- Treatment Modality Factors - the likelihood of successful treatment and side effects.
- These are the issues discussed with the urologist and radiation oncologist

Do cancer cure rates vary between treatments?

- Numerous studies
- Each with their own flaws
- Level 1 evidence-free zone!
- Accumulating evidence of superiority of surgery - particularly for higher risk disease
- Recent meta-analysis of 19 studies (118000 patients) adjusted for patient and tumour factors favours surgery
- PROTECT trial: RCT comparing surgery, RT and Active surveillance has finished recruiting - report due 2016

Surgery– the good and the ugly!

Good

- Most accurate prognosis from surgical pathology
- Early detection of disease persistence so early delivery of salvage therapy possible
- Possible survival advantage but Level 1 data pending…

Ugly

- Disruptive & painful
- Early incontinence common
- Adverse pathology may lead to a requirement for radiotherapy

Radiotherapy – the good and the ugly!

Good

- Avoids a painful wound and catheter
- Minimally disruptive - Continue working through the treatment
- Easy delivery in men who may not be good surgical candidates
- Usually better early erectile function

Ugly

- Assessment of response to therapy delayed – this delays salvage
- Salvage therapy difficult
- Bowel morbidity
- Increased second cancer risk – Rectum and Bladder
- Severe toxicity rare but devastating & repair may not be possible

Summary

1. Diagnostic Workup

   pre-biopsy MRI, prostate biopsy techniques, minimizing biopsy risk, staging scans

2. Risk Adjusted Management
   - Watchful waiting
   - Active Surveillance
   - Surgical Management