
**THE LANCET
ASIA MEDICAL FORUM 2007**

**Early diagnosis of prostate cancer
without unnecessary treatment in
those who will not benefit**

2007 Perspective

**A new blood marker that is negative
when PC is absent!**

From Johns Hopkins:

EPCA-2

Will this be the end of PSA?

No, PSA will remain a useful risk assessment and monitoring tool

Presently our assessment of lifetime risk of PC development is limited:

1. Being a man!
2. Having a family history
3. Various racial / dietary factors

Now there are helpful data from the longitudinal studies:

Single PSA estimates in the 40s and 50s may identify:

~ 30% of males with **less than half** average overall life time risk

~10% of males with **more than double** average overall life time risk

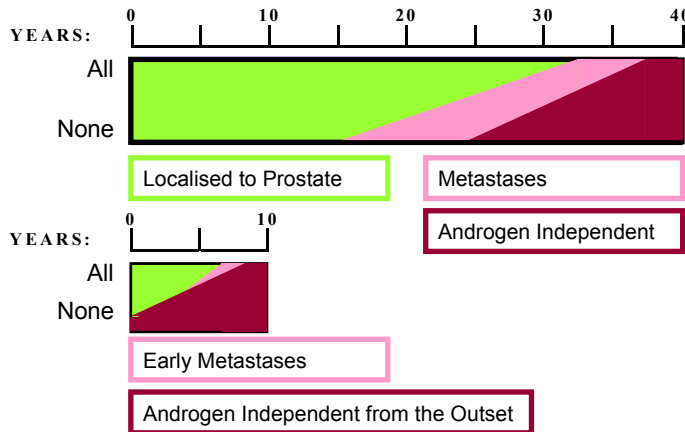
Age Range (median)	Fang et al (2001)				Lilja et al (2007)	
	40 – 50 yrs 43		50 – 60 yrs 53		44 – 50 yrs	
	PSA	RR	PSA	RR	PSA	RR
	<0.3	1	<0.4	1	<0.5	1
	0.3-0.6	3.4	0.4-0.7	2.0	0.5-1	2.5
	0.6-0.9	7.9	0.7-1.4	4.9	1-2	7
	>0.9	7	>1.4	5.5	2-3	19
					>3	39

Fang et al, Urol 58: 411-416, 2001
Lilja et al, J Clin Oncol 25: 431-436, 2007

See also:
Antenor et al, J Urol 172 : 90-93, 2004
Gann et al, JAMA 25: 273-274, 1995

.... More data will come from the screening trials

... together with clinical and autopsy data a better perspective of the natural history of PC can be visualised



... compatible with the stem cell concept of PC growth
e.g. Signoretti and Loda, *Semin Cancer Biol* 17: 219-224, 2007,
Lam and Reiter, *Urol Oncol* 24 : 131-140, 2006

... length of natural history may be deducible from repeated PSA measures

Screening produces a large stage shift...

ERSPC trial data:

	Goteborg		Rotterdam	
	Subjects: 20,000 (2 year interval)		Subjects: 42,400 (4 year interval)	
	Year 0	Year 2	Year 0	Year 4
Tx	0%	→ 1.8%	-	-
T1	60%	→ 74%	35.4%	→ 59%
T2	33%	→ 22.5%	46%	→ 37.6%
T3-4	6.9%	→ 1.8%	18.7%	→ 3.5%
N1	1.4%	→ 0%	-	-
M1	0%	→ 1%	-	-

Hugosson et al, *J Urol* 169: 1720-1728, 2003
Ingrid et al, *Urol* 68: 615-620, 2006

... it reduces metastases (?)

ERSPC trial data: Goteborg

- An absolute reduction in metastases in the screening arm of 48.9%
- Balanced by increased risk of PC diagnoses of 1.8 times

	Screening arm	(Difference)	Control Arm	
T1,2	765	(+395)	370	
T3,4	36	(-24)	60	
TX	10	(-2)	12	
N0	309	(+159)	150	
NI	10	(-4)	14	
NX	491	(+213)	278	
M0	235	(+69)	166	
MI	20	(-17)	37	
MX	555	(+316)	239	
PSA >100	14	(-23)	37	
Total PCs	810	(+368)	442	
MI ± PSA>100	24	(-25)	47	(p= 0.0084)

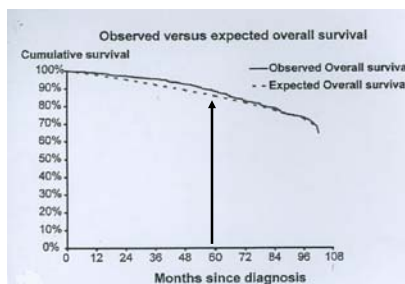
Aus et al Eur Urol 51 : 659-664, 2007

... it improves survival (?)

To demonstrate an improvement in overall survival – the trial(s) must be highly powered.

For example: in Australia only 4% of male deaths are due to PC

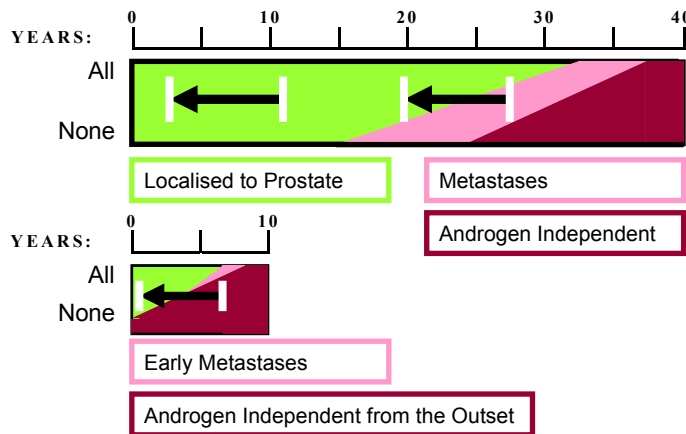
ERSPC trial data: Rotterdam



Overall survival is significantly improved in the screening arm of the trial when compared with a non-screened “control” population remote from Rotterdam (in the first 5 years of follow up)

de Vries et al Eur. Urol 51 : 366-374, 2007

Lead time to diagnosis produced by screening is between 6 and 12 years



... not all patient subgroups will benefit

... likely benefits to be derived from emerging PSA risk factor and screening data

1. More efficient population based screening programs with screening intervals based on risk
2. A basis for **rational** opportunist screening practices

The problem posed by the diagnosis of "harmless" PC will be significantly reduced.

If the promise shown by EPCA2 is realised:

The problem of unnecessary biopsy will all but disappear!

... however the diagnosis of sizeable numbers of "harmless" cancers is inevitable

... the development of Active Surveillance Clinics is therefore welcome

Goals

1. Make sure that “harmless” cancers remain untreated (and therefore truly harmless) for as long as possible.
2. Make sure that the cancers that do progress receive curative treatment while it is still curative.

Klotz L, J Clin Oncol, 23: 8165-8169, 2005

Parker C, Lancet Oncol, 5:101-106, 2004

... but can harmless cancers be identified?

- T1, 2a
- Gleason score <7
- One or two biopsies positive only
- PSA <10

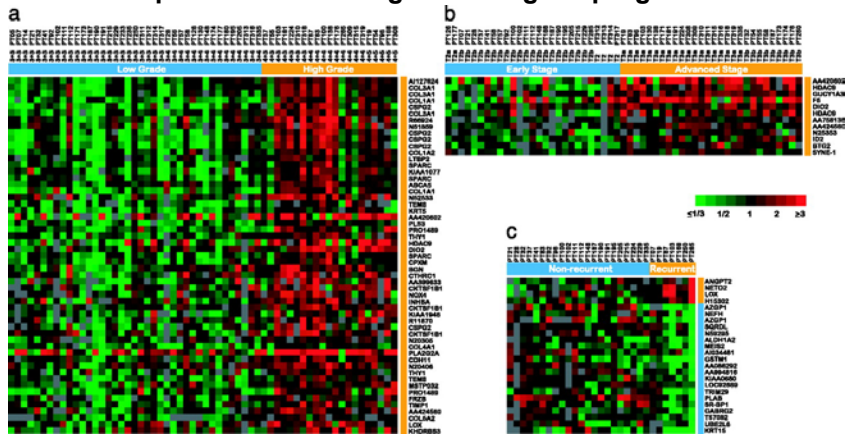
Further assistance will come from screening data
e.g. *Roemeling et al, Eur Urol 50: 475-482 (2006)*

and tissue micro array (TMA) data

e.g. *Lapointe et al, PNAS 101: 811-816, 2004*

... the exciting potential for TMAs is well demonstrated by Lapointe et al

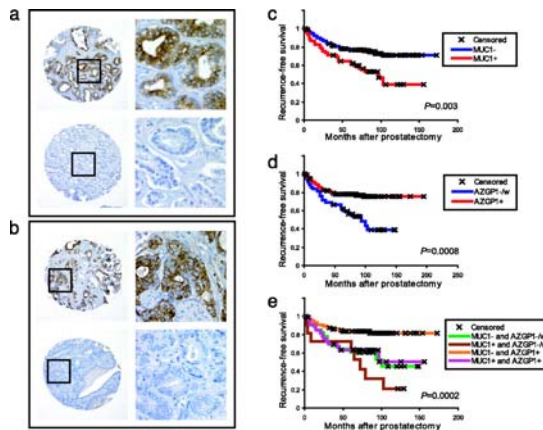
TMA Supervised Clustering according to "progression"



Lapointe et al, PNAS 101: 811-816, 2004

In this study TMA data have been backed by IHC stratification

Survival according to AZGPI + MUC1



MUC1 expression is indicative of a poor outcome, while AZGPI expression indicates a favourable outcome

**... but can progression of “harmless”
cancers be reliably diagnosed?**

At present:

- Changes in PSA DT
- Clinical progression
- Repeated biopsies

Future prospects:

- ? *New blood markers*
- ? *Use of MR ER coils*
- ? *Serial TMAs*

Zhang et al J. Urol 176 : 1392-1398, 2006
