Approccio attendista:

Sorveglianza Attiva vs Vigile Attesa

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Sorveglianza Attiva ≠ Vigile Attesa

	Active Surveillance	**Watchful Waiting**
Aim	To individualize strategy according to the biologic behavior of cancer	Maintain QoL by avoiding palliative treatment when PCa is unlikely to cause mortality
Patient characteristics	Fit for radical treatments Age < 80	Life expectancy < 5-10 years
Disease characteristics	e. g. PRIAS: cT1-2a; GPS ≤ 3+3; PSA ≤ 10 ng/ml, pos cores <3	Any T stage and any PSA; GPS ≤ 7
Monitoring	Re-biopsies: systematic PSA	PSA, DRE No re-biopsy
Indications for Treatment	Upgrading/upsizing PSA kinetic	Symptomatic progression
Treatment Timing	Early	Delayed
Treatment Intent	Radical	Palliative

Modified from Packer C

Changed face of PCa

Starting in the Nineties introducing the opportunistic screening with PSA

Dramatic increase in the diagnostic biopsies

Early diagnosis of prostate cancer before any clinical symptom (early identification of potentially aggressive and lethal cancers)
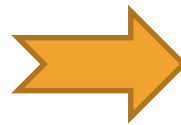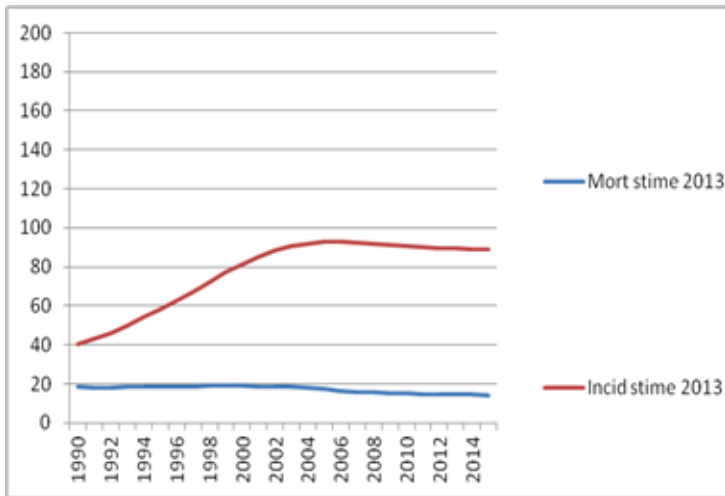
Diagnosis of clinically insignificant tumors
(indolent and non aggressive which would not cause death/morbidity in one's life)

OVER-DIAGNOSIS

INDISCRIMINATE TREATMENT OF ALL THE DIAGNOSED TUMORS

OVER-TREATMENT

Incidence – mortality discrepancy

Overdiagnosis
Around 40-50% of PCa over-diagnosed (tumors that would never cause symptoms in lifetime) in population based screening studies like the ERSPC (PSA cut-off value of 3 ng/ml).

Phase III: Radical treatment vs observation

	SPCG-4 (Bill-Axelson)	**PIVOT** (Wilt)	**PROTECT** (Hamdy)
Intevention	RP vs WW	RP vs WW	RP vs RT vs AM
Recruitment period	1989-1999	1994-2002	1999 - 2009
Recruited men – total nr (nr per arm)	695 (347 – 348)	731 (364 vs 367)	1643 (553 vs 545 vs 545)
Mean age	65	67	61
Median PSA	13	7.8	5.8
Clinical Stage			
T1	11%	50%	76%
T2	75%	40%	24%
T3	0	0	0
Unknown	14%	10%	0
Gleason score (RP/WW)			
<7	60%	74%	77%
≥7	28%	19%	23%
Unknown	12%	7%	0
PCa specific-mortality (RP – WW)	17.7 vs 28.7% at 18 ys FU RR 0.56 p = 0.001	5.8%/8.4% at 12 ys FU, HR 0.63; p=0.09	HR 0.94 (RT vs AM) HR 0.93 (RP vs AM) p=0.92

Guidelines advice AS

National Comprehensive Cancer Network – NCCN

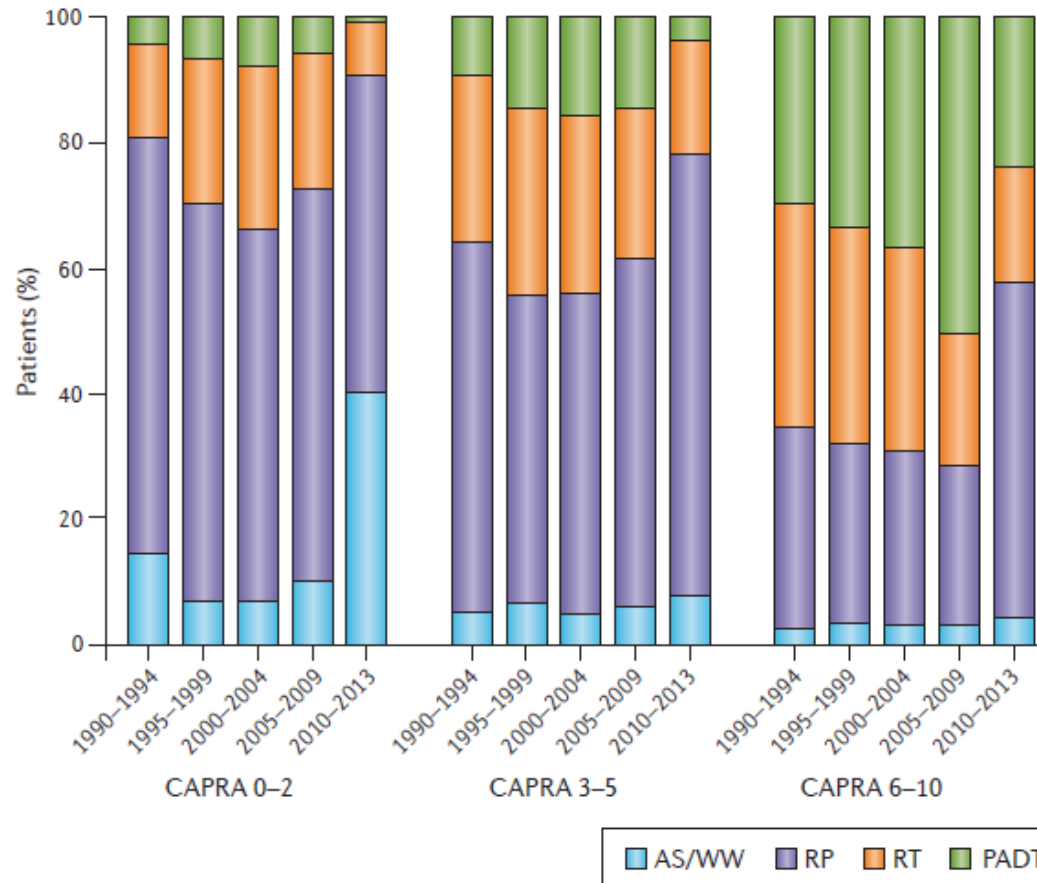National Institute for Health and Care Excellence - NICE

European Association of Urology – EAU

Cancer care Ontario Guideline, endorsed by American Society of Clinical Oncology – ASCO

American Urological Association - AUA

Guidelines recommand to
Inform patient about treatment options including AS

Trends in initial treatment

Data from Capsure DB (Cooperberg)
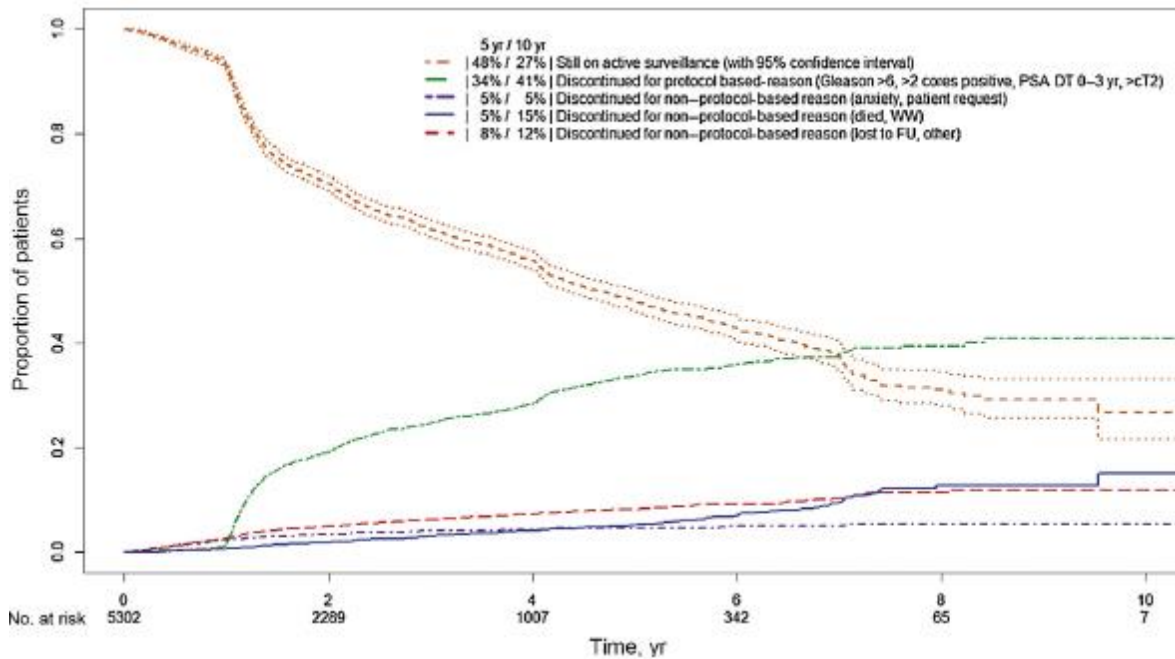
Protocol selection criteria

Table 1 | Selection criteria for AS

Programme	Clinical stage	Gleason score	Positive cores*	Maximum % cancer in any core*	Serum PSA level (ng/ml)	PSAD	Other
Johns Hopkins	T1c	≤6	≤2	≤50	N/A	<0.15	N/A
	≤T2a	≤6	N/A	N/A	≤10	N/A	N/A
Sunnybrook‡	N/A	≤6	N/A	N/A	≤10	N/A	N/A
		≤3+4	N/A	N/A	10–20	N/A	LE <10 years
Göteborg§	≤T2a	≤6	N/A	N/A	≤10	N/A	N/A
UCSF	≤T2	≤6	≤33%	≤50	≤10	N/A	N/A
Royal Marsden	≤T2	≤6	≤50%	N/A	N/A	N/A	Age 50–80 years
		≤3+4	≤50%	N/A	<15	N/A	Age >65 years
Australian	≤T2a	≤6	<20%	<30	<10	N/A	N/A
PRIAS	≤T2	≤6	≤2	N/A	≤10	<0.20	N/A
University of Copenhagen	≤T2a	≤6	≤3	<50	≤10	N/A	N/A
University of Miami	≤T2	≤6	≤2	≤20	≤10	N/A	Age ≤80 years

Tosoian 2016

Protocol outcomes

Institution	No of pts	Median Age (yrs)	Median FU (mos)	Met (%)	Cancer- specific survival (%)
UCSF (Welty)	810	62 (mean)	60	0	100
Miami (Soloway)	230	63 (mean)	44 (mean)	0	100
Sunnybrook (Klotz)	993	68	82	2.8	98.1 at 10 yrs 94.3 at 15 yrs
JHU (Tosoian)	1298	66	60	0.4	99.9 at 15 ys
PRIAS (Bokhorst)	5302	65.9	19	0.15	99 at 10 ys
Goteborg (Godtman)	439	65	72	0.5	99.7
Royal Marsden (Selvadurai)	471	66	68	NA	99.6
Copenhagen (Thomsen)	167	65	41	0	100
Australia [58]	650	63	67	0	100

Drop-out from AS

5 yr / 10 yr
- |48% / 27% | Still on active surveillance (with 95% confidence interval)
- |34% / 41% | Discontinued for protocol based-reason (Gleason >6, >2 cores positive, PSA DT 0–3 yr, >cT2)
- | 5% / 5% | Discontinued for non–protocol-based reason (anxiety, patient request)
- | 5% / 15% | Discontinued for non–protocol-based reason (died, WW)
- | 8% / 12% | Discontinued for non–protocol-based reason (lost to FU, other)

PRIAS Bokhorst 2016

— 41% 10 ys drop-out due to protocol based-reason (GPS>6, >2 cores positive, PSADT 0-3 ys, >cT2) (Bokorst 2016),

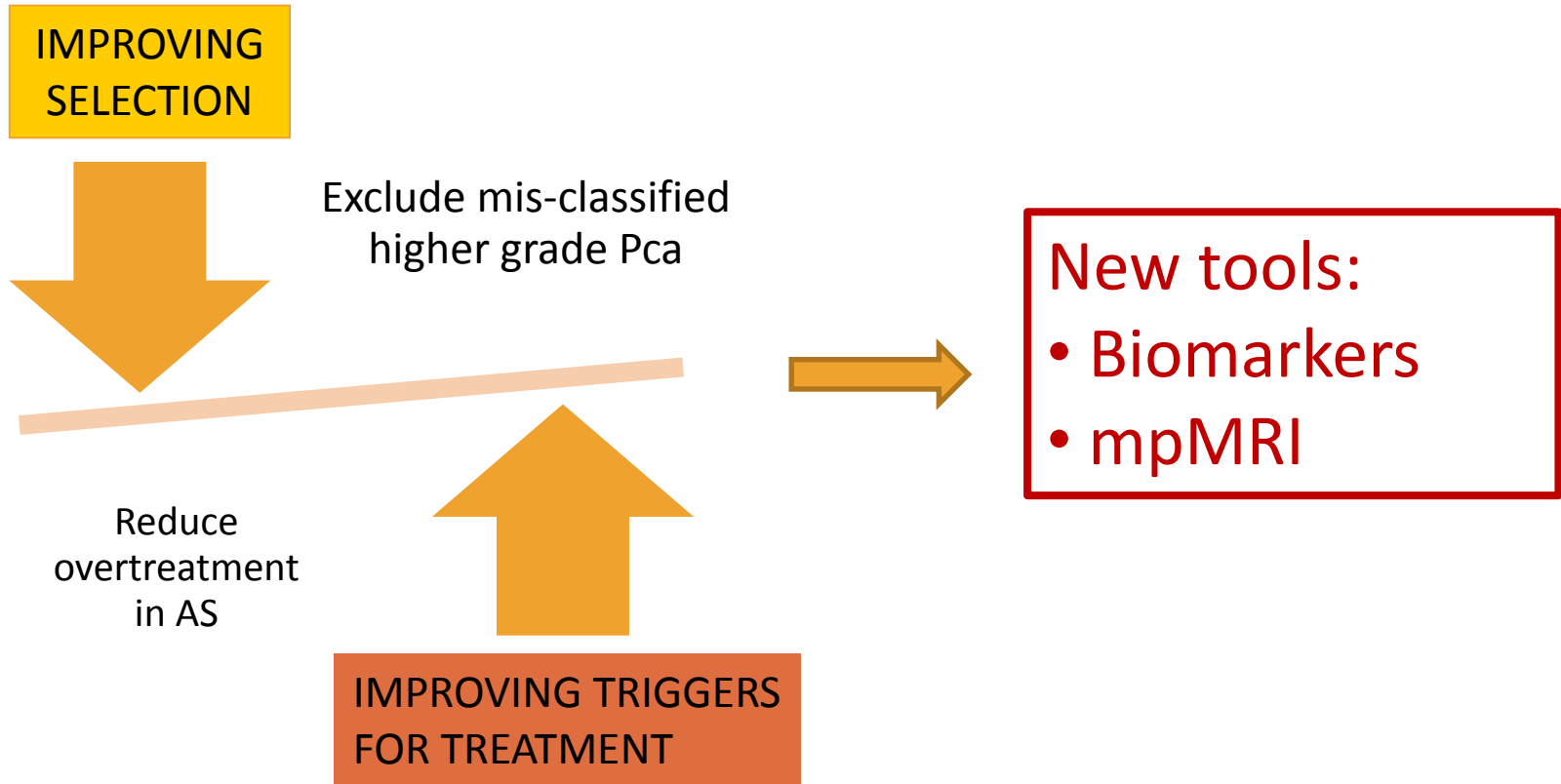Metanalysis AS studies: 8.8% treated men per year (Simpkin 2015)

VS

10-yr cancer-specific survival (CSS) of men undergoing WW in the Scandinavian protocol was 85.3% (Bill-Axelson)

10 ys PCa-specific mortaliy in Canadian AS series < 2.0% (Klotz)
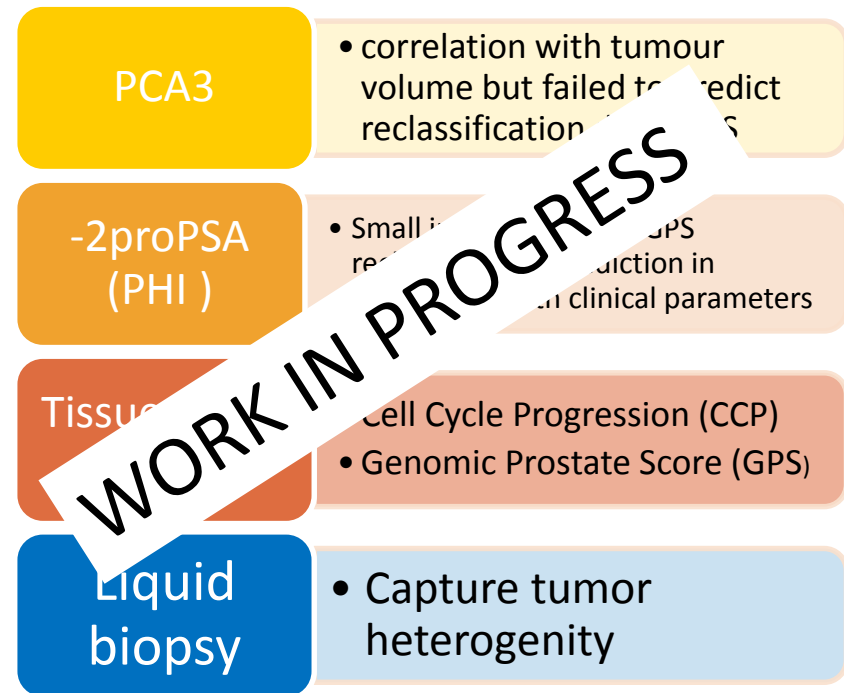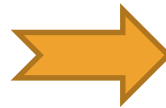
OVERTREATMENT?

Evolving concepts

IMPROVING SELECTION

Exclude mis-classified higher grade Pca

Reduce overtreatment in AS

IMPROVING TRIGGERS FOR TREATMENT

New tools:
- Biomarkers
- mpMRI

Biomarkers: agressiveness prediction beyond fixed criteria

Table 1 Gleason 3 lacks the hallmarks of cancer

Characteristic of cancer	Gleason 3	Gleason 4
Expression of pro-proliferation embryonic, neuronal, haematopoietic stem cell genes, EGF, EGFR [7]	Not present	Overexpressed
AKT pathway [7]	Not present	Aberrant
HER2neu [8]	Not present	Amplified
Insensitivity to antigrowth signals such as cyclin D2 methylation, CKDN1β [9, 16]	Expressed	Absent
Resistance to apoptosis: DAD1 [12]	Negative	Strong expression
BCL2 [12]	Mostly negative	Upregulated
Absence of senescence: [13]	Normal	Increased
Sustained angiogenesis: VEGF [14]	Expression low	Increased
Other pro-angiogenic factors and microvessel density [15]	Normal	Increased
Tissue invasion and metastasis markers (CXCR4, others) [19]	Normal	Overexpressed
PTEN [18][a]	Present (7 % deleted)	Deleted
TMPRSS2-ERG translocation [22, 23]	Present 45 %	Present 50–60 %
Clinical evidence of metastasis and mortality [24••, 26]	Virtually absent	Present

PCA3
- correlation with tumour volume but failed to predict reclassification in AS

-2proPSA (PHI)
- Small in____ GPS re____ ____iction in ____ clinical parameters

Tissue
- Cell Cycle Progression (CCP)
- Genomic Prostate Score (GPS)

Liquid biopsy
- Capture tumor heterogenity

WORK IN PROGRESS

Multiparametric MRI

- High NPV: 63%-98% (depending on threshold for significance (Fütterer JJ 2015)

- Suspicious lesions (PIRADS ≥ 3) in 70%   uitable for AS.

- Highly suspicious preopera   MRI (PI-RADS 4-5) associated with a high   nce of high-grade disease compared with a l   spicious (PI-RADS 1-2): 43% vs 27% (Schoots IG

- targeting   ious areas through direct MRI-guided (in bore) or software co-registration (fusion biopsy) techniques

- PRECISE task force recommendation for mpMRI reporting in AS (Moore 2016)

NEED FOR OPTIMIZATION

Psycho-emotional aspects

From pt point of view, AS aims to preserve quality of life, avoiding treatment associated side effects

Burden of living with untreated cancer

Treatment side effects
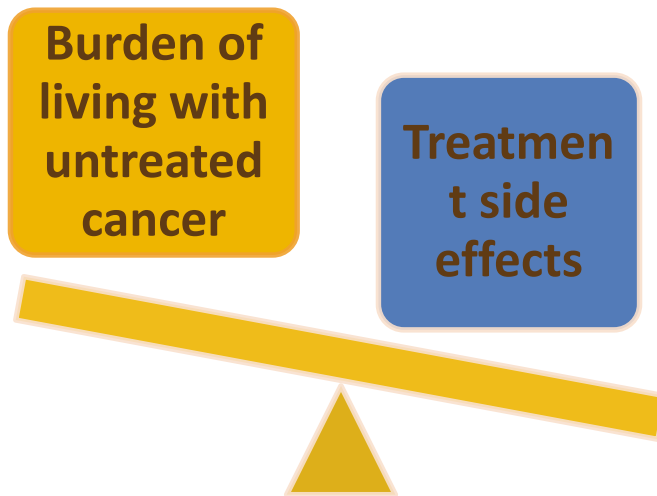
Drop out from AS due to anxiety: 4-15%

Meta-analysis of 10 AS studies: Health-related Quality of Life (HRQoL) is generally good, with favourable anxiety and depression scores (Bellardita 2015).

Anxiety after 9 mos of surveillance, independent of PSA variations (van den Berg)

Predictors of low HRQoL scores:
➢identified as a lack of a partner
➢impaired mental health
➢**quality of the relationship with the physician**
➢**perception of the disease by the patient**

Multidisciplinary approch

> • Different options for very low/low risk Pca: surgery, radiotherapy, AS
>
> •Different specialists involved in the path of care
>
> •Need for exaustive and balanced information
>
> •Support in decision-making phase

Multidisciplinary Care and Pursuit of Active Surveillance in Low-Risk Prostate Cancer

Ayal A. Aizer, Jonathan J. Paly, Anthony L. Zietman, Paul L. Nguyen, Clair J. Beard, Sandhya K. Rao, Irving D. Kaplan, Andrzej Niemierko, Michelle S. Hirsch, Chin-Lee Wu, Aria F. Olumi, M. Dror Michaelson, Anthony V. D'Amico, and Jason A. Efstathiou

Choice of AS in pts seen at a MDC was double than choice made by pts seen by individual practitioners: 43% vs 22%"

Selection of Active Surveillance in pts seen at our MDC:
43% in 2006 and **73%** in 2010

The 6-year attendance of a multidisciplinary prostate cancer clinic in Italy: incidence of management changes

BJUI

Tiziana Magnani*, Riccardo Valdagni*†, Roberto Salvioni†, Sergio Villa†, Lara Bellardita§, Simona Donegani§, Nicola Nicolai†, Giuseppe Procopio¶, Nice Bedini†, Tiziana Rancati* and Nadia Zaffaroni††

Conclusions

- Active Surveillance responded to the need for appropriateness of cure and for reduction of overtreatment

- Major guidelines recommend to inform patients about AS

- Overtreatment awareness and AS acceptance increased among phisicians in current practice

- Intermediate/long-term outcomes from AS studies are favorable and Pca specific mortality rate is low

- New tools to improve pts:
  - Markers of aggressivennes : liquid biopsy
  - mpMRI and Targeted biopsy

- Low anxiety level and high Quality of life during AS

- Multidisciplinary approach enhances AS

Grazie per l'attenzione