

Identification and results of management of potentially indolent prostate cancer (PC)

Fritz H. Schröder, M.D., Ph.D.

Professor of Urology

Erasmus MC, University Medical
Centre Rotterdam

The Netherlands

To be covered

- Background: Opportunistic screening and overdiagnosis
- Identification of indolent PC
- Early results – outcome of active surveillance in ERSPC

Definitions – screening versus early detection

- Screening = application of test procedures to the general population
- Early detection = application of test procedures upon request (opportunistic screening)

Opportunistic screening: USA and The Netherlands

- NHIS 2000: PSA use in 7889 men was 24%, 28.5% - 37% for ages 55-74 (Lu Yao 2003)
- California Men's Health Study: 75% testing in 84,170 men (Enger et al, 2006)
- Netherlands CBS 2006: 2,000 men age > 40, 19% age 40, 38% age > 70 years

Overdiagnosis Definition

- Cancer otherwise not diagnosed during lifetime
- Zappa et al (1998) - screening at
age 60 - 51% overdiagnosis
age 65 - 93% overdiagnosis
- Etzioni et al (2001) - overdetected 15, 25 or 35% with leadtimes of 3, 5, 7 years
- Draisma et al (2003): Overdiagnosis 54% for age 55-74 and 4 year interval

Overdiagnosis - Overtreatment

- Overdiagnosis is inherent to screening – how much is acceptable?
- Cystoprostatectomy prevalence of incidental PC – 42% (Montironi 2005)
- ERSPC 8 year detection rate 8.3%, 20% of incidental rate
- PCPT placebo arm – all men biopsied, 7 year detection 21.9%, > 50% of incidental rate

Distribution of PSA ranges in 9779 men age 55-74 (ERSPC Rotterdam)

PSA	N	%	PSA	N	%
ng/ml			ng/ml		
0-0.9	3559	36.4	3-3.9	707	7.2
1-1.9	3051	31.2	4-9.9	1063	10.9
2-2.9	1198	12.3	>10	206	2.1
Total	7808	80%		1971	20%

Effect of using PSA > 2.5 ng/ml as biopsy indication in the USA

- Welch et al (2005): 2.74 million men, age 50-69 in the US have PSA > 2.5 ng/ml
- PCPT (Thompson et al 2003): PPV of PSA 2.1-4.0 ng/ml = 24.7%
- Biopsying all these men with PSA ≥ 2.5 will diagnose 676,780 PC, 457,890 more than expected in 2006, 15.1 times more than the 30,350 PC deaths in 2006

To be covered

- Background: Opportunistic screening and overdiagnosis
- Identification of indolent PC
- Early results – outcome of active surveillance in ERSPC

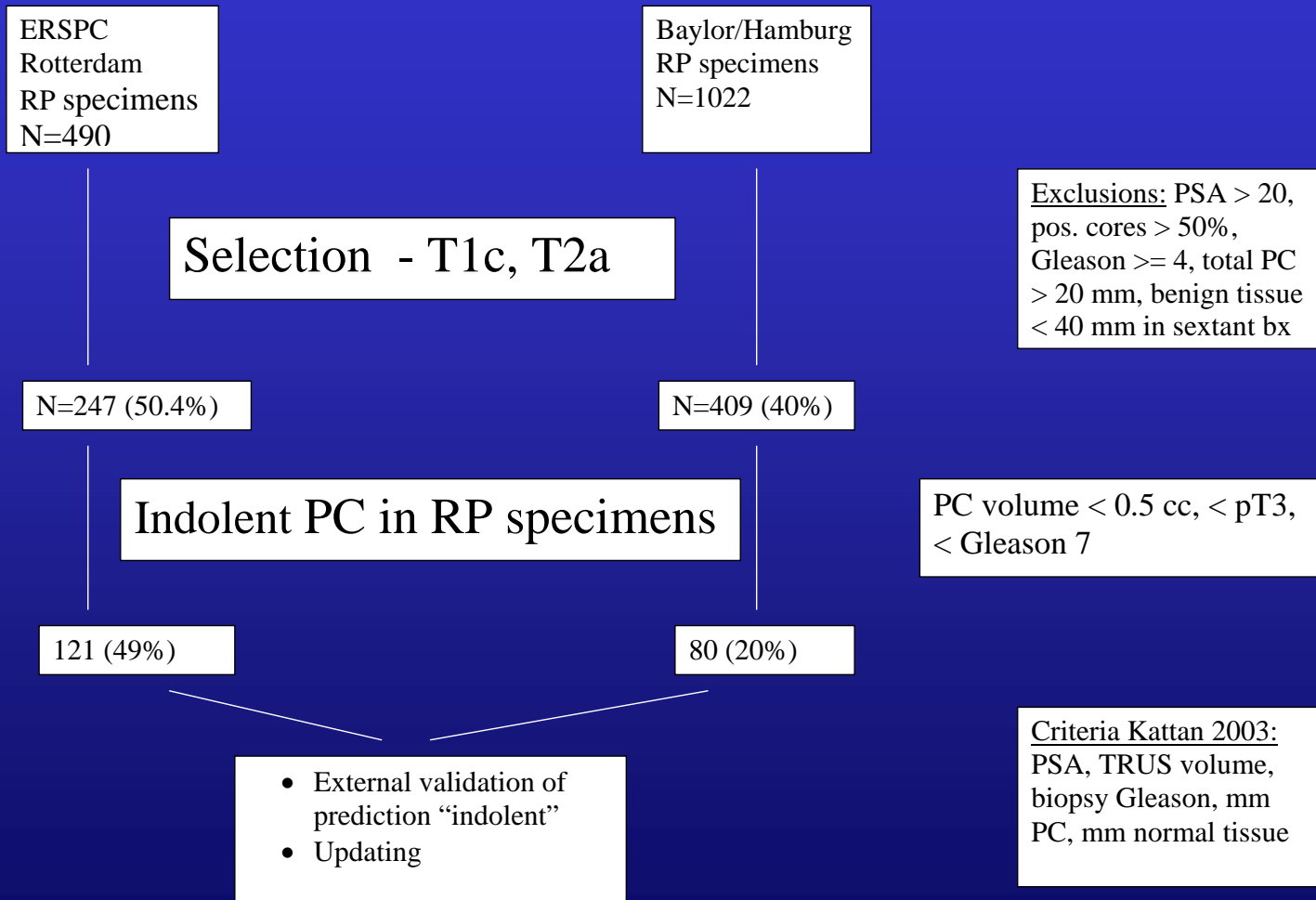
Identification of “indolent PC”

- Kattan 2003: 409 cases of PC treated by RP contained 80 (20%) classified “indolent”
- Steyerberg et al (2006): 121 of 247 cases 49% identified as indolent in ERSPC Rotterdam, using Kattan criteria
- Data reflect the difference of clinical and screen detected PC

Minimal (“insignificant”, “indolent” PC in reported series of radical prostatectomies

Reference	Detection mode	Rad.prostat-ectomies (N)	Insignificant PC %
Epstein et al (1998)	Clinical T1c	163	30.7
Krumholtz et al (2002)	Clinical T1c	94	11.5
Augustin et al (2003)	Clinical T1 – T3	1254	5.8
Kattan et al (2003)	Clinical T1 – T2a	409	20.0
Sokoloff et al (2002)	Clinical PSA < 4.0	79	48.0
Postma et al (2005)	Screen det. 2nd round	386 164	33 43

Flow of validation procedure – Indolent PC in ERSPC Rotterdam versus Kattan et al (2003)



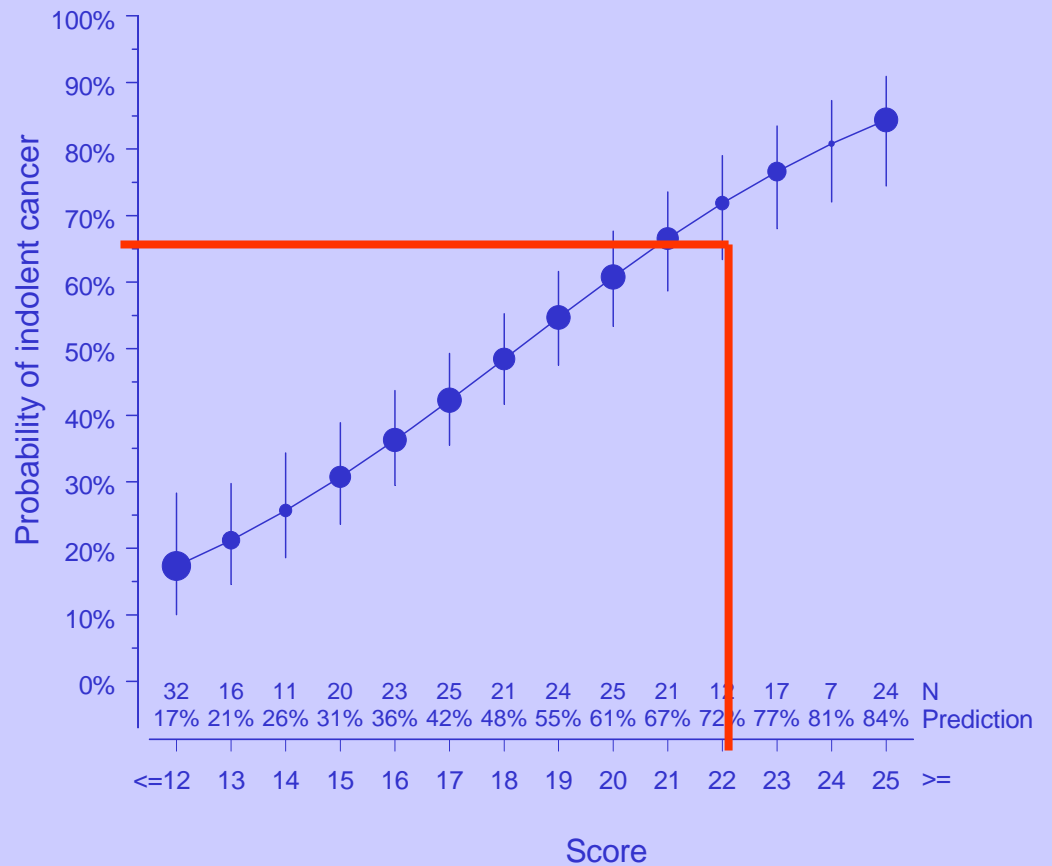
Updating and extension of the model, N=278, ERSPC Rotterdam

- 31 T2b or T2c patients had probabilities of indolent PC of 53 and 44%, not different from T1c (48%) or T2a (52%) and were added to the data
- Model extension: age, family history, positive US, lesion diameter and screening round, earlier biopsy, PSAV – no improvement
- Updating and extension produced only small model improvements

Score chart + graph for probabilities (n=278)

Variable	Values	Score	Sum
PSA (ng/ml)	20	0	
	13	2	
	9.0	4	
	6.0	6	
	5.0	7	
	4.0	8	
	3.3	9	
	2.2	11	
	1.0	15	
Ultrasound volume (cc)	20	0	
	40	2	
	60	4	
	80	6	
Biopsy Gleason scores 1 and 2	33	0	
	23	1	
	22	3	
	20	0	
mm Cancer (total over biopsy cores)	12	2	
	7	4	
	6	5	
	4.5	6	
	3.5	7	
	2	9	
	1	12	
mm non Cancer (total over biopsy cores)	40	0	
	60	2	
	80	4	
Score (sum all subscores)			22

Correction for clinical setting: - 6



Proportions of immediate versus delayed treatment for important (N=142) and indolent (N=136) PC using different score cut-offs (total N=278). ERSPC

Treatment (Tx)	Important PC – treated N (%)	Indolent PC Tx delayed N (%)
No tx if probability indolent >30% (score >=15)	50/142 (35)	126/136 (93)
No tx if probability indolent > 60% (score > 20)	120/142 (85)	62/136 (46)
No tx if probability indolent > 70% (score > 21)	133/142 (94)	43/136 (32)

To be covered

- Background: Opportunistic screening and overdiagnosis
- Identification of indolent PC
- Early results – outcome of active surveillance in ERSPC

Prediction of indolent disease in screen detected prostate cancer (PC) (Roemeling et al 2007)

- PC incidence screening round 1: n=1079
PC incidence screen round 2 (year 4) 550
- Cumulative prevalence indolent:
 - Round 1: 243/1078 PC (23%)
 - Round 2: 242/550 PC (44%)
 - All PC: 485/1629 PC (30%)
- Cut-off 60% probability indolent:
 - Round 1: 185/1079 (17%)
 - Round 2: 247/550 (45%)
 - All PC: 432/1629 (37%)
- None of 29 PC deaths in screen-detected PC had a probability of indolent PC > 52%

Active surveillance in ERSPC Rotterdam (Roemeling et al 2006)

- 293 of 1014 PC (28.9%) qualified
- Choices: RP 136 (46.4%), RT 91 (31.1%), WW 64 (21.8%)
- Mean F.U. 80.8 months
- 8 year PC specific survival evaluated

Outcome – active surveillance vs active treatment, ERSPC Rotterdam

(Roemeling et al 2006)

	RP	RT	WW	Total
N	136	91	64	293
Progression to M+	2	2	0	4
PC deaths	1	2	0	3
8 year PC – specific survival	99.2%	98.6%	100%	99.2%

Conclusions

- Opportunistic screening cannot be refused to **well-informed** men
- A probability cut-off of 70% identifies as “indolent” about 30% of screen detected cases
- Overtreatment can be curbed by applying active surveillance to potentially indolent cases.

Recurrence free survival after radical prostatectomy (N=8265) (Han, Catalona, Walsh, AUA 2007)

